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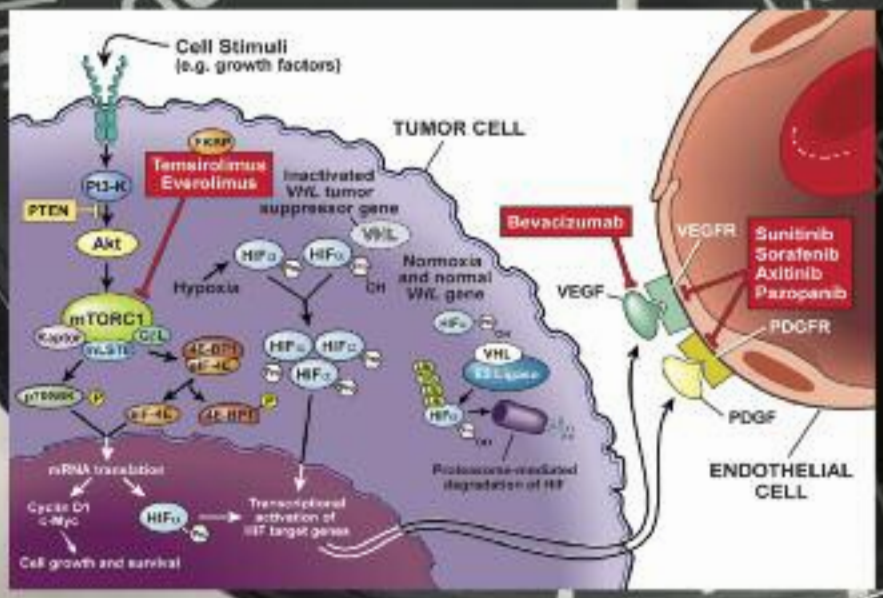

Hypertension as Biomarker for Anti-VEGF Efficacy

Managing Toxicities of High-Dose IL-2

An Educational Service for Medical Oncologists, Hematologist-Oncologists, and Urologists

SUTENT is indicated for the treatment of advanced renal cell carcinoma (RCC).

LEAD WITH EFFICACY. LEAD WITH SUTENT.

(SUNITINIB MALATE)

SUTENT: PROVEN EFFICACY IN 1ST-LINE mRCC VS IFNα*

MORE THAN DOUBLED MEDIAN PFS

- 11 months vs 5 months with IFNα (95% CI: 9.8, 11.7 and 3.8, 5.5, respectively; *P*<.000001)
- 58% reduced risk of progression or death (HR=0.42; 95% CI: 0.32, 0.54)

DEMONSTRATED 5-FOLD HIGHER ORR

- 39% vs 8% with IFNα (95% CI: 34.0, 44.3 and 5.7, 11.8, respectively; *P*<.000001) in the second analysis (June 2007)[1]
- 28% vs 5% with IFNα (95% CI: 23.0, 32.3 and 3.3, 8.1, respectively; *P*<.001) in the first analysis (November 2005)

ALSO ACHIEVED MORE THAN 2 YEARS' MEDIAN OS

- 26.4 months vs 21.8 months with IFNα (HR=0.82; 95% CI: 0.673, 1.001; *P*=.051)[1]

AN ESTABLISHED SAFETY PROFILE

- The most common adverse reactions (ARs) occurring in ≥20% of patients receiving SUTENT for treatment-naïve metastatic RCC (all grades, vs IFNα) were diarrhea (66% vs 21%), fatigue (62% vs 56%), nausea (58% vs 41%), anorexia (48% vs 42%), altered taste (47% vs 15%), mucositis/stomatitis (47% vs 5%), pain in extremity/limb discomfort (40% vs 30%), vomiting (39% vs 17%), bleeding, all sites (37% vs 10%), hypertension (34% vs 4%), dyspepsia (34% vs 4%), arthralgia (30% vs 19%), abdominal pain (30% vs 12%), rash (29% vs 11%), hand-foot syndrome (29% vs 1%), back pain (28% vs 14%), cough (27% vs 14%), asthenia (26% vs 22%), dyspnea (26% vs 20%), skin discoloration/yellow skin (25% vs 0%), peripheral edema (24% vs 5%), headache (23% vs 19%), constipation (23% vs 14%), dry skin (23% vs 7%), fever (22% vs 37%), and hair color changes (20% vs <1%)

*All data are from the large (N=750), phase 3, randomized, multicenter trial comparing SUTENT with IFNα in patients with treatment-naïve metastatic RCC.

ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Reference: 1. Data on file. Pfizer Inc, New York, NY.

Please see study description and brief summary, including boxed warning, on the following page.

Important safety information

Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution.

Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant.

Left ventricular ejection fraction declines to below the lower limit of normal have occurred. Monitor patients for signs and symptoms of congestive heart failure (CHF) and, in the presence of clinical manifestations, discontinuation is recommended. Patients who presented with cardiac events, pulmonary embolism, or cerebrovascular events within the previous 12 months were excluded from clinical studies.

SUTENT has been shown to prolong QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including torsades de pointes, which has been seen in <0.1% of patients. Monitoring with on-treatment electrocardiograms and electrolytes should be considered.

Hypertension may occur. Monitor blood pressure and treat as needed.

Hemorrhagic events including tumor-related hemorrhage, some of which were fatal, have occurred. Perform serial complete blood counts (CBCs) and physical examinations.

Thyroid dysfunction may occur. Monitor thyroid function in patients with signs and/or symptoms of hypothyroidism or hyperthyroidism and treat per standard medical practice.

Adrenal hemorrhage was observed in animal studies. Monitor adrenal function in case of stress such as surgery, trauma, or severe infection.

CBCs and serum chemistries should be performed at the beginning of each treatment cycle.

Dose adjustments are recommended when administered with CYP3A4 inhibitors or inducers.

The most common grade 3/4 ARs (occurring in ≥5% of SUTENT patients) were fatigue (15% vs 15%), hypertension (13% vs <1%), asthenia (11% vs 6%), diarrhea (10% vs <1%), hand-foot syndrome (8% vs 0%), dyspnea (6% vs 4%), nausea (6% vs 2%), back pain (5% vs 2%), pain in extremity/limb discomfort (5% vs 2%), vomiting (5% vs 1%), and abdominal pain (5% vs 1%).

The most common grade 3/4 lab abnormalities occurring in ≥5% of patients receiving SUTENT (vs IFNα) included lymphocytes (18% vs 26%), lipase (18% vs 8%), neutrophils (17% vs 9%), uric acid (14% vs 8%), platelets (9% vs 1%), hemoglobin (8% vs 5%), sodium decreased (8% vs 4%), leukocytes (8% vs 2%), glucose increased (6% vs 6%), phosphorus (6% vs 6%), and amylase (6% vs 3%).

capsules
SUTENT®
sunitinib malate
The Proven Path

Results of the phase 3, randomized, multicenter, international trial. 750 treatment-naïve patients were treated with either 50-mg SUTENT once daily in cycles of 4 weeks on/2 weeks off, or 9 MIU IFNα 3 times per week (administered subcutaneously) until disease progression or study withdrawal. Primary endpoint was progression-free survival, and secondary endpoints included objective response rate by Response Evaluation Criteria in Solid Tumors, overall survival, and safety.

SUTENT® (SUNITINIB MALATE) CAPSULES, ORAL

Brief Summary of Prescribing Information

WARNING: HEPATOTOXICITY.
Hepatotoxicity has been observed in clinical trials and post-marketing experience. This hepatotoxicity may be severe, and deaths have been reported. *[See Warnings and Precautions]*

INDICATIONS AND USAGE: SUTENT is indicated for the treatment of advanced renal cell carcinoma (RCC).

DOSAGE AND ADMINISTRATION

Recommended Dose. The recommended dose of SUTENT for advanced RCC is one 50 mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). SUTENT may be taken with or without food.

Dose Modification. Dose interruption and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Hepatotoxicity. SUTENT has been associated with hepatotoxicity, which may result in liver failure or death. Liver failure has been observed in clinical trials (7/2281 [0.3%]) and post-marketing experience. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor liver function tests (ALT, AST, bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. SUTENT should be interrupted for Grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart SUTENT if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Safety in patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN has not been established.

Pregnancy/Pregnancy Category D. As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be expected to result in adverse effects on pregnancy. There are no adequate and well-controlled studies of SUTENT in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT.

Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities were observed in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] in patients administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD).

Left Ventricular Dysfunction. In the presence of clinical manifestations of congestive heart failure (CHF), discontinuation of SUTENT is recommended. The dose of SUTENT should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

Cardiovascular events, including heart failure, myocardial disorders and cardiomyopathy, some of which were fatal, have been reported through post-marketing experience. More patients treated with SUTENT experienced decline in left ventricular ejection fraction (LVEF) than patients receiving either placebo or interferon-α (IFN-α).

In the treatment-naïve RCC study, 103/375 (27%) and 54/360 (15%) patients on SUTENT and IFN-α, respectively, had an LVEF value below the LLN. Twenty-six patients on SUTENT (7%) and seven on IFN-α (2%) experienced declines in LVEF to >20% below baseline and to below 50%. Left ventricular dysfunction was reported in four patients (1%) and CHF in two patients (<1%) who received SUTENT.

Patients who presented with cardiac events within 12 months prior to SUTENT administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic CHF, cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. **These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT. Baseline and periodic evaluations of LVEF should also be considered while these patients are receiving SUTENT. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.**

QT Interval Prolongation and Torsade de Pointes. SUTENT has been shown to prolong the QT interval in a dose dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of SUTENT-exposed patients.

SUTENT should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUTENT, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and dose reduction of SUTENT should be considered.

Hypertension. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In cases of severe hypertension, temporary suspension of SUTENT is recommended until hypertension is controlled.

Of patients receiving SUTENT for treatment-naïve RCC, 127/375 patients (34%) receiving SUTENT compared with 13/360 patients (4%) on IFN-α experienced hypertension. Grade 3 hypertension was observed in 50/375 treatment-naïve RCC patients (13%) on SUTENT compared to 1/360 patient (<1%) on IFN-α. SUTENT dosing was reduced or temporarily delayed for hypertension in 21/375 patients (6%) on the treatment-naive RCC study. Four treatment-naïve RCC patients, including one with malignant hypertension, discontinued treatment due to hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 32/375 treatment-naïve RCC patients (9%) on SUTENT and 3/360 patients (1%) on IFN-α.

Hemorrhagic Events. Hemorrhagic events reported through post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract and brain hemorrhages. In patients receiving SUTENT in a clinical trial for treatment-naïve RCC, 140/375 patients (37%) had bleeding events compared with 35/360 patients (10%) receiving IFN-α. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in gastrointestinal stromal tumor (GIST) or RCC patients included rectal, gingival, upper gastrointestinal, genital, and wound bleeding. Most events in RCC patients were Grade 1 or 2; there was one Grade 5 event of gastric bleed in a treatment-naïve patient.

Tumor-related hemorrhage has been observed in patients treated with SUTENT. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Fatal pulmonary hemorrhage occurred in 2 patients receiving SUTENT on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. SUTENT is not approved for use in patients with NSCLC. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation have occurred rarely in patients with intra-abdominal malignancies treated with SUTENT.

Thyroid Dysfunction. Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of SUTENT treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on SUTENT treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.

Hypothyroidism was reported as an adverse reaction in sixty-one patients (16%) on SUTENT in the treatment-naïve RCC study and in three patients (1%) in the IFN-α arm.

Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience.

Adrenal Function. Physicians prescribing SUTENT are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

Laboratory Tests. CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT.

ADVERSE REACTIONS

The data described below reflect exposure to SUTENT in 577 patients who participated in the double-blind treatment phase of a placebo-controlled trial (n=202) for the treatment of GIST or an active-controlled trial (n=375) for the treatment of RCC. The patients received a starting oral dose of 50 mg daily on Schedule 4/2 in repeated cycles.

The most common adverse reactions (≥20%) in patients with GIST or RCC are fatigue, asthenia, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding. The potentially serious adverse reactions of hepatotoxicity, left ventricular dysfunction, QT interval prolongation, hemorrhage, hypertension, thyroid dysfunction, and adrenal function are discussed in *Warnings and Precautions*. Other adverse reactions occurring in RCC studies are described below.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in the Treatment-Naïve RCC Study. The as-treated patient population for the treatment-naive RCC study included 735 patients, 375 randomized to SUTENT and 360 randomized to IFN-α. The median duration of treatment was 11.1 months (range: 0.4 - 46.1) for SUTENT treatment and 4.1 months (range: 0.1 - 45.6) for IFN-α treatment. Dose interruptions occurred in 202 patients (54%) on SUTENT and 141 patients (39%) on IFN-α. Dose reductions occurred in 194 patients (52%) on SUTENT and 98 patients (27%) on IFN-α. Discontinuation rates due to adverse reactions were 20% for SUTENT and 24% for IFN-α. Most treatment-emergent adverse reactions in both study arms were Grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 77% versus 55% of patients on SUTENT versus IFN-α, respectively.

The following table compares the incidence of common (≥10%) treatment-emergent adverse reactions for patients receiving SUTENT versus IFN-α.

