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EDITORIAL

In Search of the Black Sheep: Is It Bevacizumab or Extended Chemotherapy?

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A critical determinant of outcome in patients undergoing hepatectomy is the degree of liver regeneration that occurs after surgery. Animal studies have demonstrated that liver regeneration depends on vascular endothelial growth factor (VEGF) and angiogenesis.[1] In a murine model, anti-VEGF receptor therapy slightly impaired liver regeneration and cell proliferation after partial hepatectomy compared with control.[2] However, there are no preclinical animal data on the effect of the anti-VEGF monoclonal antibody bevacizumab on liver regeneration because bevacizumab specifically recognizes human VEGF, not murine VEGF.

The first clinical study analyzing the effects of bevacizumab on liver regeneration showed that bevacizumab had no effect on the increase in future liver remnant volume and the degree of hypertrophy after portal vein embolization.[3] In the current issue of *Annals of Surgical Oncology,* Aussilhou et al. present the second study on the effect of bevacizumab on liver regeneration in humans.[4] The authors report a decrease in hepatic regeneration induced by portal vein occlusion in patients who received extended oxaliplatin or irinotecan chemotherapy with bevacizumab compared with limited oxaliplatin or irinotecan chemotherapy with bevacizumab.

However, in interpreting these results, the effect of extended chemotherapy itself needs to be considered. In other words, was bevacizumab or extended chemotherapy responsible for the observed pathophysiologic effect on liver regeneration? Recent data from our group indicated that extended preoperative chemotherapy (nine or more cycles) was an independent predictor of postoperative hepatic insufficiency after hepatic resection for colorectal liver metastases.[5] We also found that bevacizumab significantly reduced the incidence of oxaliplatin-associated sinusoidal injury and that only duration of chemotherapy, not bevacizumab, independently predicted an increased risk of hepatic insufficiency.[5] These data, although not conclusive regarding liver regeneration, suggested that in patients treated with oxaliplatin, prolonged chemotherapy, rather than bevacizumab therapy, adversely affected hepatic regeneration.

Aussilhou et al. have provided a useful study focusing on the adverse effects of extended preoperative chemotherapy on hepatic function.[4] Their report, however, has to be considered preliminary because the group treated with short-course bevacizumab was small (three patients), and the authors do not present a separate comparison of the hypertrophy rate with or without bevacizumab in patients who received more than six cycles of chemotherapy. In summary, although the current report expands on previous studies indicating an increase in surgical complications with extended preoperative chemotherapy, the jury is still out on whether preoperative bevacizumab should be considered a black sheep in hepatic regeneration in humans.[6,7]

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