Available online at www.sciencedirect.com

ScienceDirect

EJSO 40 (2014) 559–566

EJSO the Journal of Cancer Surgery

www.ejso.com

Splenic volume may be a useful indicator of the protective effect of bevacizumab against oxaliplatin-induced hepatic sinusoidal obstruction syndrome

K. Imai [a], Y. Emi [b], K.-I. Iyama [c], T. Beppu [a], Y. Ogata [d], Y. Kakeji [e], H. Samura [f], E. Oki [b], Y. Akagi [g], Y. Maehara [b], H. Baba [a,*], Kyusyu Study Group of Clinical Cancer (KSCC) ancillary study

[a] *Department of Gastroenterological Surgery, Graduate School of Life Sciences, Kumamoto University, Kumamoto, Japan*
[b] *Department of Surgery and Science, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan*
[c] *Department of Surgical Pathology, Kumamoto University Hospital, Kumamoto, Japan*
[d] *Department of Surgery, Kurume University Medical Center, Kurume, Japan*
[e] *Department of Surgery, Division of Gastrointestinal Surgery, Graduate School of Medicine, Kobe University, Kobe, Japan*
[f] *Division of Digestive and General Surgery, Faculty of Medicine, University of the Ryukyus, Okinawa, Japan*
[g] *Department of Surgery, Kurume University Hospital, Kurume, Japan*

Accepted 6 December 2013
Available online 20 December 2013

Abstract

Aims: The aim of this study was to investigate the relationship between the use of bevacizumab (Bmab) in addition to oxaliplatin (OX), the development of sinusoidal obstruction syndrome (SOS) and the changes in splenic volume as an indicator of the protective effect of Bmab against OX-induced SOS.
Methods: Seventy-nine patients who received OX-based chemotherapy with (OX + Bmab group: $n = 48$) or without Bmab (OX group: $n = 31$) for colorectal liver metastases were included in this study. The changes in splenic volume after chemotherapy were evaluated in the two groups. Furthermore, the relationship between the changes in splenic volume and SOS were analyzed in the 55 patients who underwent hepatectomy.
Results: A significant increase in the splenic volume was observed in the OX group, but not in the OX + Bmab group. The increase in the splenic volume relative to baseline was significantly higher in the OX group than in the OX + Bmab group (39.1% vs. 2.3%, $p < 0.0001$). The incidence of moderate or severe SOS was significantly higher in the OX group than in the OX + Bmab group (50.0% vs. 16.0%, $p = 0.0068$), and the increase in the splenic volume was significantly higher in the patients with SOS than in those without SOS (42.9% vs. 9.9%, $p = 0.0001$). A multivariate analysis identified the increase in the splenic volume as an independent predictor of the development of SOS. Conclusions: This study demonstrated that the inhibition of splenic volume enlargement might be a useful indicator of the protective effect of Bmab against OX-induced SOS.

Keywords: Sinusoidal obstruction syndrome; Colorectal liver metastases; Bevacizumab; Oxaliplatin; Splenic volume

Abbreviations: CRLM, colorectal liver metastases; OX, oxaliplatin; FU, fluorouracil; LV, leucovorin; SOS, sinusoidal obstruction syndrome; Bmab, bevacizumab; VEGF, vascular endothelial growth factor; FDA, Food and Drug Administration; FOLFOX, 5-fluorpuracil/leucovorin/oxaliplatin regimen; XELOX, capecitabine/oxaliplatin regimen; CT, computed tomography; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; HR, hazard ratio; ICG-R15, indocyanine green retention rate at 15 min.

* Corresponding author. Department of Gastroenterological Surgery, Graduate School of Life Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan. Tel.: +81 96 373 5211; fax: +81 96 371 4378.
E-mail address: hdobaba@kumamoto-u.ac.jp (H. Baba).

0748-7983/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejso.2013.12.009

Introduction

Colorectal cancer is one of the most common malignancies worldwide and its incidence has been rapidly increasing during the past few decades. The liver is the most common site of metastatic spread, and nearly half of the patients with colorectal cancer develop liver metastases at some point during the course of their disease.[1–3] In patients with liver-only metastases, liver resection remains the only treatment modality that potentially achieves long-term survival and offers the hope of a cure. Previous studies reported a five-year survival rate of 40–58% after potentially curative liver resection.[4–7] These favorable outcomes of patients with colorectal liver metastases (CRLM) are attributed not only to the improvements in surgical techniques and perioperative management, but also to the emergence of more effective chemotherapy.

