HEM/ONC News

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The U.S. Food and Drug Administration (FDA) Approves New Treatment for Advanced Kidney Cancer

On October 19, the FDA approved pazopanib (Votrient, GlaxoSmithKline) for the treatment of advanced kidney cancer. Pazopanib is the sixth drug to be approved for kidney cancer treatment since 2005, joining sorafenib, sunitinib, temsirolimus, everolimus, and bevacizumab. Pazopanib is indicated for patients with advanced renal cell carcinoma. The approval of pazopanib was based on a study in which 435 patients were evaluated for progression-free survival, which was achieved for an average of 9.2 months in patients receiving pazopanib compared to 4.2 months in patients receiving placebo. Side effects of the drug include diarrhea, hypertension, hair color changes, nausea, loss of appetite, vomiting, fatigue, weakness, abdominal pain, and headache; severe and fatal liver toxicity has also been reported. Pazopanib has also been linked with heart rhythm irregularities.

FDA Approves Rasburicase as Initial Therapy for Patients at Risk for Tumor Lysis Syndrome

On October 16, the FDA approved a new indication for rasburicase, a recombinant uricolytic agent, that can now be used for initial management of plasma uric acid levels in adult patients with leukemia, lymphoma, and solid tumor malignancies and who are receiving anticancer therapy associated with increases in plasma uric acid and tumor lysis syndrome. Rasburicase is already approved for use in preventing tumor lysis syndrome in pediatric patients. The approval of rasburicase for adult patients was based on a phase III, randomized, multicenter, open-label trial (EFC 4978), which demonstrated a significant improvement in uric acid response rates among patients treated with rasburicase compared to those receiving allopurinol, the current standard treatment. The patients enrolled in the study either had hyperuricemia secondary to malignancy or an aggressive hematologic malignancy. A total of 275 patients were randomized on a 1:1:1 basis to: intravenous rasburicase for 5 days (n=92); rasburicase on days 1–3 followed by allopurinol on days 3–5 (n=92); or allopurinol for 5 days (n=91). The plasma uric acid response rate was 87% in patients who received rasburicase alone, 78% in patients receiving both rasburicase and allopurinol, and 66% in patients receiving allopurinol alone. The incidence of developing tumor lysis syndrome was similar in all groups. Adverse events occurring at a frequency of 10% or higher in the rasburicase groups versus the allopurinol group were peripheral edema, vomiting, hyperbilirubinemia, sepsis, and fluid overload.

Ofatumumab Receives FDA Approval for Refractory Chronic Lymphocytic Leukemia (CLL)

On October 26, the FDA announced the approval of ofatumumab (Arzerra, GlaxoSmithKline), a monoclonal antibody targeting the CD20 antigen on the surface of B cells, for the treatment of refractory CLL. Ofatumumab was approved for patients specifically refractory to fludarabine and alemtuzumab treatment. The study leading to FDA approval included 59 patients with CLL who did not respond to fludarabine and alemtuzumab. Of these patients, 42% had an objective response rate and a median duration of response of 6.5 months. Ofatumumab was approved under the FDA's accelerated approval process. A major side effect reported with ofatumumab is increased risk of infection; adverse reactions reported in at least 10% of patients in the study were neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections.

TPF Regimen Produces Survival Benefit in TAX 324 Trial

Results of a phase III trial (TAX 324) in patients with locally advanced squamous cell carcinoma of the head and neck found that induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (5-FU; TPF) demonstrated a sustained survival advantage compared to cisplatin plus 5-FU (PF). The findings were reported by Dr. Jochen Lorch and colleagues at the joint congress of the European Cancer Organization and European Society of Medical Oncology. In 88% of the 501 patients enrolled in the study, at a minimum of 5 years' follow-up, 52% of patients treated with TPF were alive compared to 42% of those treated with PF. Median overall survival (OS) was 71 months versus 35 months. Sustained improvement

was observed in patients with laryngeal and hypopharyngeal primary tumors who received TPF therapy (50% reduction in risk of progression or death compared with those receiving PF). OS was not significantly different between patients in the 2 treatment groups with laryngeal or hypopharyngeal tumors. No significant differences were noted in adverse events at 3 and 5 years. TPF and PF treatment groups had similar rates of enteral feeding and tracheostomy. The TAX 323 trial in Europe and the TAX 324 trial in the United States contributed to the establishment of TPF as a standard treatment for induction chemotherapy in locally advanced head and neck cancer. However, it remains unknown whether this treatment approach is better than the use of definitive combined chemoradiotherapy.

