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LETTER TO THE EDITOR

New recommendation of doses in an ongoing phase II study of docetaxel, oxaliplatin and capecitabine as first line therapy in advanced gastro-oesophageal cancer

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To the Editor,

Recently we reported our results from a phase I study of docetaxel, oxaliplatin and capecitabine (TEX) as first line therapy to patients with advanced gastro-oesophageal cancer [1]. To establish the recommended dose (RD) for further therapy, a total of 23 patients were enrolled in cohorts of three at five different dose levels. The TEX regimen was investigated in order to find an easily administered, well tolerated three weeks regimen in the out-patient setting, maintaining the efficacy of DCF (docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 and 5-FU 750 mg/m^2/d day 1–5 every three weeks) seen in the V-325 trial [2]. At dose level V, two of four patients experienced dose limited toxicity (DLT) and therefore we included additional seven patients at dose level IV. Only one of seven patients experienced DLT but because of hematologic toxicity dose-intensity was reduced to 75% in four of seven patients after three courses of TEX. Overall eight patients (35%) had febrile neutropenia. Probably, the use of granulocyte colony-stimulating factor (G-CSF) might have minimized these problems, but since it is not recommended routinely in the palliative setting in Denmark, we decided to use dose level III as the RD for the ongoing phase II study. Our phase I trial was not designed to evaluate efficacy but we found a promising response rate (RR) of 35%, progression free survival (PFS) of 9.4 months and overall survival (OS) of 12.5 months indicating high efficacy of this three-drug combination.

Due to a case of febrile neutropenia grade 5 in phase II we evaluated toxicity in all six patients who had completed therapy. In spite of the safety data seen at dose level III in phase I, we observed substantial hematologic toxicity in all six patients. Therapy was administered with a median of seven courses (range 6–8). Neutropenia grade 3 or 4 was observed in all six patients and furthermore all patients were hospitalized with febrile neutropenia. One patient had fatal sepsis after the eight course of TEX. Dose reduction of 25% was performed early (after course one, two or three) in all patients because of hematologic toxicity (Table I). Peripheral neuropathy grade 3 was observed in three (50%) patients, diarrhoea in two (33%) patients and nail toxicity in two (33%) patients, respectively. Despite early dose reduction, efficacy is promising. Three patients obtained complete response (CR) and three patients obtained partial response (PR) (Table I).

In order to maintain treatment cadence without dose reductions and hopefully lesser toxicity we amended the phase II protocol and reduced the dose of docetaxel with 15% to 51 mg/m^2 and the dose of oxaliplatin from 115 to 100 mg/m^2 [3]. The new recommendation has been amended to and approved by the local ethics committee and the Danish Health Authority. Very recently a randomized phase II trial evaluating the DCF regimen with prophylactic G-CSF versus a modified DCF (mDCF) regimen was presented at ASCO 2010 [4]. The mDCF arm was administered every second week with doses of docetaxel and cisplatin at 40 mg/m^2 respectively, and FU 400 mg/m^2, leukovorin 400 mg/m^2 and FU 1000 mg/m^2/days 1 and 2. The DCF+ G-CSF arm was closed prematurely due to unacceptable grade 3–4 toxicity,

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Table I. Treatment and toxicity among the first six patients completing TEX in phase II.

Patient number	A	B	C	D	E	F
No. of courses	7	8	7	6	8	6
Dose reduction after course no.	1	2	1	1	3	3
Response	CR	PR	CR	CR	PR	PR
Hematologic toxicity (grade 3–5)						
Neutropenia	4	4	4	3	3	3
Febrile neutropenia	3	5	3	3	3	3

neutropenia 74% and febrile neutropenia 16%. In the mDCF arm both neutropenia and febrile neutropenia grade 3–4 was reduced to 54% and 9% respectively. The mDCF regime appeared considerably more tolerable without compromising efficacy with RR at 52% and OS 15.1 months indicating it is possible to reduce doses of docetaxel [4]. The new RD for our ongoing phase II study is docetaxel 51 mg/m², oxaliplatin 100 mg/m² every third week and oral capecitabine 625 mg/m² twice daily continuously.

We are sorry for the inconvenience our phase I manuscript may have caused.

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