Adverse Reactions Reported in at Least 10% of Patients with RCC Who Received SUTENT or IFN-α*

	SUTENT (n=375)		IFN-α (n=360)	
Adverse Reaction, n (%)	**All Grades**	**Grade 3/4[a]**	**All Grades**	**Grade 3/4[b]**
Any	372 (99)	290 (77)	355 (99)	197 (55)
Constitutional				
Fatigue	233 (62)	55 (15)	202 (56)	54 (15)
Asthenia	96 (26)	42 (11)	81 (22)	21 (6)
Fever	84 (22)	3 (1)	134 (37)	1 (<1)
Weight decreased	60 (16)	1 (<1)	60 (17)	3 (1)
Chills	53 (14)	3 (1)	111 (31)	0 (0)
Chest Pain	50 (13)	7 (2)	24 (7)	3 (1)
Influenza like illness	18 (5)	0 (0)	54 (15)	1 (<1)
Gastrointestinal				
Diarrhea	246 (66)	37 (10)	76 (21)	1 (<1)
Nausea	216 (58)	21 (6)	147 (41)	6 (2)
Mucositis/stomatitis	178 (47)	13 (3)	19 (5)	2 (<1)
Vomiting	148 (39)	19 (5)	62 (17)	4 (1)
Dyspepsia	128 (34)	8 (2)	16 (4)	0 (0)
Abdominal pain[c]	113 (30)	20 (5)	42 (12)	5 (1)
Constipation	85 (23)	4 (1)	49 (14)	1 (<1)
Dry mouth	50 (13)	0 (0)	27 (7)	1 (<1)
GERD/reflux esophagitis	47 (12)	1 (<1)	3 (1)	0 (0)
Flatulence	52 (14)	0 (0)	8 (2)	0 (0)
Oral pain	54 (14)	2 (<1)	2 (1)	0 (0)
Glossodynia	40 (11)	0 (0)	2 (1)	0 (0)
Hemorrhoids	38 (10)	0 (0)	6 (2)	0 (0)
Cardiac				
Hypertension	127 (34)	50 (13)	13 (4)	1 (<1)
Edema, peripheral	91 (24)	7 (2)	17 (5)	2 (1)
Ejection fraction decreased	61 (16)	10 (3)	19 (5)	6 (2)
Dermatology				
Rash	109 (29)	6 (2)	39 (11)	1 (<1)
Hand-foot syndrome	108 (29	32 (8)	3 (1)	0 (0)
Skin discoloration/ yellow skin	94 (25)	1 (<1)	0 (0)	0 (0)
Dry skin	85 (23)	1 (<1)	26 (7)	0 (0)
Hair color changes	75 (20)	0 (0)	1 (<1)	0 (0)
Alopecia	51 (14)	0 (0)	34 (9)	0 (0)
Erythema	46 (12)	2 (<1)	5 (1)	0 (0)
Pruritus	44 (12)	1 (<1)	24 (7)	1 (<1)
Neurology				
Altered taste[d]	178 (47)	1 (<1)	54 (15)	0 (0)
Headache	86 (23)	4 (1)	69 (19)	0 (0)
Dizziness	43 (11)	2 (<1)	50 (14)	2 (1)
Musculoskeletal				
Back pain	105 (28)	19 (5)	52 (14)	7 (2)
Arthralgia	111 (30)	10 (3)	69 (19)	4 (1)
Pain in extremity/ limb discomfort	150 (40)	19 (5)	107 (30)	7 (2)
Endocrine				
Hypothyroidism	61 (16)	6 (2)	3 (1)	0 (0)
Respiratory				
Cough	100 (27)	3 (1)	51 (14)	1 (<1)
Dyspnea	99 (26)	24 (6)	71 (20)	15 (4)
Nasopharyngitis	54 (14)	0 (0)	8 (2)	0 (0)
Oropharyngeal Pain	51 (14)	2 (<1)	9 (2)	0 (0)
Upper respiratory tract infection	43 (11)	2 (<1)	9 (2)	0 (0)
Metabolism/Nutrition				
Anorexia[e]	182 (48)	11 (3)	153 (42)	7 (2)
Hemorrhage/Bleeding				
Bleeding, all sites	140 (37)	16 (4)[f]	35 (10)	3 (1)
Psychiatric				
Insomnia	57 (15)	3 (<1)	37 (10)	0 (0)
Depression[g]	40 (11)	0 (0)	51 (14)	5 (1)

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[a]Grade 4 ARs in patients on SUTENT included back pain (1%), arthralgia (<1%), dyspnea (<1%), asthenia (<1%), fatigue (<1%), limb pain (<1%) and rash (<1%)
[b]Grade 4 ARs in patients on IFN-α included dyspnea (1%), fatigue (1%), abdominal pain (<1%), and depression (<1%)
[c]Includes flank pain
[d]Includes ageusia, hypogeusia and dysgeusia
[e]Includes decreased appetite
[f]Includes one patient with Grade 5 gastric hemorrhage
[g]Includes depressed mood

Treatment-emergent Grade 3/4 laboratory abnormalities are presented below.

Laboratory Abnormalities Reported in at Least 10% of Treatment-Naïve RCC Patients Who Received SUTENT or IFN-α

Laboratory Parameter, n (%)	SUTENT (n=375)		IFN-α (n=360)	
	All Grades*	Grade 3/4*[a]	All Grades*	Grade 3/4*[b]
Gastrointestinal				
AST	211 (56)	6 (2)	136 (38)	8 (2)
ALT	192 (51)	10 (3)	144 (40)	9 (2)
Lipase	211 (56)	69 (18)	165 (46)	29 (8)
Alkaline phosphatase	171 (46)	7 (2)	132 (37)	6 (2)
Amylase	130 (35)	22 (6)	114 (32)	12 (3)
Total bilirubin	75 (20)	3 (1)	8 (2)	0 (0)
Indirect bilirubin	49 (13)	4 (1)	3 (1)	0 (0)
Renal/Metabolic				
Creatinine	262 (70)	2 (<1)	183 (51)	1 (<1)
Creatine kinase	183 (49)	9 (2)	40 (11)	4 (1)
Uric acid	173 (46)	54 (14)	119 (33)	29 (8)
Calcium decreased	156 (42)	4 (1)	145 (40)	4 (1)
Phosphorus	116 (31)	22 (6)	87 (24)	23 (6)
Albumin	106 (28)	4 (1)	72 (20)	0 (0)
Glucose increased	86 (23)	21 (6)	55 (15)	22 (6)
Sodium decreased	75 (20)	31 (8)	55 (15)	13 (4)
Glucose decreased	65 (17)	0 (0)	43 (12)	1 (<1)
Potassium increased	61 (16)	13 (3)	61 (17)	15 (4)
Calcium increased	50 (13)	2 (<1)	35 (10)	5 (1)
Potassium decreased	49 (13)	3 (1)	7 (2)	1 (<1)
Sodium increased	48 (13)	0 (0)	38 (10)	0 (0)
Hematology				
Neutrophils	289 (77)	65 (17)	178 (49)	31 (9)
Hemoglobin	298 (79)	29 (8)	250 (69)	18 (5)
Platelets	255 (68)	35 (9)	85 (24)	2 (1)
Lymphocytes	256 (68)	66 (18)	245 (68)	93 (26)
Leukocytes	293 (78)	29 (8)	202 (56)	8 (2)

*Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0
[a]Grade 4 laboratory abnormalities in patients on SUTENT included uric acid (14%), lipase (3%), neutrophils (2%), lymphocytes (2%), hemoglobin (2%), platelets (1%), amylase (1%), ALT (<1%), creatine kinase (<1%), creatinine (<1%), glucose increased (<1%), calcium decreased (<1%), phosphorous (<1%), potassium increased (<1%), and sodium decreased (<1%)
[b]Grade 4 laboratory abnormalities in patients on IFN-α included uric acid (8%), lymphocytes (2%), lipase (1%), neutrophils (1%), amylase (<1%), calcium increased (<1%), glucose decreased (<1%), potassium increased (<1%) and hemoglobin (<1%)

Venous Thromboembolic Events. Thirteen (3%) patients receiving SUTENT for treatment-naïve RCC had venous thromboembolic events reported. Seven (2%) of these patients had pulmonary embolism, one was Grade 2 and six were Grade 4, and six (2%) patients had DVT, including three Grade 3. One patient was permanently withdrawn from SUTENT due to pulmonary embolism; dose interruption occurred in two patients with pulmonary embolism and one with DVT. In treatment-naïve RCC patients receiving IFN-α, six (2%) venous thromboembolic events occurred; one patient (<1%) experienced a Grade 3 DVT and five patients (1%) had pulmonary embolism, all Grade 4.

Reversible Posterior Leukoencephalopathy Syndrome. There have been rare (<1%) reports of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). None of these subjects had a fatal outcome to the event. Patients with seizures and signs/symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness should be controlled with medical management including control of hypertension. Temporary suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Pancreatic and Hepatic Function. If symptoms of pancreatitis or hepatic failure are present, patients should have SUTENT discontinued. Pancreatitis was observed in 5 (1%) patients receiving SUTENT for treatment-naïve RCC compared to 1 (<1%) patient receiving IFN-α. Hepatotoxicity was observed in patients receiving SUTENT *[See Boxed Warning and Warnings and Precautions]*.

Post-marketing Experience. The following adverse reactions have been identified during post-approval use of SUTENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported. Cases of myopathy and/or rhabdomyolysis with or without acute renal failure, in some cases with fatal outcome, have been reported. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice. Thrombotic microangiopathy has been reported in patients on SUTENT. Suspension of SUTENT is recommended; following resolution, treatment may be resumed at the discretion of the treating physician. Cases of fatal hemorrhage associated with thrombocytopenia have been reported. Pulmonary embolism, in some cases with fatal outcome, has been reported. Cases of renal impairment and/or failure, in some cases with fatal outcome, have been reported. Cases of proteinuria and rare cases of nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. The safety of continued SUTENT treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue SUTENT in patients with nephrotic syndrome. Hypersensitivity reactions, including angioedema, have been reported. Cases of fistula formation, sometimes associated with tumor necrosis and/or regression, in some cases with fatal outcome, have been reported.

DRUG INTERACTIONS/CYP3A4 Inhibitors. Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib. A dose reduction for SUTENT should be considered when it must be co-administered with strong CYP3A4 inhibitors.

CYP3A4 Inducers. CYP3A4 inducers such as rifampin may **decrease** sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of SUTENT with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT in healthy volunteers. Co-administration of SUTENT with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving SUTENT should not take St. John's Wort concomitantly. A dose increase for SUTENT should be considered when it must be co-administered with CYP3A4 inducers.

In Vitro Studies of CYP Inhibition and Induction. *In vitro* studies indicated that sunitinib does not induce or inhibit major CYP enzymes. The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

USE IN SPECIFIC POPULATIONS

Pregnancy. Pregnancy Category D *[see Warnings and Precautions]*.

Nursing Mothers. Sunitinib and its metabolites are excreted in rat milk. In lactating female rats administered 15 mg/kg, sunitinib and its metabolites were extensively excreted in milk at concentrations up to 12-fold higher than in plasma. It is not known whether sunitinib or its primary active metabolite are excreted in human milk. Because drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother *[see Nonclinical Toxicology]*.

Pediatric Use. The safety and efficacy of SUTENT in pediatric patients have not been established.

Physeal dysplasia was observed in cynomolgus monkeys with open growth plates treated for ≥ 3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were > 0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥ 5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at >5 mg/kg. The incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment; however, findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no effect level in bones was ≤ 2 mg/kg/day.

Geriatric Use. Of 825 GIST and MRCC patients who received SUTENT on clinical studies, 277 (34%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

Hepatic Impairment. No dose adjustment is required when administering SUTENT to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUTENT were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. SUTENT was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN.

OVERDOSAGE

Treatment of overdose with SUTENT should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. A few cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of SUTENT, or without adverse reactions. A case of intentional overdose involving the ingestion of 1,500 mg of SUTENT in an attempted suicide was reported without adverse reaction. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m^2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although definitive carcinogenicity studies with sunitinib have not been completed, carcinoma and hyperplasia of the Brunner's gland of the duodenum have been observed at the highest dose tested in H2ras transgenic mice administered doses of 0, 10, 25, 75, or 200 mg/kg/day for 28 days. Sunitinib did not cause genetic damage when tested in *in vitro* assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an *in vivo* rat bone marrow micronucleus test.

Effects on the female reproductive system were identified in a 3-month repeat dose monkey study (2, 6, 12 mg/kg/day), where ovarian changes (decreased follicular development) were noted at 12 mg/kg/day (approximately 5.1 times the AUC in patients administered the RDD), while uterine changes (endometrial atrophy) were noted at ≥2 mg/kg/day (approximately 0.4 times the AUC in patients administered the RDD). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 6 mg/kg/day in the 9-month monkey study (0.3, 1.5 and 6 mg/kg/day administered daily for 28 days followed by a 14 day respite; the 6 mg/kg dose produced a mean AUC that was approximately 0.8 times the AUC in patients administered the RDD). A no effect level was not identified in the 3 month study; 1.5 mg/kg/day represents a no effect level in monkeys administered sunitinib for 9 months.

Although fertility was not affected in rats, SUTENT may impair fertility in humans. In female rats, no fertility effects were observed at doses of ≤5.0 mg/kg/day [(0.5, 1.5, 5.0 mg/kg/day) administered for 21 days up to gestational day 7; the 5.0 mg/kg dose produced an AUC that was approximately 5 times the AUC in patients administered the RDD], however significant embryolethality was observed at the 5.0 mg/kg dose. No reproductive effects were observed in male rats dosed (1, 3 or 10 mg/kg/day) for 58 days prior to mating with untreated females. Fertility, copulation, conception indices, and sperm evaluation (morphology, concentration, and motility) were unaffected by sunitinib at doses ≤10 mg/kg/day (the 10 mg/kg/day dose produced a mean AUC that was approximately 25.8 times the AUC in patients administered the RDD).

PATIENT COUNSELING INFORMATION

Gastrointestinal Disorders. Gastrointestinal disorders such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received SUTENT. Supportive care for gastrointestinal adverse events requiring treatment may include anti-emetic or anti-diarrheal medication.

Skin Effects. Skin discoloration possibly due to the drug color (yellow) occurred in approximately one third of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet.

Other Common Events. Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

Concomitant Medications. Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements *[see Drug Interactions]*.

