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Letter to the Editor

Is repeating FOLFIRINOX in the original dosage and treatment schedule tolerable in Japanese patients with pancreatic cancer?

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Dear Editor,

The incidence of and mortality from pancreatic cancer are increasing in Japan. Pancreatic cancer remains one of the most serious malignancies.[1] Although phase III studies in patients with advanced pancreatic cancer report that overall survival is prolonged by gemcitabine alone[2] or gemcitabine plus nab-paclitaxel,[3] investigations of new treatment options are essential. Intensive three-drug combination chemotherapy with fluorouracil, oxaliplatin and irinotecan (FOLFIRINOX) can dramatically prolong overall survival in pancreatic cancer.[4] FOLFIRINOX was reported in this journal to have favorable efficacy and acceptable toxicity profiles in chemotherapy-naive Japanese patients with metastatic pancreatic cancer. However, a critical review of the article indicated that repeating FOLFIRINOX in the original dosage and treatment schedule is intolerable even in selected Japanese patients because the dose intensity of bolus fluorouracil was only 15.4%, and dose reduction and cycle delay were required by 88.9% of the patients.[5] The authors should have stressed the need for dose reduction and prolongation of treatment interval. We suppose that the study by Okusaka *et al.* underestimated toxicity in Japanese patients for several reasons. First, the authors and sponsor of the study did not adequately evaluate the safety of FOLFIRINOX because they did not conduct any phase I dose-escalation studies to determine the optimal dosage of the three drugs. We have reported the results of a phase I study of FOLFOXIRI in patients with colorectal cancer, which used a similar three-drug combination regimen,[6] and the recommended dosage was much lower than that in the study by Falcone *et al.*[7] Second, the threshold criteria defining tolerability in the 10 patients were unrealistically higher than the conventional criteria used to define dose-limiting toxicity in phase I trials.[6] Third, both the Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devises Agency strongly recommend that new drug applications in Japan should include the identical dosage and regimen used in global or bridging studies.[8] Topotecan was approved for the treatment of ovarian cancer in Japan on the basis of a "public knowledge-based application"without conducting large clinical trials; in clinical practice, however, the approved dose is too toxic for Japanese patients with ovarian cancer.[9] In conclusion, the dosage and treatment schedule of FOLFIRINOX combination chemotherapy should be more carefully evaluated in Japanese patients with pancreatic cancer treated in a clinical practice setting to avoid severe life-threatening toxic effects.

Disclosure Statement

The authors have no conflict of interest to declare.

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