However, only about 20% of patients with CRLM are eligible for liver resection.[8,9] In such patients with initially inoperable liver metastases, the recently introduced chemotherapeutic and biologic agents can increase the number of candidates for potentially curative resection.[8,10,11] When marked tumor shrinkage is obtained by chemotherapy, an unresectable tumor may become resectable, and in such cases, a favorable long-term outcome can be expected by hepatic resection with curative intent. In patients with initially unresectable liver diseases that become resectable after preoperative chemotherapy, the five-year survival rates have reached 30%.[8]

Oxaliplatin (OX), a third-generation platinum compound, is widely used in the treatment of CRC in combination with either 5-fluorouracil/leucovorin (FU/LV) or capecitabine. OX-based chemotherapy has been increasingly utilized in the adjuvant, neoadjuvant and metastatic settings. However, several studies have demonstrated sinusoidal obstruction syndrome (SOS) in the non-tumor-bearing liver in patients receiving preoperative OX-based chemotherapy, with an incidence of 19%–78%.[12–15] Other reports showed that OX-induced SOS was associated not only with intraoperative bleeding[15] and postoperative morbidity,[15,16] but also with early recurrence and a decreased overall survival.[17]

Bevacizumab (Bmab), a monoclonal humanized antibody directed against vascular endothelial growth factor (VEGF), was initially approved by the U.S. Food and Drug Administration (FDA) in 2004 for the first-line treatment of metastatic colorectal cancer based on a survival benefit,[18] and has been increasingly used in combination with chemotherapy before hepatic resection in patients with CRLM. Previous studies demonstrated that Bmab may prevent SOS in patients treated with OX-based chemotherapy for CRLM.[19,20]

In the current study, we investigated the relationship between the use of Bmab in addition to OX, the development of SOS and the changes in the splenic volume after chemotherapy to demonstrate the benefit of assessing the change in the splenic volume as an indicator of the protective effect of Bmab against OX-induced SOS.

Patients and methods

Seventy-nine patients with CRLM who received OX-based preoperative chemotherapy with or without Bmab between 2004 and 2012 were retrospectively analyzed in the current study. Thirty-nine patients were treated in the Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University (Kumamoto, Japan), and the remaining 40 were patients who were enrolled in the Kyushu Study Group of Clinical Cancer (KSCC) 0802 ancillary study. The patients treated in Kumamoto University were administrated preoperative chemotherapy with the intent of both neoadjuvant and conversion. KSCC 0802 study was a prospective multicenter phase II trial in Japanese patients, and the aim of this study was to evaluate the resectability and safety of mFOLFOX6 + Bmab on H2 and H3 liver-limited CRLM. The patients enrolled in KSCC 0802 study were also administrated chemotherapy with the intent of both neoadjuvant and conversion.

To elucidate the effects of Bmab, patients were grouped as follows: OX group ($n = 31$), patients who received OX-based chemotherapy without Bmab; OX + Bmab group ($n = 48$), patients who received OX-based chemotherapy with Bmab. In the OX group, 29 patients were treated with a 5-FU/LV/OX regimen (FOLFOX) and two patients were treated with a capecitabine/OX regimen (XELOX). In the OX + Bmab group, 47 patients were treated with a FOLFOX + Bmab regimen and one patient was treated with a XELOX + Bmab regimen. The exclusion criteria were patients with underlying chronic liver diseases, patients who had received previous OX- or irinotecan-based chemotherapy and patients who had received any chemotherapy within six months before initiation of the treatment. Although the patients treated at Kumamoto University received either the FOLFOX (FOLFOX4 or mFOLFOX6) or XELOX with or without Bmab regimen, the patients enrolled in the KSCC 0802 study received only the mFOLFOX6 with Bmab regimen.

Thirty of the 31 patients in the OX group underwent surgery, and 26 of the 48 patients in the OX + Bmab group underwent surgery. In the OX + Bmab group, one patient underwent exploratory laparotomy because the tumor was not detectable by intraoperative examinations, including ultrasonography. The remaining 55 patients underwent hepatic resection for CRLM. Hepatic resections were performed at least two weeks after the last course of chemotherapy. In the OX + Bmab group, the last cycle of chemotherapy was usually given without Bmab to establish a gap of five weeks between the last Bmab treatment and surgery. Major hepatectomy was defined as resection of three or more liver