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ORIGINAL ARTICLE

Addition of sunitinib to cetuximab and irinotecan in patients with heavily pre-treated advanced colorectal cancer

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Abstract

Results of continuous sunitinib, in combination with cetuximab and irinotecan every other week (SIC) for compassionate use in heavily pre-treated patients with mCRC are presented. *Patients and methods*. Patients with mCRC resistant to oxaliplatin, irinotecan, 5-FU and cetuximab received SIC at two Danish oncologic departments. The regimen consisted of sunitinib given as a continuous-dosing in combination with cetuximab and irinotecan every other week (CetIri). The first six patients started with a daily oral dose of sunitinib of 12.5 mg. Subsequent patients started at a daily dose of 25 mg with the possibility to escalate to 37.5 mg. *Results*. Twenty-nine patients received SIC. No patient had an objective response, but 13 patients had subjective relief and 42% had stable disease. The median time to progression was 3.2 months and median overall survival was 7.4 months. Fatigue and leukopenia were the most frequently reported severe adverse event (18% grade 3 and 18% grade 3/4, respectively). *Discussion*. Sunitinib continuous-dosing with 25 mg/day can safely be combined with CetIri administered every other week.

Over the last years, new medical treatment options and treatment modalities have been implemented in the treatment of patients with metastatic colorectal cancer (mCRC) resulting in a marked improvement in overall survival (OS) [1].

As third line therapy, the combination of cetuximab and irinotecan (CetIri) improves progression free survival (PFS) and OS [2,3]. Originally CetIri was administered as a weekly infusion [2], however CetIri can also be administered every other week without compromising the efficacy [4,5]. Despite progressive disease on CetIri, many patients maintain an excellent performance status but so far no treatment has proven effective in this setting. Development of new treatment regimens for this selected group of patients is warranted.

Sunitinib is an oral, multi-targeted tyrosine kinase inhibitor of tyrosine kinase receptors (VEGFRs, PDGF-R, c-KIT, RET and FLT3) [6]. Sunitinib as single agent is approved for treatment of gastrointestinal stromal tumour (GIST) and advanced renal cell carcinoma (RCC). Sunitinib was shown to induce substantial tumour regression in human colon cancer xenograft models [7]. Efficacy in other solid tumours has been demonstrated in phase II trials [6].

A preclinical study have suggested that an increased angiogenic potential may be involved in the mechanism behind resistance to anti-EGFR antibodies [8]. In the BOND-2 study [9], patients with pre-treated mCRC receiving a combination of irinotecan, cetuximab and bevazicumab had a higher response rate and longer PFS compared to historical data from BOND-1, as well as an acceptable toxicity profile [2]. Inspired by these data, we designed a regimen consisting of CetIri every other week [4] and sunitinib (SIC). To our knowledge, no data have been published on this combination.

In January 2003, the Danish government launched a national health programme for experimental therapy to patients with advanced cancer. This gave the physician in charge the possibility to request an independent assessment on potential further treatment

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from a national oncologic expert panel. If this panel recommended additional treatment, the National Board of Health would subsequently cover the costs [10]. The programme has accelerated the introduction and implementation of new regimens. The "Second Opinion Panel" was often consulted for suggestions for further therapy in Denmark or abroad to patients with mCRC resistant to cetuximab, irinotecan, oxaliplatin and 5-FU. Therefore, the Danish National Health Authorities approved compassionate use of SIC at two Danish oncologic departments with "experimental units". In this retrospective study we report the first series of heavily pre-treated patients treated with SIC at two Danish experimental oncologic departments.

Material and methods

In this report we included patients with heavily pre-treated histologically confirmed non-resectable colorectal adenocarcinoma, who started compassionate treatment with SIC at either of two Danish departments of experimental oncology.

Each patient case was evaluated by the "Second Opinion Panel" established by the Danish Health Authorities [10] and was referred to treatment with SIC at the two experimental units. Information on KRAS status or EGFR expression was not required.

Sunitinib was given as a continuous-dosing schedule in combination with biweekly CetIri [4]. The first six patients received sunitinib at a daily dose of 12.5 mg for four weeks. If no severe or unsuspected toxicity was observed, then the daily dose was increased to 25 mg. In the following patients sunitinib was administered at a starting dose of 25 mg once daily. Depending on individual patient tolerance, the daily dose could be escalated to 37.5 mg after four weeks of therapy. Cetuximab 500 mg/m^2 was infused in only 60 minutes, immediately followed by irinotecan 180 mg/m^2 in 30 minutes resulting in a total treatment time of only 90 minutes. Courses were repeated every two weeks and therapy was continued until disease progression or unacceptable toxicity.