Multinational, Double-blind, Phase III study in Patients with Castrate-refractory Prostate Cancer Progressing After Chemotherapy: the SPARC Trial

Results of a randomized phase III study, reported in the October 5 issue of *Journal of Clinical Oncology*, found that satraplatin plus prednisone improved progression-free survival (PFS) and time to pain progression (TPP) in patients with castrate-refractory prostate cancer. In this study (the SPARC trial), 950 patients with D2 adenocarcinoma of the prostate who had received 2 or more cycles of chemotherapy were enrolled from 170 multinational sites between September 2003 and January 2006. Patients were randomized in a 2:1 ratio to satraplatin (80 mg/m^2 on days 1–5 of each 35-day cycle) plus prednisone (5 mg twice daily; n=635) or placebo plus prednisone (n=315) at the same dose. Prophylactic granisetron was also administered to patients in the satraplatin group. Treatment was administered until disease progression, unacceptable toxicity, withdrawal, nonadherence, or death. The study endpoints included PFS and OS (primary) and TPP (secondary). Dose reductions were required in 20.8% and 0.3% of patients in the satraplatin and placebo groups, respectively. After 802 progression events had been noted, PFS was significantly longer in patients receiving satraplatin compared to those receiving placebo (11.1 vs 9.7 weeks). A 33% reduction in the risk of progression or death was reported in the satraplatin group. A subanalysis found that PFS benefit with satraplatin occurred regardless of prior docetaxel treatment. No differences were observed in OS in the 2 groups (61.3 vs 61.4 weeks). However, TPP was significantly extended in the satraplatin group (66.1 vs 22.3 weeks). A 36% reduction in the risk of pain progression was observed in the satraplatin group. The safety analysis found that satraplatin was generally well tolerated, but associated with a higher frequency of hematologic and gastrointestinal toxicities. Serious toxicities were also more frequently reported in patients receiving satraplatin (8.7% vs 2.9%).

Bortezomib Plus Melphalan and Prednisone in Newly Diagnosed Patients With Multiple Myeloma With Moderately Impaired Renal Function: Results of the VISTA Study

In this phase III study, reported in the October 26 issue of *Journal of Clinical Oncology,* a combination of bortezomib, melphalan, and prednisone (VMP) was compared to melphalan and prednisone (MP) in previously untreated patients with multiple myeloma with renal impairment. The study also evaluated renal impairment reversibility. Patients enrolled in the study received nine 6-week cycles of VMP (bortezomib 1.3 mg/m^2, melphalan 9 mg/m^2, prednisone 60 mg/m^2) or MP. Patients with serum creatinine greater than 2 mg/dL were not included in the study. In the VMP and MP arms, 6% and 4% of patients had a baseline glomerular filtration rate (GFR) of less than or equal to 30, 27% and 30% had a GFR of 31–50, and 67% and 66% had a GFR of higher than 50 mL/min. Response rates were found to be higher and time to progression (TTP) and OS were longer in the VMP group compared to the MP group across renal cohorts. Response rates with VMP and TTP in both groups were not significantly different between patients with GFR of 50 or higher than 50 mL/min. OS was longer in patients with normal renal function in both arms. Renal impairment reversal (baseline GFR <50 improving to >60 mL/min) was observed in 49 of 111 patients receiving VMP versus 40 of 116 patients receiving MP. A multivariate analysis found that younger age (<75 years) and less severe renal impairment (GFR of 30 mL/min) correlated with higher reversal rates. The safety analysis reported higher rates of grade 4/5 and serious adverse events in patients with renal impairment in both arms. In patients receiving VMP, rates of discontinuations and/or bortezomib dose reductions due to adverse events were not noticeably affected. The study results suggest that VMP is a well-tolerated treatment option for previously untreated patients with multiple myeloma with moderate renal impairment, producing a 44% renal impairment reversal.