

Clinical Perspectives™

Highlights from the Perspectives in Melanoma XII Conference

Scheveningen/The Hague, the Netherlands, October 2-4, 2008

TARGETED THERAPY

Targeted chemotherapy: minimally invasive percutaneous hepatic perfusion

James F. Pingpank of the University of Pittsburgh Cancer Institute in Pittsburgh, Pennsylvania, discussed the results from a phase 1 dose-escalation trial examining a novel percutaneous catheter system for the delivery of intrahepatic melphalan to cancer patients with hepatic metastases. Previous phase 2 studies from his group described the efficacy of hyperthermic-isolated hepatic perfusion (IHP) in patients with metastatic ocular melanoma or colorectal cancer. Although response rates in ocular melanoma patients were in the range of 60% to 70%, with a 1-year median duration, the majority of patients eventually succumbed to recurrent liver disease, regardless of the initial response. Ocular melanoma has a predilection to metastasize to the liver.

The new percutaneous hepatic perfusion (PHP) procedure uses an intra-artery delivery catheter placed in the hepatic artery and a venous catheter in the retrohepatic vena cava. The venous outflow is shunted through 2 activated charcoal filters before being returned to the venous circulation, which serves to remove melphalan and reduce systemic exposure to the drug. PHP is a less invasive procedure than IHP that reduces AEs related to systemic melphalan exposure and potentially enables higher dosing. Dr. Pingpank described the results from a recently completed phase 1 trial of PHP in patients with ocular melanoma or other solid tumors with liver metastases. The MTD was 3.0 mg/kg, twice that achievable via IHP. From 20% to 25% of melphalan leaked into the systemic circulation with this procedure, and grade 3/4 toxicities (eg, thrombocytopenia, anemia, elevated transaminases, and hyperbilirubinemia) were generally easily managed.

Of 16 patients with metastatic melanoma, 8 (50%) experienced a clinical response (2 clinical responses and 6 partial responses, lasting 2+ to 15 months), and 4 (25%) had stable disease. The site of disease recurrence or progression for the 12 responders was the liver (n=6), systemic (n=4), or systemic and liver (n=2). The overall response rate in this study is generally similar to that obtained with IHP in larger patient populations. A randomized phase 3 trial comparing PHP (with melphalan 3.0 mg/kg) with best available care in patients with hepatic metastases from ocular or cutaneous melanoma was recently initiated. The accrual goal is 92 patients, and the primary endpoint is hepatic progression-free survival (PFS). Crossover is permitted at the time of hepatic progression.

Dr. Pingpank concluded that regional delivery of melphalan can result in meaningful control of liver metastases from melanoma in properly selected patients. In addition, regional therapy offers the potential to “downstage” unresectable hepatic metastases. Moreover, the hope is that novel regional approaches such as PHP will enable increased drug delivery and efficacy by overcoming a low therapeutic index for the administered agent.

Targeting angiogenesis in melanoma

Paul Lorigan, of Christie Hospital NHS Trust in Manchester, United Kingdom, spoke in mostly general terms about antiangiogenic therapy for melanoma and other solid tumors. Antiangiogenic agents are currently approved treatment for colorectal, lung, breast, and renal cancer, but antiangiogenesis strategies are only beginning to be explored in melanoma. Studies have demonstrated that serum levels of VEGF and other angiogenic factors are elevated in patients with advanced melanoma and high tumor burden.^{1,2} Moreover,

VEGF has been shown to be an independent predictor of overall survival and progression-free survival in melanoma patients with different stages of disease. The rationale for using antiangiogenic agents in melanoma is similar to that for other tumors.

Angiogenesis refers to the formation of new vasculature from pre-existing blood vessels. Most if not all solid tumors require tumor-related angiogenesis to grow beyond an otherwise limited size of about 2 to 3 mm, and angiogenesis is required for metastasis. The main mediator of tumor angiogenesis is VEGFA, although other a variety of others factors can promote angiogenesis as well, including platelet-derived growth factors (PDGF), interleukin-8, and basic fibroblast growth factor (bFGF). Various stimuli or events—many associated with tumor development or growth—lead to increased expression of VEGF. Once released, VEGF activates VEGF receptors (VEGFRs) located on vascular endothelial cells, leading to intracellular signals that promote endothelial cell proliferation and survival. Interfering with tumor-related angiogenesis should inhibit further tumor growth and reduce the risk of metastasis, thereby enhancing survival, and results from other cancers suggest that this is often the case. In addition, antiangiogenic therapy leads to “vascular normalization” at the tumor site and a reduction in tissue edema and interstitial pressure, which can lead to improved delivery of coadministered chemotherapy. This is part of the rationale for combining antiangiogenic agents with traditional chemotherapies.

Currently available antiangiogenic agents include a monoclonal antibody directed against VEGF (bevacizumab [BEV]) and 2 small-molecule tyrosine kinase inhibitors or TKIs (sorafenib and sunitinib) that inhibit the activity of VEGFR, which is a receptor tyrosine kinase. Additional drugs are under evaluation, some with similar mechanism of action as currently available agents, and others with distinct or unique mechanisms, including antibodies to VEGFR and a soluble VEGFR to as a decoy (VEGF Trap). Other drugs under evaluation target integrins, which are cell-surface receptors that have been implicated in angiogenesis through regulation of endothelial cell migration and survival.³

Dr. Lorigan described results from a number of earlier stage trials of antiangiogenic agents in melanoma. A randomized phase 2 trial by Varker and colleagues compared BEV with or without IFN- α 2b in 32 patients with metastatic melanoma, and demonstrated prolonged disease stabilization (24 to 146 weeks) in some patients treated across the 2 regimens. Plasma VEGF levels did not correlate with clinical outcome, and IFN- α 2b did not augment the activity of BEV.⁴ Two other studies reported at the *Perspectives in Melanoma* conference evaluated BEV in combination with other agents, 1 with *nab*-paclitaxel (by Boasberg and colleagues) and the other with dacarbazine and IFN- α 2a (by Vihinen and associates), reporting response rates of 41% and 17%, respectively. Dr. Lorigan also described the results from a phase 2 trial of axitinib (a VEGFR inhibitor) in patients with metastatic melanoma.⁵ Axitinib was generally well tolerated, with an overall response rate of 19% (including 1 durable clinical response) and a median overall survival of 13 months.

Dr. Lorigan also made the point that, since angiogenesis is critical for invasion and metastasis, adjuvant antiangiogenic therapy is an important area to explore.

References

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