Acta Oncologica, 2013; 52: 1778–1790

informa
healthcare

LETTERS TO THE EDITOR

Capecitabine, irinotecan (CAPIRI) and sunitinib in metastatic colorectal cancer

M. J. BOERS-SONDEREN[1], I. M. E. DESAR[1], M. KOOPMAN[2], C. J. PUNT[3] & C. M. L. VAN HERPEN[1]

[1]*Department of Medical Oncology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands,* [2]*Department of Medical Oncology, University Medical Center, Utrecht, the Netherlands and* [3]*Department of Medical Oncology, Academic Medical Center, University of Amsterdam, The Netherlands*

To the Editor,

Carrato et al. [1] recently published their results of a randomized phase III trial of fluorouracil (5-FU), leucovorin (LV) and irinotecan (FOLFIRI) plus either sunitinib or placebo in patients with metastatic colorectal cancer (mCRC). Intravenous FOLFIRI was administered every two weeks as irinotecan 180 mg/m^2, LV 200 mg/m^2 immediately followed by 5-FU 400 mg/m^2 bolus and 5-FU 2400 mg/m^2 as a 46-hour infusion. The dosage of oral sunitinib was 37.5 mg/day in a four-weeks on/two-weeks off schedule. The study failed to demonstrate superiority for FOLFIRI plus sunitinib and showed an increased incidence of grade ≥ 3 adverse events for this combination when compared to FOLFIRI plus placebo [neutropenia (68% vs. 30%), diarrhea (16% vs. 8%, thrombocytopenia (11% vs. 1%), anemia, stomatitis, fatigue, hand-foot syndrome and febrile neutropenia). Furthermore, more deaths as a result of toxicity (n = 12 vs. n = 4) and significantly more dose delays, dose reductions and treatment discontinuations occurred in the sunitinib arm.

We performed a phase I study in a standard 3 + 3 trial design with capecitabine, irinotecan (CAPIRI) and sunitinib in patients with mCRC as second line treatment (NCT00777478). Both capecitabine and irinotecan were administered at a reduced starting dose (capecitabine 850 mg/m^2 on day 1–14 and irinotecan 200 mg/m^2 on day 1, every three weeks) due to the expected additive toxicities of the combination with sunitinib. This study was approved by the medical ethical committee and was conducted in accordance with the Principles of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

We treated four patients at dose level 1, with sunitinib given at 25 mg/day continuously, and observed two dose limiting toxicities (DLTs): a grade 3 neutropenia lasting more than seven days and a delay of more than 14 days of the second cycle because of neutropenia and thrombocytopenia. According to protocol we subsequently treated the following patients at a lower dose level with sunitinib 12.5 mg/day continuously. Both patients at this dose level experienced neutropenia grade 3, which led to dose delays of irinotecan and dose interruptions of sunitinib and capecitabine. In one of these two patients, sunitinib was definitively withdrawn after cycle 4 and thereafter this patient did not experience any hematological toxicities anymore, even when the dose of irinotecan was escalated. As any clinical benefit was not expected with lower doses of sunitinib with already reduced doses of capecitabine and irinotecan, the study was discontinued and we concluded that a combination of CAPIRI with sunitinib was not feasible.

FOLFIRI, in comparison to CAPIRI, is associated with less adverse events as has been shown in a phase III trial, in which patients were randomized between treatment with FOLFIRI and CAPIRI [2]. Grade 3 to 4 nausea, vomiting, diarrhea and dehydration occurred significantly more frequently in the CAPIRI arm, and neutropenia occurred more frequently in the FOLFIRI arm (43% vs. 32%). Although these data show that CAPIRI is associated with a higher incidence of toxic events, it is considered as a

Correspondence: M. J. Boers-Sonderen, Department of Medical Oncology, 452, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel: + 31 24 3610353. Fax: + 31 24 3615025. E-mail: m.boers-sonderen@aig.umcn.nl

(Received 15 April 2013; accepted 15 May 2013)

ISSN 0284-186X print/ISSN 1651-226X online © 2013 Informa Healthcare
DOI: 10.3109/0284186X.2013.806994

feasible regimen. The CAIRO study included the largest patient cohort that received the same CAPIRI regimen (capecitabine 1000 mg/m^2 and irinotecan 250 mg/m^2) as first line treatment (n = 402) [3]. The most frequently occurring grade ≥ 3 adverse event in this study was diarrhea (26%). Neutropenia was observed in only 7% of the patients, whereas anemia and thrombocytopenia occurred both in 1% of patients. This study showed CAPIRI to be a feasible regimen which does not require the inconvenience of using ambulatory infusion devices and more frequent patient visits as is the case with FOLFIRI [3,4]. In general practice, both CAPIRI and FOLFIRI can thus be used. In the light of the high incidence of mostly hematological toxicities that occur when adding sunitinib to either regimen, it is important to notice that the incidence of hematological toxicities does not differ between CAPIRI and FOLFIRI.

In the study of Carrato et al. sunitinib 37.5 mg/day was dosed in the four-weeks on/two-weeks off schedule, whereas we started with 25 mg/day continuously. Thereby, the total dosage of sunitinib in our study during six weeks was higher, which may have contributed to the observed toxicity. Taken together, these data show that sunitinib cannot be combined with CAPIRI or FOLFIRI regimens.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Carrato A, Swieboda-Sadlej A, Staszewska-Skurczynska M, Lim R, Roman L, Shparyk Y, et al. Fluorouracil, leucovorin, and irinotecan plus either sunitinib or placebo in metastatic colorectal cancer: A randomized, phase III trial. J Clin Oncol 2013;31:1341–7.

[2] Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: Results from the BICC-C Study. J Clin Oncol 2007;25:4779–86.

[3] Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FLG, et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): A phase III randomised controlled trial. Lancet 2007;370:135–42.

[4] Punt CJ, Koopman M. Capecitabine and irinotecan as first-line treatment of advanced colorectal cancer. J Clin Oncol 2008;26:1907–8; author reply 1908–9.