HEM/ONC News

By Stacey Small

Bevacizumab Improves PFS in Glioblastoma: Results From the Phase III AVAglio Study

According to data presented by Chinot and associates at the 17th Annual Meeting of the Society for Neuro-Oncology in November, bevacizumab (Avastin, Genentech/Roche) in combination with radiation and temozolomide (Temodar, Merck) chemotherapy yielded a 36% reduction in the risk of disease worsening or death when compared to radiation and temozolomide chemotherapy plus placebo in patients with newly diagnosed glioblastoma (hazard ratio [HR], 0.64; *P*<.0001). The co–primary endpoints in the phase III AVAglio (Study of Avastin [Bevacizumab] in Combination With Temozolomide and Radiotherapy in Patients With Newly Diagnosed Glioblastoma) study were overall survival (OS) and progression-free survival (PFS) as assessed by trial investigators. A total of 921 patients were treated. Patients were randomized to receive bevacizumab plus radiation and temozolomide chemotherapy for 6 weeks, followed by a 4-week break. Patients then received bevacizumab and temozolomide for up to 6 cycles, followed by bevacizumab alone until disease progression. There was a 4.4-month improvement in median PFS when patients received bevacizumab in combination with radiation and chemotherapy compared to those who received radiation and chemotherapy plus placebo (10.6 months vs 6.2 months, respectively). Interim OS results did not reach statistical significance (HR, 0.89; *P*=.2135). Final OS data are expected in 2013. A PFS assessment performed by an independent review committee showed a 39% reduction in the risk of disease worsening or death among patients treated with bevacizumab (HR, 0.61; *P*<.0001). The 1-year survival rate was 72% in the bevacizumab arm versus 66% in the placebo arm (*P*=.052). When bevacizumab was added to standard radiation and chemotherapy, a variety of health-related quality of life measures were maintained for longer compared to standard treatment alone, including maintenance of functional independence. Furthermore, patients who received bevacizumab required fewer corticosteroids than those who received standard treatment. By meeting its co–primary endpoint of PFS, AVAglio is the first positive phase III trial in newly diagnosed glioblastoma since 2005.

Everolimus for the Treatment of Subependymal Giant Cell Astrocytomas Associated With Tuberous Sclerosis

According to results from a double-blind, placebo-controlled, phase III trial by Franz and colleagues, everolimus (Afinitor, Novartis) may be effective in the treatment of subependymal giant cell astrocytomas (SEGAs) associated with tuberous sclerosis. The study, which was published in the November 14 online issue of *The Lancet*, randomized 117 patients (aged 0–65 years; mean age, 9.5 years) at 24 centers to oral everolimus 4.5 mg/m^2 daily (titrated to achieve blood trough concentrations of 5–15 ng/mL; 78 patients) or placebo (39 patients). Enrollment criteria included a definite diagnosis of tuberous sclerosis complex and at least 1 lesion with a diameter of 1 cm or greater, and either serial growth of a SEGA, a new lesion of 1 cm or greater, or new or worsening hydrocephalus. No patients in the placebo arm had any reduction in SEGA volume, but 27 patients (35%) in the everolimus arm experienced at least a 50% reduction in volume. A total of 76 patients (97%) in the everolimus arm and 31 patients (79%) in the placebo arm were still undergoing double-blind treatment at a median follow-up of 9.7 months. The median duration of treatment was 41.9 weeks in the everolimus arm and 36.1 weeks in the placebo arm. Adverse events were mostly grade 1 or 2; the most common adverse events in the everolimus and placebo arms, respectively, included mouth ulceration (32% vs 5%), stomatitis (31% vs 21%), convulsion (23% vs 26%), and pyrexia (22% vs 15%). No patients discontinued treatment due to adverse events.

Bone Marrow Biopsy Adds Little to PET/CT Staging in Hodgkin Lymphoma

El-Galaly and associates conducted a retrospective study in patients with newly diagnosed Hodgkin lymphoma (HL) to determine whether bone marrow biopsy (BMB) adds useful information to [18F]fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) staging. Among the 454 patients involved in the study, 27 patients (6%) had a positive BMB. A total of 106 patients (23%) had abnormal PET scans, 82 patients (18%) had focal skeletal lesions (20 unifocal, 10 bifocal, and 52 multifocal), and 24 patients had diffusely homogeneous FDG uptake involving most

of the axial skeleton. Among patients assessed as having stage I–II disease by PET/CT staging, none had a positive BMB. Five patients assessed as being stage III before BMB had a higher stage after BMB, but none of the patients were allocated to a different treatment based on the results of the BMB. For identification of positive and negative BMBs, focal skeletal PET/CT lesions had a sensitivity of 85% and a specificity of 86%; the sensitivity and specificity of BMB results were 28% and 99%, respectively. The study, which was published in the November 13 online issue of the *Journal of Clinical Oncology*, demonstrated that routine BMB has little or no therapeutic consequence. The investigators concluded that the omission of staging BMB would not have changed the risk assessment or treatment strategy in this cohort of 454 newly diagnosed patients with HL. In an accompanying editorial, Bruce D. Cheson, MD, stated that this study "provides perhaps the most convincing evidence that we can now spare all patients the pain and expense of the bone marrow biopsy."

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The most recently FDA-approved G-CSF is tbo-filgrastim (Neutroval, Sicor Biotech), a filgrastim biosimilar. All agents are well tolerated. Most importantly, the duration of severe neutropenia, the depth of the absolute neutrophil count nadir, and complications associated with febrile neutropenia are all significantly reduced.

There is ongoing research for new myeloid cell line growth agents, but just as important has been the emphasis on developing clinical assessment tools, which can be applied to more accurately "risk-stratify" patients with neutropenia and febrile neutropenia. Examples of such tools are being validated in prospective clinical trials examining patients with febrile neutropenia to determine who can be safely managed with close follow-up in the outpatient setting versus which patients will require hospitalization.

Generally, there is no role for corticosteroids in neutropenia management in cancer patients. In patients with septic shock with or without neutropenia, corticosteroids may be indicated. In addition, alternate-day dosing of corticosteroids has been used in patients without malignancy who have human cyclic neutropenia.

Intravenous immunoglobulin (IVIG) therapy is not indicated for patients with febrile neutropenia as a consequence of chemotherapy. IVIG therapy has been used for autoimmune and chronic neutropenias unrelated to chemotherapy.

H&O Do cancer patients pose particular treatment challenges?

ML Patients are very frightened by the prospect of neutropenia, so additional education on this topic can be helpful. Sometimes they are unsure of what activities should be avoided to minimize infectious complications during neutropenia. Our thinking about neutropenia has changed in recent years. Neutropenic precautions now depend on the degree of neutropenia and the type of cancer. Good hand hygiene is very important. In patients with prolonged neutropenia as experienced during hematologic malignancies and bone marrow transplantation, minimizing exposure to pets and live plants is recommended during periods of profound neutropenia. However, in solid tumor malignancies, most patients do not experience very long periods of neutropenia, and these precautions are more relaxed. A recently published Cochrane review on the benefit of a low-bacterial diet was not conclusive regarding evidence for or against recommending this approach. It is very important that each patient discuss these precautions with his or her doctor so that they can be tailored to specific needs.

It is very distressing for cancer patients to develop febrile neutropenia and to require frequent hospitalizations. This outcome tends to occur with the first cycle of chemotherapy, and it can be quite challenging because patients become frightened about what future cycles of chemotherapy will be like. Anything we can do to safely prevent febrile neutropenia is beneficial.

Suggested Readings

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