Rx only

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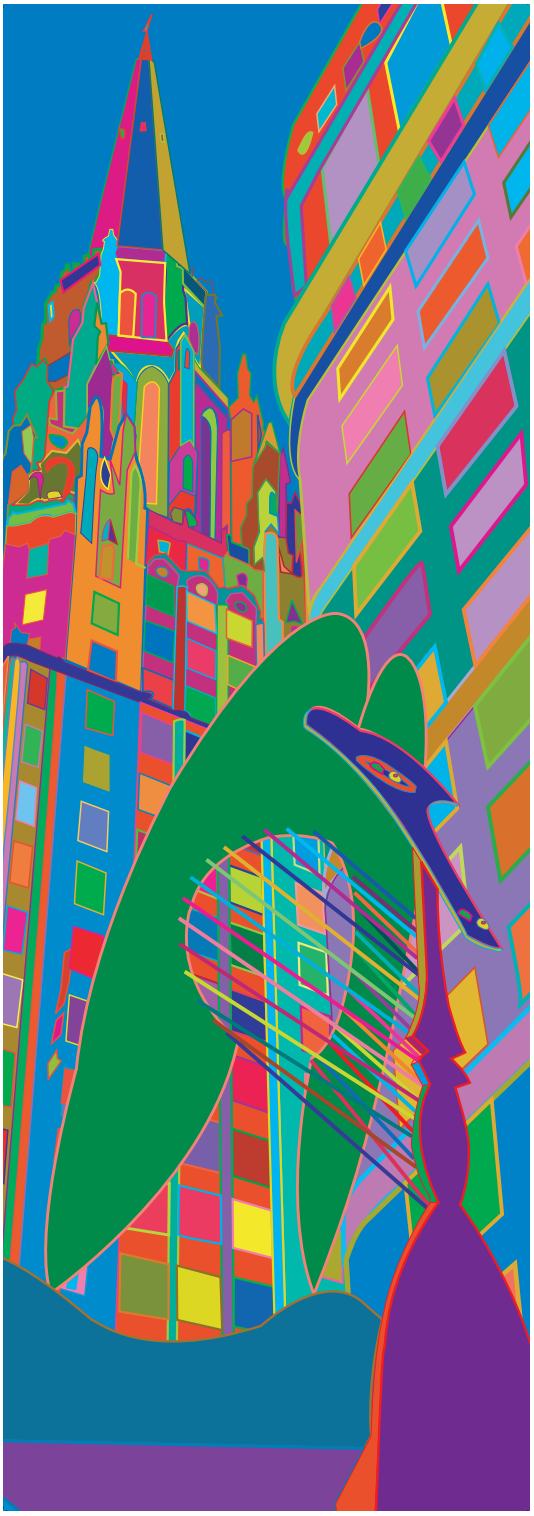

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About the Cover
Blood pressure gauge signifying hypertension and schematic illustrating cellular mechanisms underlying efficacy of anti-VEGF therapy. Evidence from recent trials suggests the extent to which hypertension is considered a biomarker for effectiveness of agents in this drug class and how it may be related to outcomes. © Saturn Stills / Photo Researchers, Inc. (Illustration courtesy of Brian I. Rini, MD).

KCJ TABLE OF CONTENTS

KCJ EDITOR'S MEMO

New ASCO Recommendations Stress Greater Focus on Palliative Care Issues, Need for Earlier Intervention


Robert A. Figlin, MD

There were disturbing results from a new, preliminary analysis of 5500 patient records from the Quality Oncology Practice Initiative (QOPI) of the American Society of Clinical Oncology (ASCO). The QOPI is an innovative quality improvement program that involves about 600 oncology practices nationwide. The ASCO report indicates that less than half (45%) of cancer patients are enrolled in hospice care before death. Of those enrolled, one-third were enrolled in the last week of life. The analysis also found that a significant number of patients did not receive appropriate management of their pain (1 in 5 patients) or shortness of breath (2 in 3 patients) in their last 2 medical visits.

The analysis spurred a new policy statement and patient guide that calls on physicians, medical schools, insurers, and others to improve quality of life for people with advanced cancer. As providers of care to kidney cancer patients, we know how important this issue is as we confront the limitations of treatment to prevent progression and metastasis of renal cell carcinoma; initiate effective measures to provide comfort to patients, their friends, and families when end-of-life issues emerge; and palliative options when they become necessary. The key elements identified by ASCO to individualize advanced cancer care are as follows:

- Physicians should initiate candid discussions about prognosis with their patients soon after an advanced cancer diagnosis. Such conversations currently occur with less than 40% of patients with advanced cancer.
- Quality of life should be an explicit priority throughout the course of advanced cancer care. Physicians must help their patients fully understand their prognosis, the potential risks and benefits of available cancer treatments, and quality of life considerations. In cases where active treatment is unlikely to extend survival, palliative care should be discussed as a concurrent or alternate therapy.
- Clinical trial opportunities should be increased. Currently, very few patients with advanced cancer participate in trials because of strict eligibility criteria, a dearth of trials that address quality of life issues, and other barriers. Increasing opportunities for these patients to potentially benefit from trials and to contribute to improving cancer care should be a high priority.

One of the outstanding resources available to providers are the programs offered by the Kidney Cancer Association (KCA), through its support groups, referrals, and published material. For example, the KCA offers the book, *Reflections: A Guide to End of Life Issues*, written by Roger C. Bone, MD, a physician and kidney cancer patient. The book (in PDF format) may be downloaded by clicking its title on the KCA website at http://www.kidneycancer.org/knowledge/live/emotional-well-being.

(continued on page 123)

Kidney Cancer Journal Author Guidelines

Scope of Manuscripts

The *Kidney Cancer Journal* considers the following types of manuscripts for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics in a scholarly fashion and format.
- Original contributions based on original, basic, clinical, translational, epidemiological, or prevention studies relating to kidney cancer that are well documented, novel, and significant.
- Letters to the Editor on timely and relevant subjects pertaining to the diagnosis and treatment of renal cell carcinoma.
- Clinical case studies.

Manuscript Submission

Authors are required to submit their manuscripts in an electronic format, preferably by email to the Editor-in-Chief, Robert A. Figlin, MD, at rfiglin@coh.org. Please provide in a word processing program. Images should be submitted electronically as well.

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Manuscripts will be peer reviewed. Accepted manuscripts will be edited for clarity, spelling, punctuation, grammar, and consistency with American Medical Association (AMA) style. Authors whose manuscripts are not initially accepted may have the opportunity to revise the manuscript based on recommendations from peer reviewers and at the discretion of the Editor-in-Chief.

Conflict of Interest

Kidney Cancer Journal policy requires that authors reveal to the Editor-in-Chief any relationships that they believe could be construed as resulting in an actual, potential, or apparent conflict of interest with regard to the manuscript submitted for review. Authors must disclose this information in the covering letter accompanying their submission.

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Length: Full-length manuscripts should not exceed 4000 words, including references. Please limit the reference list to 50 citations. Manuscripts should be accompanied by figures and/or tables. Generally 4-5 figures and 2-3 tables are preferred for each manuscript. Please include a brief description to accompany these items, as well as a legend for all abbreviations. Manuscripts should not contain an abstract but an introduction is recommended.

Spacing: One space after periods. Manuscripts should be double spaced.

References

All submissions should have references that are referred to in the text by superscripted numbers and that conform to AMA style.
Example:
Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. *Chest*. 2001;119:818-823.

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Tracking Trends From Web-based Sources, Translational Research, the FDA, and Patient Registries

Combination of Gene Therapy and Chemotherapy Stops Kidney Cancer in Mouse Model

RICHMOND, VA—A novel therapeutic approach that combines a modified viral vector and a small molecular weight drug produced promising results in a mouse model of human kidney cancer. Researchers at the Virginia Commonwealth University created a unique adenovirus vector by combining the tail and shaft domains of a serotype 5 virus and the knob domain of a serotype 3 virus. This Ad.5/3 adenovirus was then loaded with the gene needed to express the cancer-killing protein MDA-7/IL-24.

The viral vector was administered to mice bearing human renal carcinoma cells, alone or together with the drug sorafenib, a small molecular-weight inhibitor of several tyrosine protein kinases. Sorafenib is unique in targeting the Raf/Mek/Erk pathway (MAP Kinase pathway). Results published in *Cancer Biology and Therapy* revealed that infection with the Ad.5/3-mda-7 vector caused kidney cancer cells and normal cells lining the kidneys to secrete MDA-7/IL-24. MDA-7/IL-24 quickly stopped the growth of the primary tumor. As the infected cells continued to secrete MDA-7/IL-24, it entered the blood stream and eventually stopped the growth of a second, distinct tumor not directly infected by the adenovirus. Only renal carcinoma cells were destroyed by this "toxic bystander effect," normal cells were unaffected. Sorafenib enhanced MDA-7/IL-24 toxicity and significantly increased its antitumor effects in the mouse model.

"While further research is needed, this therapy could be a novel and effective way to treat metastatic kidney cancer and prolong patient survival," said senior researcher Dr Paul Dent, professor of biochemistry at Virginia Commonwealth University. "This is the first study to clearly define that gene therapeutic delivery of MDA-7/IL-24 in kidney cancer should be explored in the clinic, especially since we have demonstrated an established, FDA-approved drug enhances its toxicity to cancer cells."

From *Biotech Daily International*.

NCCN Receives $2.1-Million Grant to Evaluate Axitinib

FORT WASHINGTON, PA—The National Comprehensive Cancer Network® (NCCN) has been awarded a $2.1 million grant from Pfizer to evaluate and define the clinical activity of axitinib in various tumor types. Axitinib is currently under study for its potential benefit in renal cell carcinoma.

"The funding not only helps accelerate potentially life-saving research in the field of cancer, but also creates a collaborative opportunity for investigators from NCCN member institutions," said William T. McGivney, PhD, Chief Executive Officer, NCCN. "NCCN is committed to enhancing cancer care by evaluating new investigational agents such as axitinib to determine their full potential in treating several types of cancer." The first phase of the program involves the establishment of an NCCN Axitinib Request for Proposals Development Team to evaluate existing data and to discuss and define the types of studies necessary to further evaluate the activity of axitinib in solid tumors.

Axitinib is an oral and selective inhibitor of vascular endothelial growth factor receptors (VEGF) I, II, and III, which may play roles in tumor growth, vascular angiogenesis, and metastasis. Axitinib has been tested in various phase 1, 2, and 3 trials, including thyroid cancer, non–small cell lung cancer, and advanced renal cell carcinoma. An additional phase 2 trial in hepatocellular carcinoma is under way. Pfizer recently announced that the global randomized phase 3 AXIS 1032 trial (A4061032), studying axitinib in previously treated patients with metastatic renal cell carcinoma, met its primary end point of progression-free survival. Axitinib is an investigational compound.

Aggressive Stereotactic Body Radiation Therapy May Control Metastatic Renal Cell Carcinoma

SAN DIEGO—Aggressive stereotactic body radiation therapy (SBRT) is effective in controlling metastatic renal cell carcinoma (RCC) according to findings presented at the 52nd Annual Meeting of the American Society for Radiation Oncology. In a study, researchers showed that the overall local control rate achieved with SBRT in patients with metastatic RCC was 95% at 1 year.

"At the higher doses of radiation that are delivered during SBRT we found that our local control with this type of therapy is just as good as it is for colorectal cancer or breast cancer," said Michelle Stinauer, MD, a radiation oncology resident at the University of Colorado in Denver. "I think it would be especially beneficial for renal cell [carcinoma] patients with a lower level of disease burden, such as 1 or 2 metastases. These patients can benefit from more aggressive local control. There are studies showing that in patients with metastatic disease that if you remove the primary cancer then they have better outcomes. Similarly, lowering disease burden with SBRT may help patients live longer."

RCC and melanoma traditionally have been viewed as "radio-resistant" but study findings indicate that SBRT—which involves radiation dose intensification through escalation of fraction size—can overcome this resistance. Dr Stinauer and colleagues retrospectively reviewed all patients with recurrent RCC and melanoma who had metastatic sites treated with SBRT. The patients received a minimum radiation dose of 40 Gy over 3 to 5 treatments. The researchers defined local control as radiographic or pathological evidence of a lack of tumor enlargement and/or increased standardized uptake value (SUV) on

(continued on page 123)

Essential Peer-Reviewed Reading in Kidney Cancer

The peer-reviewed articles in this section were selected by the Guest Editor, Ronald M. Bukowski, MD, for their timeliness, importance, and relevance to clinical practice or translational research.

The Role of Biomarkers

Breaking through a plateau in renal cell carcinoma therapeutics: development and incorporation of biomarkers. Pal SK, Kortylewski M, Yu H, Figlin RA. *Mol Cancer Ther*. 2010;9:3115-3125.

In this article, Pal and colleagues report on the clinical relevance of putative RCC biomarkers. Since December of 2005, the FDA has approved 6 novel targeted therapies for the treatment of metastatic renal cell carcinoma (RCC). However, because these approvals were based on studies with limited comparative trials to detect relative efficacy, the treatment of metastatic RCC remains complex.

New strategies to identify appropriate candidates for selected targeted therapy have become a focus of the research community. A potential strategy for identifying patients is the use of clinical and molecular biomarkers. A growing body of knowledge-related von Hippel Lindau-driven pathways in RCC highlights the potential of hypoxia-inducible factor subtypes to identify suitable patients. Strategies used for treating other malignancies, such as gene expression and proteomic profiling, may also ultimately provide ways for clinical stratification of patients.

An emerging understanding of immunological phenomena that may affect cancer progression (ie, tumor infiltration by CD68 lymphocytes, memory T-cells, etc) has unveiled a number of other potential biomarkers of response. Several vascular endothelial growth factor receptor-directed therapies classically thought to function as antiangiogenics may also have complex effects upon the tumor microenvironment, including associated immune cells. As such, immunological parameters may predict response to current therapies. Finally, clinical biomarkers, such as hypertension, may predict the efficacy of several currently available targeted agents, although implementation of such biomarkers remains challenging.

The Link Between Drinking Water and Risk of Death

Calcium and magnesium in drinking water and risk of death from kidney cancer. Chiu HF, Chang CC, Chen CC, Yang CY. *J Toxicol Environ Health A*. 2011;74:62-70.

A possible link between kidney cancer risk and the levels of calcium and magnesium in drinking water from municipal supplies was investigated by Chui and colleagues in a matched cancer case-control study in Taiwan. The investigators looked at kidney cancer deaths (1778 cases) that occurred from 1999 through 2008 and compared them with deaths from other causes (1778 controls); the levels of calcium and magnesium in drinking water of these residents were determined.

Data on calcium and magnesium levels in drinking water throughout Taiwan were obtained from the Taiwan Water Supply Corporation (TWSC). The control group was pair-matched to the cancer group by gender, year of birth, and year of death. The adjusted odds ratios for death attributed to kidney cancer for individuals with higher calcium levels in their drinking water, compared with the lowest tertile, were 0.89 (95% CI = 0.72-1.11) and 0.78 (95% CI = 0.62-0.98), respectively. The adjusted odds ratios were not statistically significant for the relationship between magnesium levels in drinking water and kidney cancer development. Based on their findings, the investigators concluded that there may be a significant protective effect of calcium intake from drinking water against the risk of death due to kidney cancer.

The Diagnostic and Therapeutic Implications of Sentinel Lymph Nodes

Intraoperative sentinel node identification and sampling in clinically node-negative renal cell carcinoma: initial experience in 20 patients. Bex A, Vermeeren L, Meinhardt W, Prevoo W, Horenblas S, Valdés Olmos RA. *World J Urol*. 2010 Nov 25; [Epub ahead of print].

