LETTER to the EDITOR

Bevacizumab: a New Potential Therapeutic Option in Sinusoidal Obstruction Syndrome

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Dear Editor

Sinusoidal obstruction syndrome (SOS; formerly hepatic veno-occlusive disease) is a well-established complication of hematopoietic stem cell transplantation, pyrrolizidine alkaloid intoxication, myeloablative regimen and widely used chemotherapeutic agents such as oxaliplatin. It is associated with substantial morbidity and mortality. Currently, oxaliplatin is widely used chemotherapeutic agent in the treatment of colorectal cancer patients in adjuvant and metastatic setting.

We observed that oxaliplatin-based chemotherapy used patients more frequently developed splenomegaly than the oxaliplatin-based chemotherapy plus bevacizumab in our colorectal patients. We also observed that splenomegaly that developed during oxaliplatin based chemotherapy regress rapidly the bevacizumab containing chemotherapy regimens.

The pathogenesis of SOS is poorly understood. SOS is an iatrogenic complication with significant mortality in transplantation patients. Heparin, prostaglandin E1, ursodeoxycholic acid, and pentoxifylline have been examined in randomized controlled trials for their ability to prevent SOS (DeLeve et al, 2009). Although widely used, no recommendation can be made for or against the use of prophylactic pharmacological strategies because none examined to date have consistently shown a reduction in the overall risk of SOS.

In previous studies, sinusoidal dilatation and hemorrhage were indeed found in 51% of liver specimens of hepatectomies performed after neoadjuvant chemotherapy, among which 79% had received oxaliplatin (Rubbia-Brandt et al., 2004). Hubert et al. reported the development of nodular regenerative hyperplasia and portal hypertension in three patients with metastatic colorectal cancer following the treatment with 5-FU-oxaliplatin based chemotherapy (Hubert et al., 2007).

Overman et al. reported the relationship between chemotherapy exposure and changes in spleen size. In that study, spleen size increased in 86% of patients and hepatic sinusoidal injury was reported in 22% patients treated with adjuvant fluoropyrimidine and oxaliplatin based chemotherapy (Overman et al., 2010). In another study Miura et al. reported that splenic volume index ≥50% increased in 20% percent of oxaliplatin based chemotherapy group whereas 6.6% in oxaliplatin based chemotherapy plus bevacizumab group. Also in that study, grade 2 or higher sinusoidal injury was only observed in the oxaliplatin based chemotherapy group (Miura et al., 2011).

Bevacizumab is a humanized monoclonal antibody that recognizes and blocks vascular endothelial growth factor (VEGF). VEGF is a chemical signal that stimulates the growth of new blood vessels (angiogenesis). Bevacizumab was approved by the FDA for use in metastatic colorectal, non-small cell carcinoma, glioblastoma, renal cell carcinoma and breast cancer patients.

VEGF is a key regulator of angiogenesis and is upregulated in a variety of disease states including malignacy, ocular disease and inflammatory conditions (Carmeliet et al; 2000). Bevacizumab is a humanized recombinant monoclonal antibody against VEGF. It induces the arrest of endothelial cell proliferation, thereby preventing vessel growth and causing the regression of existing vessels by increasing endothelial cell death (Carmeliet et al; 2005). In patient with hereditary hemorrhagic telengiectasia, which the high VEGF levels can be the cause of, Mitchell et al reported that bevacizumab treatment led to dramatic regression of hepatic vascular malformations and reversal of high output cardiac failure (Mitchell et al., 2008). In another study, bevacizumab improves pathologic response in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases with reduction in the incidence and severity of sinusoidal dilatation (Ribero et al., 2007). Rubbia-Brandt et al. reported that serum VEGF levels upregulated in oxaliplatin-related SOS patients. Activation of VEGF could partially explain at a molecular level the clinical observations that bevacizumab have a preventive effect in SOS (Rubbia-Brandt et al., 2011).

With these literature and our observations; it seems that bevacizumab prevents and hinder to progress of oxaliplatin related SOS. Current prophylactic pharmacotherapy for SOS is still unknown, hence antiVEGF therapy, bevacizumab may offer a promising new approach to the management of sinusoidal obstruction syndrome.

References

Carmeliet P (2005). Angiogenesis in life, disease and medicine. *Nature*, **438**, 932-6.

Carmeliet P, Jain RK (2000). Angiogenesis in cancer and other diseases. *Nature*, **407**, 249-57.

DeLeve LD, Valla DC, Garcia-Tsao A(2009). Vascular disorders of the liver. *Hepatology*, **49**, 1729-64.

Hubert C, TWO AUTHORS et al (2007). Nodular regenerative hyperplasia: a deleterious consequence of chemotherapy for colorectal liver metastases? *Liver Int*, **27**, 938-43.

Mitchell A, TWO AUTHORS et al (2008).Bevacizumab reverses

need for liver transplantation in hereditary hemorrhagic telangiectasia. *Liver Transpl*, **14**, 210-3.

Miura K, TWO AUTHORS et al (2011). Splenomegaly in FOLFOX-naive stage IV or recurrent colorectal cancer patients due to chemotherapy-associated hepatotoxicity can be predicted by the aspartate aminotransferase to platelet ratio before chemotherapy. *Int J Clin Oncol*, **??**, ??.

Overman MJ, TWO AUTHORS et al (2010). Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. *J Clin Oncol*, **28**, 2549-55.

Ribero D, TWO AUTHORS, et al (2007). Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. *Cancer*, **110**, 2761-7.

Rubbia-Brandt L, TWO AUTHORS, et al (2004). Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Ann Oncol*, **15**, 460-6.

Rubbia-Brandt L, TWO AUTHORS, et al (2011). Gene expression profiling provides insights into pathways of oxaliplatin-related sinusoidal obstruction syndrome in humans. *Mol Cancer Ther*, **10**, 687-96.

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