An Alternative Therapy for Patients with Hepatic Impairment?

Su-Pin Choo^a Alan P. Venook^a

^aMedical Oncology, National Cancer Centre, Singapore

^aDivision of Medical Oncology, UCSF Comprehensive Cancer Center, San Francisco, CA, USA

Patients with advanced cancer in the setting of liver dysfunction pose a real challenge for physicians, as many cancer chemotherapeutic agents undergo hepatic metabolism and their administration to patients with hepatic impairment often leads to compromise of patient safety. A large proportion of patients with colorectal cancer either present with or develop liver metastases and as a result, many of them have suboptimal liver function [1].

In this issue of ONKOLOGIE Moosmann et al. [2] present a case of a patient with diffuse liver metastases secondary to carcinoma of the colon who was treated successfully with the combination of bevacizumab and cetuximab despite having abnormal liver function parameters. This patient had previously failed capecitabine and oxaliplatin combination chemotherapy, making irinotecan-based chemotherapy with or without a targeted agent the standard second-line choice. However, this patient's bilirubin level was markedly elevated at 12.8 mg/dl, aspartate transaminase was elevated 8 times the upper limit of normal (ULN) at 390 U/l and the alanine transaminase was mildly elevated. Irinotecan's main metabolite, SN-38, is cleared primarily via liver glucuronidation and in the biliary system and several studies have shown that patients with bilirubin levels greater than 1.5 times ULN and transaminases greater than 5 times ULN were most susceptible to irinotecan toxicities. [3, 4]. Thus, irinotecan was not a viable option for this patient and most oncologists, faced with a similar situation, would probably have offered supportive care.

In this case, the authors opted to treat this patient with cetuximab and bevacizumab combined and achieved reduction in liver metastases. This was associated with a decrease of the bilirubin level to 1.9 mg/dl after 8 weeks of therapy, eventually rendering the patient amenable to further treatment with irinotecan-based chemotherapy.

Despite limited data on their use in colon cancer, the combined use of an epidermal growth factor (EGFR) inhibitor,

cetuximab, with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab is logical. Cetuximab as monotherapy in refractory colon cancer has modest activity with partial response rates of about 10% and stable disease in about 30% [5, 6] while bevacizumab alone achieves a stable disease rate of 29% and partial response rate of about 3% [7]. HER-1/EGFR is involved in angiogenesis [8] and its inhibition has been shown to cause VEGF down-regulation [9]. Furthermore, studies have shown that blockade of VEGF may also inhibit HER-1/EGFR autocrine signaling [10], thus suggesting the synergistic benefit of combining a VEGF inhibitor and an EGFR inhibitor. Several preclinical studies have investigated the anti-tumor activity of this dual blockade of EGFR and VEGF in colon cancer [11, 12].

To our knowledge, there have only been 2 studies that have looked at the combination of bevacizumab and cetuximab in colorectal cancer in the clinical setting. The phase II BOND II trial [13] randomized patients with irinotecan-refractory colorectal cancer to receive cetuximab (250 mg/m² weekly) and bevacizumab (5 mg/kg every other week) with or without irinotecan. Preliminary results showed that patients receiving cetuximab and bevacizumab achieved a partial response rate of 20% with time to treatment progression of 5.6 months, which was better than historical controls of patients receiving cetuximab alone ($p < 0.01$). The group receiving cetuximab, bevacizumab and irinotecan also had a better partial response of 37% and time to progression of 7.9 months compared to historical controls who received cetuximab and irinotecan alone ($p < 0.01$). No unexpected adverse effects were observed in either group of patients. This demonstrated the feasibility of this combination and its benefit in irinotecan-refractory, bevacizumab-naïve colorectal patients, with normal liver function. Similarly, results from a phase II study evaluating the combination of cetuximab and bevacizumab in colorectal patients who had failed irinotecan, oxaliplatin and fluoropy-

rimidine-based chemotherapy were presented recently [14]. In this small study, bevacizumab was given at 10 mg/kg every 2 weeks, while cetuximab was given per previous study. Amongst 14 patients evaluable for response, there was one partial response and the median time to progression was 2.4 months. While these studies suggest that this combination has activity in refractory colorectal cancer, they do not address the issue of patients with hepatic impairment.

Neither bevacizumab nor cetuximab have been reported to undergo hepatic metabolism. The use of bevacizumab in patients with liver dysfunction has not been studied [15]. In a population pharmacokinetics analysis, there was no correlation found between hepatic dysfunction and cetuximab pharmacokinetics [16]. Cetuximab has been used as a single agent in a phase II study in advanced hepatocellular carcinoma where 40% of the subjects had Childs-Pugh B liver cirrhosis. There was a non-significant trend towards higher mean serum trough cetuximab levels and a delay in achieving steady-state in those with mild to moderate hepatic impairment although this was not associated with increased toxicities. In this case report, the patient appeared to tolerate the combination of bevacizumab and cetuximab (which were given at the recom-

mended full doses) well with no significant toxicities except grade 3 skin rash.

Current clinical trials in colorectal cancer typically exclude patients with less than normal liver function status. Ongoing studies on advanced colorectal cancer patients with normal liver function will eventually tell us the optimal way of combining cetuximab and bevacizumab and other targeted therapy. With the ready availability of effective non-chemotherapy agents which do not rely on hepatic metabolism, more options are potentially available for cancer patients with hepatic impairment. As this case report illustrates, it is not unreasonable to offer targeted agents like cetuximab combined with bevacizumab (with careful monitoring) in a patient with advanced colon cancer and significant liver impairment, who cannot otherwise receive standard chemotherapy regimens. There is no doubt that more studies with targeted therapies need to be directed towards cancer patients with organ dysfunction to determine dosing and toxicities, and perhaps, in the future, this group of patients may no longer be relegated to receive 'just supportive care' but may be deemed fit enough to actually receive some effective life prolonging therapy.

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