Bex and colleagues undertook a study using single-photon emission computed tomography (SPECT) in combination with computed tomography (CT). Their goal was to identify the role of sentinel lymph nodes prior to surgery and to gauge the surgical feasibility and safety of intraoperative sampling.

The researchers examined the data from a retrospective combined interim analysis of 20 patients from 2 prospective trials who had received 99mTc-nanocolloid injection into the renal tumor for preoperative identification of sentinel lymph nodes with SPECT/CT and subsequent removal of the tumor and intraoperative sampling using a gamma probe and portable camera. Lymphadenectomy was completed locoregionally. Surgical approach, time, blood loss, intraoperative yield, Clavien complications and anatomical location of sentinel lymph nodes in correlation with preoperative imaging were evaluated.

SPECT/CT detected sentinel lymph nodes in 70% (14/20) of patients, including 4 patients with nonvisualization on planar lymphoscintigraphy. Twenty-six sentinel lymph nodes were seen: 17 para-aortic (including interaorto-caval), 4 retrocaval, 1 hilar, 1 celiac trunc, 1 internal mammary, and 2 mediastinal and pleural. The 4 latter nodes were not harvested according to protocol. All other sentinel lymph nodes, except for 2 weakly radioactive interaorto-caval nodes, were identified and excised with a mean additional time of 20 minutes. None of the removed sentinel lymph nodes and locoregional nodes was tumor-bearing.

Intraoperative sentinel lymph node identification and sampling of patients with renal cell carcinoma with preoperative detection on SPECT/CT was found to be surgically safe and feasible. Sentinel lymph nodes from the kidney are mainly localized in the para-aortic region, but aberrant nodes receive direct drainage. Nonvisualization of sentinel lymph nodes appears in almost a third of the patients. Further studies are required to demonstrate whether accurate mapping of lymphatic drainage and extent of lymphatic spread have diagnostic and therapeutic implications. KCJ

Hypertension as a Biomarker for Anti-VEGF Efficacy: Incidence, Mechanisms, and Association With Clinical Outcome

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Agents that target the vascular endothelial growth factor (VEGF) signaling pathway represent one of the cornerstones of therapy for metastatic renal cell carcinoma (mRCC). Hypertension represents an on-target toxicity, reflecting VEGF pathway inhibition. Emerging data links this treatment-related toxicity to therapeutic outcome. Relevant data, hypotheses of mechanism, and insight into future investigation are presented here.

Beginning with the first approval in 2004 of an antiangiogenic agent for clinical use in cancer and continuing to ongoing trials of additional drugs nearing or close to approval, researchers have reported an association with hypertension as an adverse effect of drugs that target the vascular signaling pathway (VSP). Since that initial approval of bevacizumab for metastatic colorectal cancer, numerous reports of patients with mRCC and other solid tumors, have further documented the development of hypertension in a significant fraction of patients who receive antiangiogenic therapies.

Four agents that target the VEGF signaling pathway (VSP) inhibitors to treat mRCC are commercially available in the United States. These include bevacizumab (Avastin®, Genentech), sorafenib (Nexavar®, Bayer), sunitinib (Sutent®, Pfizer), and pazopanib (Votrient®, Glaxo SmithKline). Two more antiangiogenic agents, axitinib and tivozanib, currently undergoing study, have also shown promise in the treatment of mRCC. With a growing body of literature on the use of these agents, it has become clear that nearly all patients who undergo treatment experience a rise in blood pressure even if they are not diagnosed with hypertension.[1]

Bevacizumab, approved in 2004, was the first antiangiogenic agent approved for clinical use in combination with fluorouracil-based chemotherapy for the treatment of metastatic colorectal cancer. It is a humanized monoclonal antibody targeted against the VEGF ligand, and it exerts its effects primarily through prevention of VEGF binding to the VEGF receptor (VEGFR), which in turn inhibits downstream signaling, preventing angiogenesis. Sorafenib, sunitinib, and pazopanib are all small molecule multityrosine kinase inhibitors that inhibit all of the VEGFRs (1, 2, and 3) in addition to other targets (eg, *CRAF, BRAF, KIT, FLT-3, RET, PDGFRs*). Each of these multitargeted agents differs slightly in the other proteins they target and also in the potency with which they inhibit VEGF and other receptors. However, the biological effects of inhibiting angiogenesis are paramount to inferring clinical activity with this class of agents.

Incidence of Hypertension Associated With Anti-VEGF Therapies

A meta-analysis by Zhu and colleagues[2] found the incidence of hypertension ranged between 2.7% and 32% in patients who received low-dose bevacizumab. For patients undergoing high-dose therapy with bevacizumab, the incidence was reported to be between 17.6% and 36%. The incidence of all-grade hypertension associated with bevacizumab was reported to be a median of 25% (range 21% to 30%) (**Table 1**).

Wu and colleague[3] reviewed data from 9 studies published between January 2006, and July 2007, which included a total of 4599 patients with RCC or other solid tumors. For patients assigned sorafenib, the overall incidence of all-grade and high-grade (ie, grade 3 or 4) hypertension was 23.4% (95% CI: 16.0%-32.9%) and 5.7% (2.5%-12.6%), respectively. No significant difference was noted between patients with RCC or a non-RCC malignancy (all grade: relative risk [RR] 1.03, 95%

Keywords: metastatic renal cell carcinoma, vascular endothelial growth factor (VEGF), vascular signaling pathway (VSP), hypertension

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Table 1. HTN Incidence With VEGF-Targeted Therapy

Drug	Disease	N	Incidence of HTN		Comments
			All grade	*≥ CTC Grade 3*	
Sorafenib[1]	Multiple solid tumors	3000+	23% (range, 16-32%)	5.7% (2.5-12.6%)	No difference between RCC and non-RCC for HTN incidence
Sunitinib[2]	Multiple solid tumors	4600	22% (19-25%)	6.8% (5.3-8.8%)	Higher HTN incidence for RCC (vs.. non-RCC) and continuous (vs. intermittent) dosing
Axitinib[3]	Multiple solid tumors	230	55%	17%	
Bevacizumab[4]	Multiple solid tumors	1,850	25% (21-30%)	9-16%	

[1]Wu S. et al. *Lancet Onc*. 2008; 9:117-23; [2]Zhu et al. *Acta Onc* 2009; 48:9-17; [3]Rini et al. *JCO* (submitted) [4]Zhu et al. *Am J Kidney Dis*. 2007 49:186-93.

CI: 0.73-1.45], P = .89; high-grade: RR 1.23, CI: 0.76-1.99, P = .40) who were assigned sorafenib. Sorafenib was associated with a significantly increased risk of all-grade hypertension in patients with cancer with an RR of 6.11, (CI: 2.44-15.32, P < .001) compared with controls.

A total of 4999 patients with RCC and other malignancies from 13 clinical trials were included in an analysis by Zhu and colleagues[4] to determine the incidence of hypertension associated with sunitinib treatment. Among patients who received sunitinib, the incidence of all-grade and high-grade hypertension was 21.6% (95% CI: 18.7%-24.8%) and 6.8% (95% CI: 5.3%-8.8%), respectively. The risk may vary with tumor type and the dosing schedule of sunitinib. Sunitinib was associated with a significantly increased risk of high-grade hypertension (RR = 22.72; 95% CI: 4.48 to 115.29; P < .001) and renal dysfunction (RR: 1.36; 95% CI: 1.20 to 1.54; P < .001) compared with controls in this analysis.

The dosing schedule of sunitinib may also be related to risk of hypertension. Zhu and colleagues[4] found a significantly increased risk of developing hypertension when being treated with the continuous daily dosing in comparison with the intermittent dosing schedule (RR 1.32; 95% CI: 1.18–1.48; P < .001). It is unclear why this difference occurred, although intermittent dosing has higher drug concentrations in tissues but shorter duration, and that may have less profound impact on the systematic vasculature than continuous dosing. When dosed continuously, sunitinib has somewhat lower concentrations but prolonged exposure. It is possible that the 2 off-weeks may allow better vascular endothelial recovery from the damage of sunitinib than continuous daily dosing.

Two phase 2 studies evaluated the effects of axitinib and determined the incidence of hypertension in axitinib-treated patients. Rixe and colleagues[5] assessed the activity and safety of axitinib in patients with mRCC who had failed previous cytokine-based treatment. Treatment-related hypertension occurred in 30 patients and resolved with antihypertensive treatment in all but 8 patients, of whom 7 had a history of hypertension at baseline. In a multicenter, open-label, phase 2 study, 62 patients with sorafenib-refractory mRCC received a starting dose of axitinib 5 mg orally twice daily. In this analysis, grade 3 to 4 hypertension occurred in 16.1% of patients.[6]

Although it is clear that a rise in hypertension with VEGF inhibition occurs across this class of agents, there are distinctions among the respective agents, including differences across tumor type. For example, Zhu and colleagues[4] reported that the risk of hypertension may vary substantially with tumor type. The absolute risk of developing hypertension was significantly higher in patients with RCC who were treated with sunitinib compared with patients who had non-RCC cancers (25.9% vs 20.4%; RR 1.27; 95% CI: 1.13%-1.43%; P < .001). However, this could be secondary to higher baseline blood pressure in patients with RCC than non-RCC. The researchers speculated that patients with RCC may have higher VEGF levels than non-RCC patients, and the resulting overall anti-VEGF effect of sunitinib may be more evident. Alternatively, the patients with RCC may have had reduced renal function due to prior nephrectomy and thus may have had reduced excretion levels of sunitinib that led to increased sunitinib exposure, which may have contributed to the development of hypertension. Indeed, a majority of patients with RCC in these trials had nephrectomy before receiving sunitinib. However, in a separate report, no significant difference was noted between patients with RCC or a non-RCC malignancy: all grade: RR 1.03; 95% CI: 0.73%-1.45; P = .89; high-grade: RR 1.23; CI: 0.76-1.99, P = 0.40 treated with sorafenib.[3]

Mechanisms of Hypertension

Knowledge about the mechanisms underlying the development of hypertension remains incomplete but possible factors have been suggested (**Table 2**). An early report by Maitland and colleagues[7] documented significant blood pressure elevation on the first day of sorafenib therapy. In exploring the phenomenon of elevated blood

Table 2. HTN as a Biomarker in VEGF-Targeted Therapy

Study	Disease (N)	Anti-VEGF Agent	HTN Definition	Results
Rini et al.[1]	Multiple solid tumors (n=230)	Axitinib	dBP ≥ 90 mmHg	OS: 30.1 vs.. 10.2 months (p<0.001) PFS: 13.1 vs. 5.8 months (p=0.1) ORR: 44% vs. 12% (p<0.001)
Rini et al.[2]	RCC (n-544)	Sunitinib	dBP ≥ 90 mmHg	OS: 32.1 vs.. 15.0 months (p<0.0001) PFS: 13.4 vs. 5.3 months (p<0.0001) ORR: 57% vs. 25% (p<0.0001)
Rini et al.[3]	RCC (n=366)	Bevacizumab (+IFN)	≥ CTC Grade 2	OS: 41.6 vs.. 16.2 months (p<0.0001) PFS: 13.2 vs. 8.0 months (p=0.0009) ORR: 13% vs. 9% (p=ns)
Escudier et al.[4]	RCC (n=337)	Bevacizumab (+IFN)	≥ CTC Grade 2	PFS: 10.2 vs. 8.4 months (p=ns)
Schneider et al.[5]	Breast Ca (n=345)	Bevacizumab (+chemo)	≥ CTC Grade 3	OS: 38.7 vs.. 25.3 months (p=0.002)
Dahlberg et al.[6]	NSC Lung Ca (n=741)	Bevacizumab (+chemo)	> 150/90 mmHg, OR > 20 mmHg increase vs. baseline by end of C#1	OS: 15.9 vs.. 11.5 months (p=0.0002) PFS: 7.0 vs. 5.5 months (p<0.0001)
Goodwin et al.[7]	NSC Lung Ca (n=148)	Cediranib (+chemo)	New onset HTN, OR Worsening HTN grade in patient with PMH of HTN	PFS: 8.5 vs. 5.1 months (p=0.0007) ORR: 52% vs. 33% (p=0.025)

[1]*Clin Ca Res* (submitted); [2]ASCO GU 2010 / JNCI (submitted); [3]JCO 2010; [4]ASCO 2008; [5]JCO 26:4672-4678 2008 [6]JCO (in press); [7]ASCO 2009

pressure soon after sorafenib is administered, the researchers suggest that VSP inhibitors may influence blood pressure through acute inhibition of endothelial-derived vasodilatory factors such as nitric oxide. Support for this concept comes from the observation that most of the rise in blood pressure among treated patients was noted during the first week of therapy; blood pressure normalized quickly when sorafenib was withheld.

In related reports, there is both preclinical and clinical evidence that endothelial cell apoptosis, which leads to a reduction in capillary density and increased afterload may be responsible for a rise in blood pressure.[8] Moreover, findings indicate that autocrine VEGF provides a survival signal to endothelial cells; in murine renal cancer xenograft models, endothelial cell loss within tumors has been observed as early as the third day of VSP inhibitor therapy. Other vasoactive proteins that include prostaglandin, thromboxane, and ET-1 deserve further study for their potential role in underlying hypertension.

If the mechanism can be further elucidated, then exploitation of this potential efficacy biomarker as well as hypertension management can be optimized. If further study supports the hypothesis that nitric oxide inhibition plays an important role in the development of hypertension, then restoration of nitric oxide signaling, achieved through the use of nitrates or phosphodiesterase inhibitors as antihypertensive therapies could help to restore vasodilatory balance in patients with hypertension. The downside to this strategy, however, is that nitric oxide is critical for angiogenesis. The question arises whether such an antihypertensive approach could reduce antitumor efficacy by promoting angiogenesis. As an alternative, perhaps angiotensin converting enzyme (ACE) inhibitors or calcium channel blockers could be effective but not inhibit the antitumor effects of VSP inhibitors.

