Cancer Science
Japanese Cancer Association JCA
Open Access

Letter to the Editor

Response to Y. Sasaki *et al.*: Is repeating FOLFIRINOX in the original dosage and treatment schedule tolerable in Japanese patients with pancreatic cancer?

Cancer Sci **106** (2015) 1101–1102

doi: 10.1111/cas.12709

Dear Editor,

We have read the Letter to the Editor from Sasaki *et al.* on our clinical study results with great interest.[1] On reading this letter, we decided that we should provide a further explanation of the methodology and results of our study.

In this trial, the dosages of the study drugs were selected in exactly the same manner as in the phase II/III study (ACCORD11) conducted by Conroy *et al.*[2] in 2011. There were two reasons for the selection. First, it was unclear whether the expected efficacy could be achieved with a different dosing regimen. Second, to introduce the FOLFIRINOX therapy as early as possible in Japan, we used the same dosing regimen as that in the ACCORD11 study.

When we planned this trial, we already knew the results of the ACCORD11 study.[2–4] Therefore, we considered that it would be more appropriate to assess the safety of the FOLFIRINOX regimen on a large cohort of Japanese patients rather than to assess dose limiting toxicity in 3–6 patients with an escalation of the patient doses by conducting a typical phase I study. First, we evaluated the safety of the first 10 patients enrolled. If five or more patients discontinued the study treatment due to toxicity or if the independent data monitoring committee recommended the discontinuation or treatment, the study needed to be terminated. In the first 10 patients, we assessed whether or not the FOLFIRINOX regimen is totally unacceptable for Japanese patients. Subsequently, we assessed the efficacy and safety of the treatment based on the responses of all patients enrolled in this trial.

Considering the safety of the patients, we set more stringent inclusion/exclusion criteria than those in the ACCORD 11 study. Patients had to have adequate bone marrow function (neutrophil count $\geq 2000/mm^3$, total bilirubin $\leq$ upper limit of normal [ULN]) and those with *UGT1A1*6/*6,*28/*28,*6/*28* genotypes were excluded from the study. These parameters were not defined in the ACCORD 11 study. Furthermore, we had more frequent examinations and safer criteria for the dose modification than in the ACCORD 11 study, which might have led to the low dose intensity of some component agents.

As a result, the response rate that was the primary endpoint was comparable to that of the ACCORD11 study. Our findings suggest that the FOLFIRINOX regimen could be a new first-line standard treatment in Japanese patients with metastatic pancreatic cancer. The toxicities were slightly more severe in the present study than in the ACCORD11 study, which presumably is attributed to the more frequent laboratory tests in the present study in Japan. We performed the laboratory tests at least once a week until the end of the fifth cycle and every 2 weeks thereafter in this study, whereas initial laboratory tests were conducted only every 2 weeks in the ACCORD11 study. In addition, the use of PEG-G-CSF might have resulted in the lower toxicities in the ACCORD11 study.

Determining the appropriate dosing regimen for FOLFIRINOX therapy is a controversial issue not only in Japan but across the globe. Although several studies have been conducted to investigate the efficacy and safety of modified FOLFIRINOX regimens, the appropriate FOLFIRINOX regimen remains unclear.[5–9] Prospective studies of modified FOLFIRINOX regimens are being conducted in Japan, Europe and the USA. In the future, we anticipate the establishment of a modified FOLFIRINOX regimen that can control toxicity successfully without compromising efficacy.

Acknowledgment

Yakult Honsha Co., Ltd.

Disclosure Statement

Takuji Okusaka received research grants from Yakult Honsha and Kyowa Hakko Kirin; he has also received honoraria from Pfizer. Masafumi Ikeda, Akira Fukutomi and Junji Furuse received honoraria from Yakult Honsha. Hiroyuki Isayama and Narikazu Boku received honoraria from Yakult Honsha and Daiichi Sankyo. Tatsuya Ioka and Shinichi Ohkawa have no conflict of interest to declare.

Takuji Okusaka,[1] Masafumi Ikeda,[2] Akira Fukutomi,[3] Tatsuya Ioka,[4] Junji Furuse,[5] Shinichi Ohkawa,[6] Hiroyuki Isayama[7] and Narikazu Boku[8]

[1]*Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo,* [2]*Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Chiba,* [3]*Department of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka,* [4]*Department of Hepatobiliary and Pancreatic Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka,* [5]*Department of Medical Oncology, Kyorin University School of Medicine, Tokyo,* [6]*Department of Hepatobiliary and Pancreatic Oncology, Kanagawa Cancer Center, Yokohama City, Kanagawa,* [7]*Department of Gastroenterology, Graduate School of Medicine, the University of Tokyo, Tokyo,* [8]*Department of Clinical Oncology, St. Marianna University School of Medicine, Kanagawa, Japan*

Correspondence: Takuji Okusaka
E-mail: tokusaka@ncc.go.jp
Received May 23, 2015; Accepted May 26, 2015

References

1 Okusaka T, Ikeda M, Fukutomi A *et al.* Phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. *Cancer Sci* 2014; **105**: 1321–6.
2 Conroy T, Desseigne F, Ychou M *et al.* FOLFIRINOX versus gemcitabine for metastatic pancreas cancer. *N Engl J Med* 2011; **364**: 1817–25.
3 Ychou M, Conroy T, Seitz JF *et al.* An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin /5-fluorouracil every 2 weeks in patients with advanced solid tumors. *Ann Oncol* 2003; **14**: 481–9.
4 Conroy T, Paillot B, François E *et al.* Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer–A Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. *J Clin Oncol* 2005; **23**: 1228–36.
5 Mahaseth H, Brutcher E, Kauh J *et al.* Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. *Pancreas* 2013; **42**: 1311–5.
6 Oikonomopoulos GM, Syrigos KN, Skoura E *et al.* FOLFIRINOX: from the ACCORD study to 2014. *JOP (online)* 2014; **15**: 103–5.
7 Maroun J, Ko Y, Ghafoor A *et al.* Standard clinical practice of FOLFIRINOX in advanced pancreatic cancer patients: a Canadian registry. Madrid, ESMO 2014-09-26/30 (abstr 702P).
8 Vaccaro V, Sperduti I, Melisi D *et al.* Clinical impact of FOLFIRINOX dose/schedule modifications (mFOLFIRINOX) and additional supportive measures in the management of pancreatic cancer (PDAC) patients (pts). Madrid, ESMO 2014-09-26/30, *Ann Oncol* 2014; **25**(suppl 4): iv234 (abstr 690P).
9 Uesugi K, Asagi A, Hino K *et al.* Effects of dose-modified FOLFIRINOX on toxicity and effectiveness in Japanese patients with unresectable pancreatic cancer (PC). San Francisco, ASCO-GI 2015-01-15/17 (abstr 480).