Other reports provide perspectives on the mechanism of hypertension. Kappers and colleagues[9] investigated the effects of sunitinib on blood pressure (BP), its circadian rhythm, and potential mechanisms involved, including the endothelin-1 system, in 15 patients with mRCC or gastrointestinal stromal tumors. Coronary microvascular function studies after 8 days of sunitinib administration showed decreased responses to bradykinin, angiotensin II, and sodium nitroprusside, which returned to normal after sunitinib was discontinued. Cardiac structure and cardiac mitochondrial function did not change. The researchers concluded that sunitinib induces a reversible rise in BP in patients and in rats, which is associated with activation of the endothelin-1 system, suppression of the renin-angiotensin system, and generalized microvascular dysfunction.

Veronese and colleagues[10] evaluated the effects of sorafenib on VEGF, catecholamines, endothelin I, urotensin II, renin, and aldosterone. They measured these levels at baseline and after 3 weeks of therapy. They also assessed vascular stiffness at baseline, after 3 to 6 weeks of therapy, and again after 9 to 10 months of therapy. They reported that 15 (75%) of 20 patients experienced an increase of ≥ 10 mmHg in systolic BP (SBP), and 12 (60%) of 20 patients experienced an increase of ≥ 20 mmHg in SBP compared with their baseline, with a mean change of 20.6 mmHg ($P < .0001$) after 3 weeks of therapy. No statistically significant changes in humoral factors were demonstrated, although there was a statistically significant inverse relationship between decreases in catecholamines and increases in SBP, which suggests a secondary response to BP elevation. Measures of vascular stiffness increased significantly during the period of observation. The lack of significant change in circulating factors suggested that these humoral factors had little effect on the rise in BP.

Evaluating Hypertension as a Biomarker for Anti-VEGF Efficacy

Sunitinib

Data from pooled phase 2 and 3 studies of sunitinib of 455 patients who had well-controlled BP at baseline showed that 81% of the patients developed SBP >140 mmHg and 67% developed diastolic BP (DBP) >90 mmHg while receiving treatment.[12] Treatment-induced hypertension was associated with improvement in clinical outcome across a variety of measures (all $P < .001$):

- Objective response of 54.8% versus 8.7% for SBP; 57.3% versus 24.6% for DBP
- Progression-free survival of 12.5 versus 2.5 months for SBP (adjusted hazard ratio [HR] 0.241); 13.4 versus 5.3 months for DBP (adjusted HR 0.553)
- Overall survival of 30.9 versus 7.2 months for SBP (adjusted HR 0.284); 32.2 versus 14.9 months for DBP (adjusted HR 0.516)

Administration of antihypertensive therapy did not affect clinical outcome. This analysis also looked at the incidence of hypertension-associated complications including prespecified cardiovascular, cerebrovascular, ocular, and renal adverse effects. The overall incidence of cardiovascular, cerebrovascular, and ocular adverse effect was low, and it was similar between patients in both groups. However, patients with hypotension had somewhat more renal adverse effects than patients without hypertension (any-grade severity: 5% vs 3%, $P = .013$; severity at grade 3 or higher: 3% vs 2%, $P = .045$).

Other reports have also focused on the correlation between sunitinib therapy and a predisposition to hypertension. Findings presented at the 2009 ASCO Annual Scientific Sessions retrospectively addressed the association between VEGF single nucleotide polymorphisms (SNPs) and the development of hypertension in mRCC patients who received sunitinib.

Kim and colleagues[12] considered this issue after previously published evidence that VEGF SNPs (–623 C/11C and –1498 T/T) were associated with protection from grade 3/4 hypertension in breast cancer patients who received bevacizumab plus paclitaxel. The aim of this study was to retrospectively evaluate the association between VEGF SNPs and the development of hypertension in mRCC patients who received sunitinib. Metastatic RCC patients who received sunitinib (50 mg 4/2) with available BP data and germline DNA were retrospectively identified. All BP measurements were recorded approximately every 4 weeks in clinic. Genomic DNA was isolated from peripheral blood lymphocytes.

Sixty-four patients were identified of which 63 had available SNP data. Median baseline SBP and DBP were 139 mmHg (range, 93-190) and 80 mmHg (range, 47-103), respectively; 57% of patients were being treated with antihypertensive therapies at baseline. VEGF-634 C/C < C/G < G/G genotypes were associated with increasing frequency and duration of hypertension (DBP >90 mmHg and/or SBP >150 mmHg) during treatment with sunitinib ($P = .03$ and $P = .007$, respectively). Hypertension remained significant after adjusting for baseline BP and use of antihypertension medication ($P = .05$ and $P = .02$, respectively). Similar correlations were not found for VEGF-1498 genotypes. Additional prospective analyses of these and other relevant genotypes is needed to validate and extend the hypotheses generated by these data in order to impact patient management.

Axitinib

Although axitinib is still in clinical development, findings about its efficacy in mRCC and other tumor types have revealed important information about the relationship between hypertension and outcome as investigators move on to study related questions and implications about its use, including dose titration. Axitinib is a potent oral selective inhibitor of VEGF receptors 1,2, and 3.

Data from a retrospective analysis across multiple tumor types show that elevated BP could be considered a potential efficacy marker and appears to be associated with longer overall survival.[13] The analysis evaluated the relationship between DBP ≥90 mmHg and overall survival (OS) across 6 separate phase 2 axitinib studies: patients with non–small cell lung cancer, cytokine-refractory RCC, sorafenib-refractory RCC, thyroid cancer or melanoma, and advanced pancreatic cancer. Patients received 5 mg BID single-agent axitinib; advanced pancreatic cancer patients received gemcit-abine 1000 mg/m^2 on days 1, 8, and 15 in 28-day cycles plus 5 mg BID axitinib. All 6 studies required BP ≤140/90 mmHg at baseline.[13] Median OS of patients with no DBP levels ≥90 mmHg during treatment was lower than in those with at least 1 DBP level ≥90 mmHg. In this retrospective analysis across multiple tumor types, the occurrence of DBP ≥90 mmHg appeared to be associated with longer OS.

Data from a pooled analysis of 2 phase 2 mRCC stud-

ies on the relationship between pharmacokinetics (PK), DBP, and clinical efficacy of axitinib confirmed these findings.[14] PK data were compiled from studies in cytokine-refractory mRCC patients (n = 109) and healthy volunteers (n = 240); the efficacy analysis included mRCC patients only. Mean steady-state area under the plasma concentration-time curve (AUC) at the end of cycle 1 and the DBP during axitinib therapy were used as predictors of clinical efficacy in the mRCC patients.

The median OS for mRCC patients with at least 1 DBP level of ≥90 mmHg (n = 59) during axitinib therapy was 130 weeks compared with 42 weeks ($P < .01$) for patients with no DBP level of ≥90 mmHg (n = 50). The median OS of patients with an AUC below the median (605 ng.hr/ml; n = 54) was 69 weeks compared with 88 weeks ($P > .05$) for patients with an AUC above the median (n = 55).

Among patients with DBP ≥90 mmHg, median OS was 120 weeks and 131 weeks ($P > 0.05$) for patients with AUC below and above the median (n = 23 and 36, respectively). Among patients with no DBP level of ≥90 mmHg, median OS was 42 weeks and 43 weeks ($P > .05$) for patients with AUC below and above the median (n = 31 and 19, respectively). An 82% increase in probability of a partial response was predicted for a 10 mmHg higher DBP during therapy. The study found no apparent correlation between the AUC and maximum DBP during axitinib therapy. The authors concluded that axitinib therapy is a strong predictor of clinical efficacy in patients with mRCC, and is not merely a reflection of higher axitinib drug levels. The next phase of investigation will involve an ongoing randomized phase 2 trial in patients with previously untreated mRCC that incorporates a dose-titration scheme based on patient tolerance and BP.

Bevacizumab

Two phase 3 studies show the role of hypertension as a biomarker for the efficacy of bevacizumab. Final results from the CALGB 90206 study that included 732 patients show that the median OS was 18.3 months (95% CI: 16.5 to 22.5 months) for bevacizumab plus IFN-α and 17.4 months (95% CI: 14.4 to 20.0 months) for IFN-α monotherapy (unstratified log-rank $P = .097$).[15] There was significantly more grade 3 to 4 hypertension for bevacizumab plus IFN-α. Patients who developed hypertension on bevacizumab plus IFN-α had a significantly improved progression free survival (PFS) and OS combined with patients who did not have hypertension.

Escudier and colleagues[16] reported an association between hypertension and outcomes. Data from 337 patients with mRCC showed that patients who had common terminology criteria (CTC) grade 2 or higher hypertension had a PFS of 10.2 months compared with 8.4 months for patients with CTC grade 2 or lower hypertension, although this difference was not statistically significant.

Tivozanib (AV-951)

Another investigational agent is tivozanib, a potent and selective inhibitor of VEGFR-1, 2, and 3 kinases. It has demonstrated activity in RCC with a reported median PFS of 11.8 months in an initial trial.[17] A retrospective analysis performed to explore the effect of hypertension, nephrectomy, and prior therapy on the efficacy of tivozanib has been reported.[18] The phase 2, randomized, discontinuation trial enrolled 272 patients with locally advanced RCC or mRCC (any histology) and no prior VEGF-targeted therapy. They received 1.5 mg/d tivozanib (1 cycle: 3 weeks on, 1 week off); 83% of patients had RCC with a clear cell component, 53% were treatment naive, and 72% had undergone nephrectomy. BP was measured in the clinic on day 1 and day 15 for the first 4 cycles, and on day 1 of subsequent cycles.

Hypertension was defined as SBP > 140 mmHg and/or DBP > 90 mmHg, and standard antihypertensive medications were used to manage hypertension. The development of hypertension at any time during therapy was associated with improved PFS and overall response rate (ORR). The ORR for patients with SBP >140 mmHg was 30% compared with 24.3% for patients with SBP ≤140 mmHg. The ORR for patients with DBP > 90 mmHg was 33% compared with 23.5% for those with DBP ≤ 140 mmHg. In this retrospective exploratory analysis, hypertension appeared to be associated with improved clinical outcomes.

Sorafenib

Unlike the other VEGF inhibitors, treatment with sorafenib has so far not been found to reflect improved efficacy in the setting of hypertension. Humphreys and Atkins[1] reported that it is uncertain whether similar associations between hypertension and clinical benefit will occur with sorafenib and other less potent VSP inhibitors or in cancers other than renal cell or breast.

Management of Hypertension Based on Expert Panel's Guidelines

As with the other antiangiogenic agents, significant adverse effects are associated with bevacizumab, the most clinically mature of these drugs.[19] A humanized antibody against VEGF, bevacizumab is associated with significant adverse effects, including thrombosis, wound-healing complications, bleeding, gastrointestinal perforation, and renal toxicity.[2] Proteinuria and hypertension are the primary renal toxicities.

In a meta-analysis of published clinical trials, Zhu and colleagues[2] assessed the risk of these renal toxicities in more than 1800 patients who received treatment for metastatic cancers of lung, breast, colon, and kidney. In most trials, bevacizumab was discontinued temporarily if urine protein excretion was ≥2 g/24 hours and resumed when protein excretion was <2 g/24 hours. Treatment with the agent was discontinued if nephrotic-range proteinuria developed. This occurred in 1% to 2%

of patients with non–renal cell cancer and 7.7% of patients with renal cancer.

The risk of these adverse effects means that bevacizumab treatment should be suspended temporarily in patients who show signs of moderate to severe proteinuria and discontinued entirely when there is evidence of nephritic syndrome, according to the package insert.[20]

Although ACE inhibitors are commonly prescribed when proteinuria is evident, it is unclear whether this drug class is effective in patients whose proteinuria is related to anti-VEGF therapy.[2]

The management of hypertension and renal toxicity in patients who received anti-VEGF treatment is still controversial. One of the issues that has come to the fore is that overexpression or underexpression of VEGF may lead to glomerulopathy. Since that is the case, bevacizumab-associated proteinuria may result, at least to some extent, from increased intraglomerular pressure caused by hypertension. Although the issue of anti-VEGF therapy and hypertension remains controversial with regard to pinpointing the mechanism, there is a dose-dependent association between bevacizumab and both proteinuria and hypertension. Since the drug is now used increasingly in metastatic cancers, early detection and management of these complications is essential to promote its safer use.

The Investigational Drug Steering Committee of the National Cancer Institute convened an interdisciplinary cardiovascular toxicities expert panel to evaluate hypertension in the setting of anti-VEGF therapy, to make recommendations on further study, and to structure an approach for safe management by treating physicians. The panel reviewed the published literature on blood pressure, hypertension, specific VSP inhibitors, abstracts from major meetings, and shared their experience with the development of VSP inhibitors and established principles of hypertension care. The panel generated a consensus report that includes recommendations on clinical concerns. To support the greatest possible number of patients to receive VSP inhibitors safely and effectively, the panel had 4 recommendations

- Conduct and document a formal risk assessment for potential cardiovascular complications
- Recognize that preexisting hypertension will be common in cancer patients and should be identified and addressed before initiation of VSP inhibitor therapy
- Actively monitor BP throughout treatment with more frequent assessments during the first cycle of treatment
- Manage BP with a goal of <140/90 mmHg for most patients (and to lower, prespecified goals in patients with specific preexisting cardiovascular risk factors)

Proper agent selection, dosing, and scheduling of follow-up should enable maintenance of VSP inhibition and avoid the complications associated with excessive or prolonged elevation in BP.[21] A variety of antihypertensive drugs can be used to lower a BP before or during treatment with angiogenesis inhibitors, but physicians should be aware of potential adverse interactions between the drugs. The panel advised that oncologists who are faced with complex cases of blood pressure management should consult cardiology or pulmonology colleagues.

Conclusions

Agents that inhibit VEGF pathway elements have revolutionized the management of advanced RCC. Hypertension as an adverse effect is increasingly recognized and characterized in this patient population. Preliminary data indicate that development of treatment-induced hypertension appears to be associated with improved clinical outcomes with this class of agents. Additional prospective studies are needed to further evaluate the mechanism(s) of this phenomenon, to characterize patient phenotype and genotype associated with hypertension, and to begin to understand how to efficiently exploit this observation for patient benefit.

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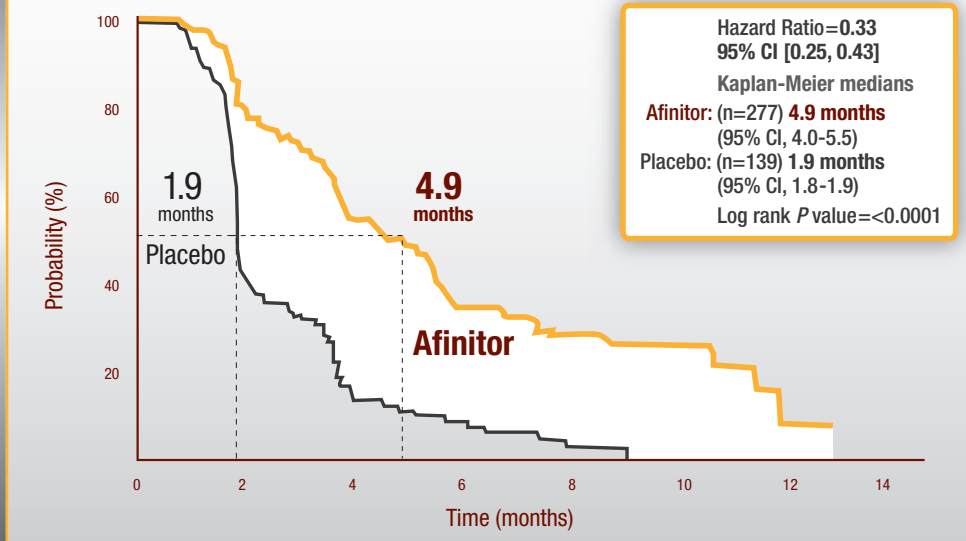
(continued on page 117)

In advanced RCC:

Afinitor doubled median PFS after progression on sunitinib*[1]

Progression-free survival (PFS) after progression on sunitinib or sorafenib[1]



- 4.9 months median PFS with Afinitor + BSC† (vs 1.9 months with placebo + BSC; *P*<0.0001)[1]
- HR 0.33=67% reduction in risk of progression
- Effective for patients with all prognostic scores[1]

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*In the RECORD-1 trial, Afinitor extended PFS after progression on sunitinib or sorafenib.[1,2]
†BSC=best supportive care.

Important Safety Information

There have been reports of non-infectious pneumonitis and infections, some with fatal outcomes. Oral ulceration has been reported. Elevations of serum creatinine, glucose, lipids, and triglycerides and reductions of hemoglobin, lymphocytes, neutrophils, and platelets have been reported.

Please see Important Safety Information on right side of page.
Please see Brief Summary of full Prescribing Information on the following pages.

Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

Important Safety Information

Afinitor is contraindicated in patients with hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients.

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Afinitor. Fatal outcomes have been observed. If symptoms are moderate or severe, patients should be managed with dose interruption until symptoms improve or discontinuation, respectively. Corticosteroids may be indicated. Afinitor may be reintroduced at 5 mg daily depending on the individual clinical circumstances.

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, and viral infections including reactivation of hepatitis B virus have occurred. Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) or fatal. Complete treatment of pre-existing invasive fungal infections prior to starting treatment. While taking Afinitor be vigilant for signs and symptoms of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor. If a diagnosis of invasive systemic fungal infection is made, discontinue Afinitor and treat with appropriate antifungal therapy.

Oral ulcerations (i.e. mouth ulcers, stomatitis, and oral mucositis) have occurred in patients treated with Afinitor. In such cases, topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided. Antifungal agents should not be used unless fungal infection has been diagnosed.

Elevations of serum creatinine, glucose, lipids, and triglycerides and reductions of hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials. Renal function, hematological parameters, blood glucose, and lipids should be evaluated prior to treatment and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on Afinitor.

Avoid concomitant use with strong CYP3A4 or PgP inhibitors. If co-administration with moderate CYP3A4 or PgP inhibitors is required, use caution and reduce dose of Afinitor to 2.5 mg daily. Increase the Afinitor dose if co-administered with a strong CYP3A4 inducer.

Afinitor should not be used in patients with severe hepatic impairment. Afinitor dose should be reduced to 5 mg daily for patients with moderate hepatic impairment.

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with Afinitor.

Fetal harm can occur if Afinitor is administered to a pregnant woman.

The most common adverse reactions (incidence ≥30%) were stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), cough (30%), and diarrhea (30%). The most common grade 3/4 adverse reactions (incidence ≥3%) were infections (9%), dyspnea (8%), fatigue (5%), stomatitis (4%), dehydration (4%), pneumonitis (4%), abdominal pain (3%), and asthenia (3%). The most common laboratory abnormalities (incidence ≥50%) were anemia (92%), hypercholesterolemia (77%), hypertriglyceridemia (73%), hyperglycemia (57%), lymphopenia (51%), and increased creatinine (50%). The most common grade 3/4 laboratory abnormalities (incidence ≥3%) were lymphopenia (18%), hyperglycemia (16%), anemia (13%), hypophosphatemia (6%), and hypercholesterolemia (4%). Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the Afinitor arm.

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Initial U.S. Approval: 2009

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

AFINITOR® is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients. Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

5 WARNINGS AND PRECAUTIONS

5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including AFINITOR. In the randomized study, non-infectious pneumonitis was reported in 14% of patients treated with AFINITOR. The incidence of Common Toxicity Criteria (CTC) grade 3 and 4 non-infectious pneumonitis was 4% and 0%, respectively *[see Adverse Reactions (6.1)]*. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, or dyspnea, and in whom infectious, neoplastic, and other causes have been excluded by means of appropriate investigations. Advise patients to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue AFINITOR therapy without dose alteration. If symptoms are moderate, consider interrupting therapy until symptoms improve. The use of corticosteroids may be indicated. AFINITOR may be reintroduced at 5 mg daily.

For cases where symptoms of non-infectious pneumonitis are severe, discontinue AFINITOR therapy and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with AFINITOR may be re-initiated at a reduced dose of 5 mg daily depending on the individual clinical circumstances.

5.2 Infections

AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoan infections, including infections with opportunistic pathogens *[see Adverse Reactions (6.1)]*. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis, and viral infections including reactivation of hepatitis B virus have occurred in patients taking AFINITOR. Some of these infections have been severe (e.g., leading to respiratory or hepatic failure) or fatal. Physicians and patients should be aware of the increased risk of infection with AFINITOR. Complete treatment of pre-existing invasive fungal infections prior to starting treatment with AFINITOR. While taking AFINITOR be vigilant for signs and symptoms of infection; if a diagnosis of an infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of AFINITOR. If a diagnosis of invasive systemic fungal infection is made, discontinue AFINITOR and treat with appropriate antifungal therapy.

5.3 Oral Ulceration

Mouth ulcers, stomatitis, and oral mucositis have occurred in patients treated with AFINITOR. In the randomized study, approximately 44% of AFINITOR-treated patients developed mouth ulcers, stomatitis, or oral mucositis, which were mostly CTC grade 1 and 2 *[see Adverse Reactions (6.1)]*. In such cases, topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed *[see Drug Interactions (7.1)]*.

5.4 Laboratory Tests and Monitoring

Renal Function

Elevations of serum creatinine, usually mild, have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of AFINITOR therapy and periodically thereafter.

Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of fasting serum glucose and lipid profile is recommended prior to the start of AFINITOR therapy and periodically thereafter. When possible, optimal glucose and lipid control should be achieved before starting a patient on AFINITOR.

Hematological Parameters

Decreased hemoglobin, lymphocytes, neutrophils, and platelets have been reported in clinical trials *[see Adverse Reactions (6.1)]*. Monitoring of complete blood count is recommended prior to the start of AFINITOR therapy and periodically thereafter.

5.5 Drug-drug Interactions

Due to significant increases in exposure of everolimus, co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or P-glycoprotein (PgP) should be avoided. Grapefruit, grapefruit juice and other foods that are known to affect cytochrome P450 and PgP activity should also be avoided during treatment *[see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.1)]*.

A reduction of the AFINITOR dose is recommended when co-administered with a moderate CYP3A4 inhibitor (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem) or PgP inhibitor *[see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.1)]*.

An increase in the AFINITOR dose is recommended when co-administered with a strong CYP3A4 inducer (e.g., St. John's Wort (Hypericum perforatum), dexamethasone, prednisone, prednisolone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) *[see Dosage and Administration (2.2) in the full prescribing information and Drug Interactions (7.2)]*.

5.6 Hepatic Impairment

The safety and pharmacokinetics of AFINITOR were evaluated in a study in eight patients with moderate hepatic impairment (Child-Pugh class B) and eight subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment, therefore a dose reduction is recommended.

AFINITOR has not been studied in patients with severe hepatic impairment (Child-Pugh class C) and should not be used in this population *[see Dosage and Administration (2.2) in the full prescribing information and Use in Specific Populations (8.7)]*.

5.7 Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with AFINITOR. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5.8 Use in Pregnancy

Pregnancy Category D

There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while using AFINITOR and for up to 8 weeks after ending treatment *[see Use in Specific Populations (8.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Non-infectious pneumonitis *[see Warnings and Precautions (5.1)]*.
- Infections *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to AFINITOR (n=274) and placebo (n=137) in a randomized, controlled trial in patients with metastatic renal cell carcinoma who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (range 27-85), 88% were Caucasian, and 78% were male. The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving AFINITOR and 60 days (range 21-295) for those receiving placebo.

The most common adverse reactions (incidence ≥30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3/4 adverse reactions (incidence ≥3%) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence ≥50%) were anemia,

hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence ≥3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) were observed on the AFINITOR arm but none on the placebo arm. The rates of treatment-emergent adverse events (irrespective of causality) resulting in permanent discontinuation were 14% and 3% for the AFINITOR and placebo treatment groups, respectively. The most common adverse reactions (irrespective of causality) leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Table 1 compares the incidence of treatment-emergent adverse reactions reported with an incidence of ≥10% for patients receiving AFINITOR 10 mg daily versus placebo. Within each MedDRA system organ class, the adverse reactions are presented in order of decreasing frequency.

Table 1
Adverse Reactions Reported in at least 10% of Patients and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm

	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Any Adverse Reaction	**97**	**52**	**13**	**93**	**23**	**5**
Gastrointestinal Disorders						
Stomatitis[a]	44	4	<1	8	0	0
Diarrhea	30	1	0	7	0	0
Nausea	26	1	0	19	0	0
Vomiting	20	2	0	12	0	0
Infections and Infestations[b]	37	7	3	18	1	0
General Disorders and Administration Site Conditions						
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Edema peripheral	25	<1	0	8	<1	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	30	<1	0	16	0	0
Dyspnea	24	6	1	15	3	0
Epistaxis	18	0	0	0	0	0
Pneumonitis[c]	14	4	0	0	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	29	1	0	7	0	0
Pruritus	14	<1	0	7	0	0
Dry skin	13	<1	0	5	0	0
Metabolism and Nutrition Disorders						
Anorexia	25	1	0	14	<1	0
Nervous System Disorders						
Headache	19	<1	<1	9	<1	0
Dysgeusia	10	0	0	2	0	0
Musculoskeletal and Connective Tissue Disorders						
Pain in extremity	10	1	0	7	0	0
Median Duration of Treatment (d)	**141**			**60**		

CTCAE Version 3.0
[a]Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.
[b]Includes all preferred terms within the 'infections and infestations' system organ class, the most common being nasopharyngitis (6%), pneumonia (6%), urinary tract infection (5%), bronchitis (4%), and sinusitis (3%), and also including aspergillosis (<1%), candidiasis (<1%), and sepsis (<1%).
[c]Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of <10% include:

Gastrointestinal disorders: Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)

General disorders and administration site conditions: Weight decreased (9%), chest pain (5%), chills (4%), impaired wound healing (<1%)

Respiratory, thoracic and mediastinal disorders: Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)

Skin and subcutaneous tissue disorders: Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasis (4%), skin lesion (4%), acneiform dermatitis (3%)

Metabolism and nutrition disorders: Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (<1%)

Psychiatric disorders: Insomnia (9%)

Nervous system disorders: Dizziness (7%), paresthesia (5%)

Eye disorders: Eyelid edema (4%), conjunctivitis (2%)

Vascular disorders: Hypertension (4%)

Renal and urinary disorders: Renal failure (3%)

Cardiac disorders: Tachycardia (3%), congestive cardiac failure (1%)

Musculoskeletal and connective tissue disorders: Jaw pain (3%)

Hematologic disorders: Hemorrhage (3%)

Key treatment-emergent laboratory abnormalities are presented in Table 2.

Table 2
Key Laboratory Abnormalities Reported at a Higher Rate in the AFINITOR Arm than the Placebo Arm

Laboratory Parameter	AFINITOR 10 mg/day N=274			Placebo N=137		
	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Hematology[a]						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical Chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase (AST) increased	25	<1	<1	7	0	0
Alanine transaminase (ALT) increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

CTCAE Version 3.0
[a]Includes reports of anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia.

Information from further clinical trials
In clinical trials, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcomes.

7 DRUG INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

7.1 Agents that may Increase Everolimus Blood Concentrations

CYP3A4 Inhibitors and PgP Inhibitors: In healthy subjects, compared to AFINITOR treatment alone there were significant increases in everolimus exposure when AFINITOR was coadministered with:

- ketoconazole (a strong CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 3.9- and 15.0-fold, respectively.
- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.0- and 4.4-fold, respectively.
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor) - C_{max} and AUC increased by 2.3- and 3.5-fold, respectively.

Concomitant strong inhibitors of CYP3A4 and PgP should not be used *[see Warnings and Precautions (5.5)]*.

Use caution when AFINITOR is used in combination with moderate CYP3A4 or PgP inhibitors. If alternative treatment cannot be administered reduce the AFINITOR dose. *[See Dosage and Administration (2.2) in the full prescribing information]*

7.2 Agents that may Decrease Everolimus Blood Concentrations

CYP3A4 Inducers: In healthy subjects, co-administration of AFINITOR with rifampin, a strong inducer of CYP3A4, decreased everolimus AUC and C_{max} by 64% and 58% respectively, compared to everolimus treatment alone. Consider a dose increase of AFINITOR when co-administered with

strong inducers of CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) or PgP if alternative treatment cannot be administered. St. John's Wort may decrease everolimus exposure unpredictably and should be avoided *[see Dosage and Administration (2.2) in the full prescribing information]*.

7.3 Agents whose Plasma Concentrations may be Altered by Everolimus

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of AFINITOR.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.8)]*

There are no adequate and well-controlled studies of AFINITOR in pregnant women. However, based on mechanism of action, AFINITOR may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while receiving AFINITOR and for up to 8 weeks after ending treatment.

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft) and retarded skeletal development. These effects occurred in the absence of maternal toxicities. Embryo-fetal toxicities occurred at approximately 4% the exposure ($AUC_{0\text{-}24h}$) in patients receiving the recommended dose of 10 mg daily. In rabbits, embryotoxicity evident as an increase in resorptions occurred at an oral dose approximately 1.6 times the recommended human dose on a body surface area basis. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At approximately 10% of the recommended human dose based on body surface area, there were no adverse effects on delivery and lactation and there were no signs of maternal toxicity. However, there was reduced body weight (up to 9% reduction from the control) and slight reduction in survival in offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

Doses that resulted in embryo-fetal toxicities in rats and rabbits were ≥0.1 mg/kg (0.6 mg/m^2) and 0.8 mg/kg (9.6 mg/m^2), respectively. The dose in the pre- and post-natal development study in rats that caused reduction in body weights and survival of offspring was 0.1 mg/kg (0.6 mg/m^2).

8.3 Nursing Mothers

It is not known whether everolimus is excreted in human milk. Everolimus and/or its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from everolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

In the randomized study, 41% of AFINITOR-treated patients were ≥65 years in age, while 7% percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

No dosage adjustment is required in elderly patients *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.6 Renal Impairment

No clinical studies were conducted with AFINITOR in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.7 Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily *[see Dosage and Administration (2.2) in the full prescribing information, Warnings and Precautions (5.6) and Clinical Pharmacology (12.3) in the full prescribing information]*.

The impact of severe hepatic impairment (Child-Pugh class C) has not been assessed and use in this patient population is not recommended *[see Warnings and Precautions (5.6)]*.

10 OVERDOSAGE

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity were observed in either mice or rats given single oral doses of 2000 mg/kg (limit test).

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been administered. The acute toxicity profile observed with the 70 mg dose was consistent with that for the 10 mg dose.

16 STORAGE

Store AFINITOR (everolimus) tablets at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F). [See USP Controlled Room Temperature.] Store in the original container, protect from light and moisture. Keep this and all drugs out of the reach of children.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.

AFINITOR tablets should not be crushed. Do not take tablets which are crushed or broken.

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(continued from page 111)

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High-Dose Interleukin-2 for the Treatment of Renal Cell Carcinoma: Managing Toxicities for Better Outcomes

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Interleukin-2 (IL-2) has been used to treat renal cell carcinoma (RCC) for more than 20 years; it was approved by the FDA for treatment of RCC in 1992. Because it has both immune-modulating and antitumor properties, high-dose IL-2 administered as a single agent has proven to be one of the most effective regimens for metastatic RCC.[1] Results of clinical trials have shown that the systemic administration of recombinant high-dose bolus intravenous IL-2 can mediate objective tumor regression in 20% of patients with metastatic RCC with complete response seen in 9% of patients.[2]

Evidence has shown that IL-2 is effective in killing renal cancer cells in vitro and patients can be successfully treated with IL-2, including the outcomes of durable complete responses that may in fact be cures.

However, its many serious adverse effects have precluded widespread use, and this treatment requires careful selection of patients who are physiological candidates for high-dose IL-2 therapy. Over the years, studies have attempted to modulate toxicity without inhibiting efficacy and to identify immune parameters that predict activity, with limited success. More recently, researchers have studied and characterized histology, T-cell characteristics, and expression of cell surface markers, to attempt to identify patients likely to respond. To date, it appears that clinical selection based on performance status, prior nephrectomy, clear cell histology, and limited visceral metastatic disease, still are the predictors of success, and have led to a doubling of the response rate.[3]

If the toxicities associated with IL-2 can be managed successfully, patient outcomes can be maximized, and a percentage of patients will achieve durable, long-term response after 1 or 2 courses of therapy. This article revisits some of what has been known about managing high-dose IL-2 toxicities for many years and some of the physiology, and presents more recent findings.

Keywords: Interleukin-2 (IL-2), renal cell carcinoma, toxicities, fever, chills, infections, hypotension, delirium

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Toxicities Associated With IL-2 Therapy

The multiple toxicities associated with IL-2 treatment include infections as well as cardiopulmonary, neuropsychiatric, dermatological, renal, and hepatic adverse effects. Patients undergoing their first course of IL-2 therapy will experience fever and chills soon after the first or second dose of IL-2.[4] Soon after the start of therapy patients may develop mild to moderate hypotension. During the first 24 hours following initiation of therapy, many patients experience hypotension and tachycardia and require additional fluids to restore urine output.

Toward the end of the cycle, hypotension and oliguria may worsen and will need to be managed pharmacologically; nausea, vomiting, and diarrhea will likely manifest toward the end of the cycle as well. Furthermore, some patients will develop edema, weight gain, and pulmonary congestion, which are all progressive. A rise in serum creatinine and a fall in platelet count are the most clinically consequential laboratory abnormalities.[4] Many of the adverse effects (eg, pulmonary edema), are thought to be a result of vascular leak and lymphoid infiltration as well as the effects of secondary cytokines.[4,5]

The exact mechanism underlying neurologic toxicity with IL-2 is unknown; however, it has been suggested that vascular-leakage syndrome may play a role.[6] Study findings indicate that IL-2 can affect gene expression, neuronal activity, and release of transmitters in brain regions, which affect sleep and arousal, memory and cognition, locomotion, and neuroendocrine function.[6] Moreover, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may play a crucial role in cytokine-induced neurotoxicity.[7]

High-dose IL-2 efficacy and toxicity are dose and schedule dependent[5]: high-dose IL-2 administered as an IV bolus is more toxic than low-dose IL-2 administered as either an IV bolus or subcutaneously.[8] Many toxicities associated with IL-2 therapy are self limiting and transient—once the treatment is stopped, the adverse effects generally resolve spontaneously. Other adverse effects can be safely managed with strategies that focus on pre-

Recommended Approaches for Managing of the Most Common IL-2–Induced Toxicities

Toxicity	Symptom management
Fever/chills	• Premedicate with acetaminophen 650 mg, with or without a nonsteroidal anti-inflammatory (eg, indomethacin 25 mg po) and continue every 6 h until 24 h after discontinuation of IL-2 • Treat chills/rigors with meperidine 25-50 mg IV
Infections	• Prophylactic use of antibiotics
Gastrointestinal	• Premedicate with dopamine antagonist if moderate to severe nausea and/or vomiting occurs; provide alternative antiemetic for break through nausea and/or vomiting; do not use corticosteroids as antiemetics • Use H2-receptor antagonist prophylactically to minimize epigastric pain • Treat diarrhea with antimotility agents (eg, loperamide) • Encourage patient to eat small, frequent meals
Hypotension	• Expect drop in blood pressure of at least 20-30 mm Hg; establish new baseline blood pressure; base treatment on drop in blood pressure below new baseline • Minimize fluid resuscitation to avoid fluid overload • Limit use of crystalloid solutions (eg, saline) to 1-1.5 L/d • Administer colloidal solutions (eg, albumin, hetastarch) if systolic blood pressure is lower than new baseline blood pressure, patient is symptomatic, or urine output declines • Administer phenylephrine 0.1-2.0 g/kg/min to stabilize blood pressure • Expect routine weight gain of 10 lb
Neurological	• Withhold IL-2 for persistent confusion, disorientation, hallucinations, progressive agitation, or somnolence unrelated to concomitant medication • May resume therapy when symptoms resolve, if no grade 4 toxicity occurred; if symptoms recur, discontinue therapy
Dermatological	• Treat symptomatically with emollients (nonsteroidal) and antihistamines; consider gabapentin19
Renal	• Use fluids judiciously to increase urine output (eg, 1-1.5 L/d) • Use dopamine 2-5 g/kg/min if patient is unresponsive to or unable to tolerate fluids • Withhold or delay IL-2 therapy for urine output < 10 mL/h for 16-24 h with rising SCr level, SCr level ≥ 4.0 mg/dL in the presence of severe volume overload, acidosis, or hyperkalemia, or SCr level > 4.5 mg/dL

Adapted from Schwartz et al.[9]
IL-2, interleukin-2; IV, intravenous; SCr, serum creatinine.

vention. With proper management, the toxicities can be reduced or even eliminated, thus improving patient outcomes.

Management of Adverse Effects

The first step in the management of toxicities associated with IL-2 treatment is careful patient selection followed by a pragmatic approach to management of adverse effects as they become apparent. The **Table** presents some practical strategies for increasing the safety of IL-2 administration.

Constitutional symptoms

The release of secondary cytokines such as TNF-α after IL-2 administration may be the cause of fever, chills, myalgias, and arthralgias, which present soon after the initiation of IL-2 therapy. Prophylactic treatment before and during therapy with acetaminophen and indomethacin reduces the frequency and severity of fevers.[9] Although steroids can block the induction of TNF-α, their use is not recommended because they have been found to negatively impact immune system activation and IL-2 antitumor activity.[10] Chills can be treated with repeated doses of meperidine and warm blankets.[5] Generally, myalgias and arthralgias resolve soon after the end of treatment.[9]

Infections

Higher rates of infection have been found with the continuous infusion method of IL-2 administration compared with high-dose bolus administration, but were common in the early years of this treatment.[10] Most IL-2-related infections—*Staphylococcus aureus* and *S epidermidis* are the commonly isolated pathogens—were found to occur in the urinary tract or at the site of venous catheter placement.[5,11] Klempner and colleagues[11] demonstrated that IL-2 induces a granulocyte chemotactic defect that is reversible once treatment is completed. This has led to the routine use of prophylactic antibiotics, which has greatly reduced the number of infections in patients with IL-2 administered through a central venous catheter.[2,12]

Gastrointestinal toxicities

Nausea, vomiting, diarrhea, and anorexia are frequent occurrences with IL-2 therapy, and increase with the number of doses per course. The complications of diarrhea (eg, gross blood diarrhea, need for parenteral nutrition) can be eliminated with the use of antidiarrheals and if necessary, holding doses of IL-2. The use of antidiarrheals should be monitored carefully because antimotility agents may worsen abdominal distention related to ileus. If severe symptoms persist, IL-2 dosing should be stopped and resumed when symptoms resolve.[2] Abdominal pain, gastritis, mucositis, and xeros-

tomia may also be associated with IL-2 therapy but resolve shortly after discontinuation of IL-2. Routine medications are given before initiation of IL-2 for potential nausea, gastritis, and diarrhea. Severe gastritis can be controlled with drugs such as ranitidine or famotidine.[5] Antiemetic drugs (either dopamine antagonist or serotonin antagonist) can be used before and during therapy to minimize nausea and vomiting. Magic mouthwash is helpful early on for xerostomia or mucositis.

Cardiopulmonary toxicities

Hypotension, tachycardia, and dyspnea are some of the cardiopulmonary toxicities associated with IL-2.[13] Because hypotension is a common complication of IL-2 therapy, antihypertensive agents should be discontinued 24 hours before initiation of therapy. They may be resumed after IL-2 therapy is completed and blood pressure has stabilized. A step-wise approach is needed for patients who are receiving beta-blockers to avoid reflex tachycardia.[9]

Mild hypotension is resolved with the administration of fluids with colloid solutions added as needed. Hypotension that is unresponsive to fluid administration is managed with intravenous dopamine hydrochloride and phenylephrine hydrochloride. Sodium bicarbonate administration is often necessary to keep the serum HCO_3 concentration above 18 meq/L.[10]

Vasopressor support with phenylephrine has been found to be an effective treatment for IL-2-induced hypotension, but generally requires administration in an intensive care unit. Concomitant low-dose dopamine, 2 to 5 µg/kg/min, can be used with phenylephrine to improve renal perfusion and urine output.[5,10,13] In cases of severe toxicity, such as hypotension that requires multiple pressor agents administration of IL-2 can be discontinued and resumed once the patient is hemodynamically stable.[9,10]

Underlying cardiac dysfunction is considered a contraindication to IL-2 therapy and careful prescreening of patients has reduced the incidence of cardiotoxicity.[2] Baseline cardiac function with electrocardiograms (ECG) and thallium stress tests are recommended before initiation of IL-2. Patients with abnormal left-ventricular ejection fraction or significant wall motion abnormalities or ischemia should be excluded from treatment with high-dose IL-2.[14] The incidence of myocardial infarction and myocarditis with high-dose IL-2 therapy is extremely rare, but myocarditis can still occur.[10,14]

Myocarditis is commonly asymptomatic and associated with temporary left-ventricular dysfunction. Because myocarditis may resolve completely, subsequent therapy with IL-2 is not automatically excluded; instead, continuation is based on ECG and/or thallium stress tests.[14]

Lee and colleagues[15] performed careful hemodynamic studies in 10 patients treated with IL-2 and demonstrated the physiology of decreased peripheral vascular resistance, increase in heart rate, decrease in left ventricular stroke work and mild decrease in left ventricular ejection fraction during IL-2 treatment. Central venous pressure, pulmonary capillary wedge pressure were only reduced slightly, such that the hemodynamic changes measured did not appear to be directly related to central pressures. They also studied circulation of I-131 labeled albumin and showed rapid clearance from the circulation (14% to 135 %), thus demonstrating capillary leak.

Before initiating IL-2 therapy, pulmonary function tests should be performed, and patients with abnormal results should not be treated with high-dose IL-2. Pulmonary complications that occur during high-dose IL-2 therapy are directly related to the development of vascular-leak syndrome and may be more severe in patients with coexisting cardiac toxicities or extensive pulmonary metastases. The results of one study showed that during the first 5 days of IL-2 administration, alveolar edema was seen in 21% (n = 4) of patients and interstitial edema in 53% (n = 10) of patients; pleural effusions were seen in 42% (n = 8) of patients.[16]

Findings from a correlative analysis of radiographic and clinical findings suggest that the etiology of pulmonary edema is likely related to increased pulmonary vascular permeability rather than to renal insufficiency, fluid overload, or hypotension.[17] Pulmonary edema is usually preceded or accompanied by clinical symptoms of edema and weight gain, often greater than or equal to 5% of baseline body weight.[9] Progressive pulmonary edema can be problematic and may lead to severe respiratory distress that requires intubation.[9] However, in the era of fewer doses, where recovery between doses is the standard management, severe respiratory distress is rare.[2]

Alternatively, Glauser and colleagues[18] suggest that although IL-2 administration is linked to various cardiopulmonary toxicities, including increased pulmonary microvascular permeability, infiltration of the lung parenchyma with large esterase negative lymphoid cells, hypoxemia, systemic hypotension, and positive fluid balance, the toxicities may not be directly caused by IL-2 but rather that they are mediated by IL-2 activated lymphocytes or other IL-2 activated cellular mediators.

Neurological problems

The most common neuropsychiatric toxicities associated with IL-2 treatment include behavioral changes and agitation, cognitive impairment and disorientation, and delusions and hallucinations, ie, delirium. Several longer-lasting neuroendocrine (eg, thyroiditis) and memory disturbances have also been seen.[6] Symptoms appear at the end of treatment and may worsen before resolving after treatment discontinuation.[5] Early evaluations at the National Cancer Institute attempted to fully characterize the neuropsychiatric effects of this treatment and noted a latency period and full recovery.[19]

It is important that patients being treated with IL-2 are routinely monitored for altered mental status and changes in behavior or sleep patterns. Management of

neurotoxicity includes prompt discontinuation of IL-2 therapy, evaluation of concomitant medications, informing patients and family that neurotoxicity will resolve after the end of therapy, and providing a safe environment for recovery.[5,10,13,19]

Neurological toxicity can be progressive through the course of a week of treatment. Initial insomnia or irritability can be treated with benzodiazepines. However, if the level of agitation accelerates or there are hallucinations or delusions, neuroleptics are the first choice for these symptoms. Haloperidol has been recommended to control agitation.[5] Atypical neuroleptics, such as risperidone, olanzapine, and quetiapine, can also be considered.[7] Low-potency neuroleptics, because of their anticholinergic properties, are contraindicated because they can exacerbate medication-induced delirium. Once there is delirium, the use of benzodiazepines should be avoided, because they can exacerbate the delirium. Anticholinergics and antihistamines should also be avoided. Selective serotonin reuptake inhibitors should be considered first-line treatment of patients with IL-2 associated depression although the time of onset is likely to be slow, and these symptoms resolve rather quickly.[7]

Brain metastases may be the underlying cause for delirium and a magnetic resonance imaging (MRI) or computed tomography (CT) scan is recommended prior to IL-2 therapy. Edema as a result of high-dose IL-2 therapy may cause increased intracranial pressure and increase the risk of hemorrhage into brain lesions.[5] However, some patients may safely receive high-dose IL-2, for example, those with effectively controlled brain lesions, a limited number of small metastases, and limited or no intracranial edema.[20]

Dermatological problems

High-dose IL-2 (HDIL-2) therapy is well known to cause pruritus, but the pathogenic mechanism is not well understood.[21] It may be the direct effect of IL-2 or an effect of the downstream cascade of cytokines, consequently, the result is sensitization of peripheral pruriceptive nerve endings. Lee and colleagues[22] looked at gabapentin to stabilize this nerve synapse. By inhibiting the $\alpha 2\delta$-subunit of the voltage-dependent calcium channel, gabapentin may increase the threshold for neuronal excitation.

Traditionally, IL-2–induced pruritus was treated with antihistamines and topical emollients. However, the routine use of antihistamine is not always beneficial. The understanding of pruritis continues to advance, and we now know it is not solely dependent on histamines. Clinically, IL-2-induced pruritus resembles histamine-independent pruritis, associated with dryness of skin. Redness may be associated with severe dryness, but the initial process is unlikely to be histamine-dependent.[21,23,24]

The researchers hypothesized the likely mechanism for pruritus in IL-2 treated patients—the activation of cutaneous C-fiber polymodal nociceptors through keratinocyte-neuron inflammatory interaction mediated by IL-31.[22] Through activation of IL-4 and IL-10, IL-2 activates the T helper 2 (TH2) pathway, which consequently increases the production of IL-5, which, in turn, increases the number of eosinophils in the peripheral blood. Eosinophils propagate the IL-2-induced inflammatory response through differential release of TH2 cytokines and polarize the immune response toward the TH2 pathway. This TH2 shift can lead to increased secretion of IL-31. Furthermore, the toxic effect of eosinophils may directly damage or disrupt unmyelinated C-fibers, the pruriceptive primary afferents, thus, sensitizing the pruriceptive pathway.

The results of the study by Lee and colleagues[22] demonstrated that gabapentin provided significant relief from IL-2–induced pruritis at a tolerable dose range. Their findings suggest that gabapentin can be effectively and safely—the major adverse effect was somnolence—used for managing IL-2–induced pruritus.

Renal and hepatic toxicity

Renal insufficiency is frequently observed in patients treated with high dose IL-2. Certainly a proportion of this is pre-renal, with the reduced cardiac output and hypotension resulting in renal hypoperfusion.[15] However, other mechanisms may also be at work. Shalmi and colleagues[25] hypothesized that acute renal dysfunction during IL-2 treatment may in part be due to an intrinsic renal lesion. The researchers found that glomerular filtration rate fell on day 4 or earlier of treatment. Nine out of 10 patients had a mean decrease of 43% (±8%), and renal plasma flow fell in 5 of the 10 patients with a mean decrease of 5% (±10%). They calculated the average pretherapy filtration fraction to be 23% (±1%), after 4 days of treatment, this decreased to a mean value of 15% (±2%). In addition, the serum urea nitrogen to creatinine ratio declined in all patients. Their findings suggest that nephrotoxicity due to IL-2 treatment may have a component of an intrarenal defect in addition to the pre-renal effects from hypotension.

Renal function should be assessed at baseline and daily throughout IL-2 therapy. Factors that increase the risk for IL-2–induced renal toxicity include RCC, older age, male gender, prior nephrectomy, preexisting hypertension, and sepsis.[26,27] IL-2 should be withheld if serum creatinine levels increase significantly but can be resumed once the levels return to normal (or to baseline levels). Renal toxicity is most effectively managed by administering fluid boluses at the onset of oliguria, with a relative limit on the total volume of 1 to 1.5 L/d above maintenance needs.[5] Renal doses of dopamine are marginally useful. Renal dysfunction will generally resolve within 7 to 14 days and return to normal or baseline values once IL-2 therapy is discontinued.[5]

Hepatic dysfunction related to IL-2 therapy usually manifests as reversible hyperbilirubinemia but transient elevations in serum hepatic transaminase levels are also possible.[10] In addition, mild elevations in prothrombin

time and decreases in albumin levels may occur.[5] Liver function usually returns to normal within 5 to 6 days after IL-2 treatment ends.

Conclusion

The incidence and/or severity of adverse effects with IL-2 treatment has been declining over the years, in part because of a general reduction in the number of doses given per week of therapy.[2] With careful patient selection and experienced management of the toxicities associated with IL-2 therapy, treatment can be administered safely and provide good outcomes in patients with RCC, with durable complete response in a small subset of patients.[2] Careful patient selection and screening remains a major component of entry into this treatment protocol.

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As we seek to address these issues with our patients, many of us remain disappointed that most public and private insurance plans provide little or no compensation for discussions with patients about palliative care options, despite their demonstrated value. ASCO's policy statement also grapples with this barrier as part of its recommendations. It remains uncertain if this issue will become part of the public health policy debate but it also needs to be raised as part of our continuing effort to deliver quality care for all patients.

As ASCO President George W. Sledge, Jr., MD, points out: "Patients have a right to make informed choices about their care. Oncologists must lead the way in discussing the full range of curative and palliative therapies to ensure that patients' choices are honored."

Robert A. Figlin, MD
Editor-in-Chief

MEDICAL INTELLIGENCE

(continued from page 104)

positron emission tomography/computed tomography scans. The SUV indicates how "bright" or "hot" a lesion is on a scan.

Researchers analyzed outcomes of 13 RCC patients with a total of 25 lesions and 17 melanoma patients who had a total of 28 lesions. The mean gross tumor volume was 6 cc (range 1-275 cc). Treated sites included the liver (11 lesions), lung (39 lesions), and bone (3 lesions). The median follow-up for patients alive at the time of the analysis was 11.5 months (range, 2-65 months). At 1 year, the overall rate of local control was 85%. It was 95% for RCC patients. The findings from this study suggest that an aggressive SBRT regimen is an effective modality for controlling metastatic melanoma and metastatic RCC. The local control rates achieved in this series were comparable to those obtained with SBRT for other tumor histologies.

New Biopsy Device Could Speed Renal Cancer Diagnosis

BLOOMINGTON, IN—Cook Medical has introduced BIGopsy Backloading Biopsy Forceps, a device that has a 4 mm^3 biopsy cup to obtain large renal or ureteral tissue specimens for cancer diagnosis. The larger sample size helps produce biopsy results without the need for repeat tissue sampling associated with other biopsy devices, according to Cook Medical. To accommodate the large biopsy cup, BIGopsy has a replaceable handle that allows it to be backloaded through the working channel of an endoscope. One of the inventors of the device, Jaime Landman, MD, Director of Minimally Invasive Urology in the Department of Urology at Columbia University, New York, said, "There have been a number of significant advancements in how we assess, view, and treat a tumor in the ureter or kidney, but what's been missing is our ability to obtain adequately sized tissue samples for biopsy."

WILEX Launches Interim Analysis for its Phase III ARISER Registration Trial With Rencarex®

MUNICH, GERMANY—WILEX AG has announced the achievement of a major clinical milestone. Over 340 recurrences have now been reported to WILEX by the local sites, enabling the company to launch an interim analysis of efficacy in the Phase III registration trial with Rencarex® for treatment of renal cancer. The process involves the central analysis of the data from all 864 patients by independent radiologists. The interim analysis will be carried out by an Independent Data Monitoring Committee (IDMC) and should provide definitive information regarding the endpoint of the trial relevant for approval, namely "disease-free survival". Results of the interim analysis of efficacy are expected to be available in about 6 months.

Rencarex® is based on the antibody Girentuximab, which binds to the tumor-specific antigen CAIX, an antigen overexpressed in clear cell renal cell carcinomas (RCC). The therapeutic antibody makes the tumor visible to the endogenous immune system, recruiting natural killer cells which can destroy any existing cancer cells. Rencarex® should inhibit further growth and recurrence of clear cell RCC and kill cancer cells, thereby prolonging the disease-free survival.

ARISER (Adjuvant Rencarex Immunotherapy trial to Study Efficacy in non-metastasised Renal cell carcinoma) is an international, multicenter, randomized trial that examines the efficacy of the antibody Rencarex® in comparison to placebo in the treatment of clear cell renal cell cancer patients following complete or partial surgical removal of the affected kidney in patients with no detectable metastases. The Phase III ARISER trial involves 864 patients, who received the study medication in once-weekly infusions over a period of 24 weeks. The last patient completed treatment in February 2009. Following the occurrence of the 100th relapse, the first interim analysis for futility was carried out in late 2007. The IDMC recommended that the trial be continued because it will probably deliver a significant result. No drug has been approved to date by the FDA or EMA for the adjuvant therapy of non-metastatic clear cell RCC. KCJ

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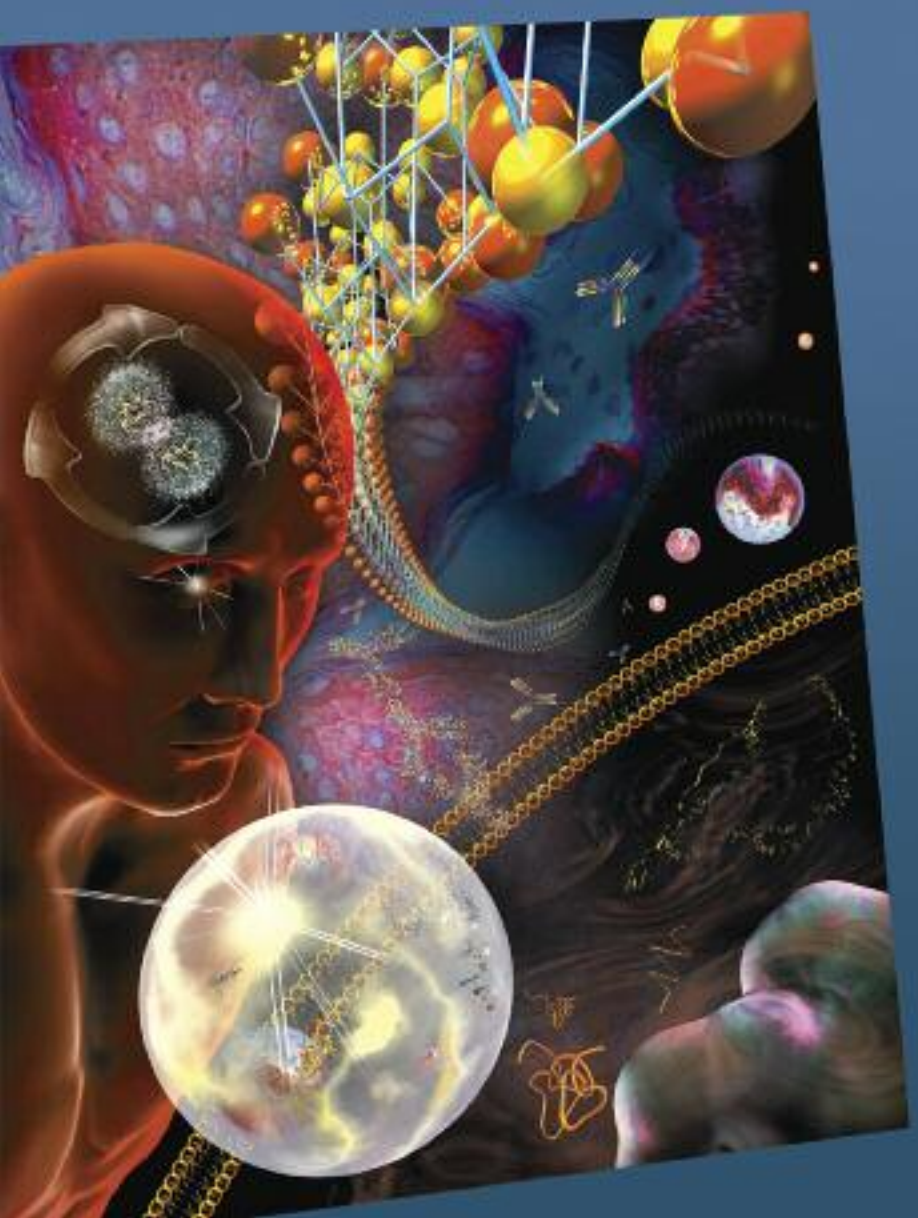

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