Tumour response was routinely assessed with either CT or MR scans every eight weeks according to the RECIST v. 1.0.

Routine pre-treatment evaluation included a medical history, physical examination, complete blood count, chemistry profile of renal and liver function, thyroid function and a radiological tumour evaluation. A complete blood count was obtained prior to each irinotecan infusion.

Toxicity was prospectively evaluated according to NCI-CTCAE v3.0. In the case of toxicity grade 3 or 4, drug doses were reduced by 25% in the subsequent treatment cycles.

Data were recorded and analysed in a Medlog® database. Non-parametric statistics were applied. All median values are followed by range in brackets. PFS was calculated from the first administration of SIC to the first observation of disease progression, to death from any cause, or to the most recent assessment. OS was calculated as the period from the first administration of SIC until death from any cause. Data were updated October 1, 2009. Both PFS and OS were estimated by the Kaplan-Meier method.

Results

Patient characteristics

Patient characteristics are listed in Table I. Twenty-nine patients started therapy with SIC between March 2007 and November 2008. All patients had been exposed to 5-FU, oxaliplatin, irinotecan and cetuximab. In addition, three patients had received bevacizumab (when these patients received first or second line therapy, bevacizumab was not recommended by the Danish Health Authorities routinely). Median age was 60 years (33–74), 19 patients were males.

The median time interval from diagnosis of non-resectable disease to start of therapy with SIC was 29 months (14.5–89) (Table II). Most patients were in a good performance status (PS) with four patients in PS = 0, 21 patients in PS = 1 and four patients in PS = 2.

Efficacy

Efficacy data are listed in Table II. The median duration of therapy with SIC was 9.7 weeks (3.9–37) and the median number of SIC was 4 (2–17). There was no objective response, however 42% had stable disease with a median duration of 6.1 months (4.4–6.6 months), and 13 patients experienced subjective relief of tumour symptoms after introduction of SIC. Median PFS was 3.2 months (95% CI: 2.1–4.6 months) and median OS was 7.4 months (95% CI: 5.1–9.1 months) (Figure 1).

Table I. Characteristics for 29 patients treated with SIC.

Characteristic	Biweekly CetIri and sunitinib
Treatment period	March 2007 to November 2008
Age, years (median, range)	60 (33-74)
Sex (male/female)	19/10
WHO performance status	
0	4 (14%)
1	21 (72%)
2	4 (14%)
Number of organs involved	
1	5 (17%)
2	9 (31%)
3+	15 (52%)

Table 2. Treatment Characteristics and Efficacy of SIC.

	Biweekly CetIri and sunitinib
Number	29
Time from non-resectable disease to indication for SIC, months (range)	28.9 (14.5-89)
Median number of weeks of treatment with sutent, weeks (range)	9.7 (3.9-37)
Median numbers of treatment with SIC, numbers (range)	4 (2-17)
Response rate	
Complete response (CR)	0 (0%)
Partial response (PR)	0 (0%)
Stable disease (NC)	12 (42%)
Progression (PD)	14 (48%)
Not evaluable	3 (10%)
Median PFS, months (95% CI)	3.2 (2.1-4.6)
Median OS, months (95% CI)	7.4 (5.1-9.1)

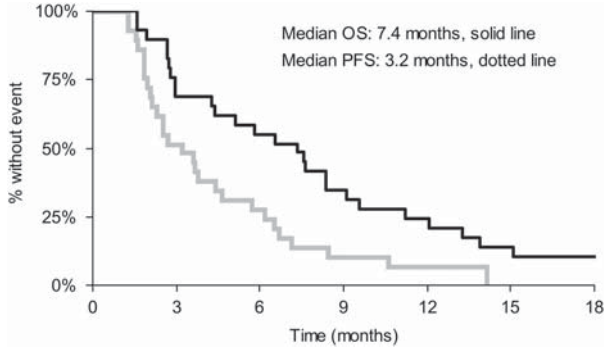

Figure 1. Kaplan-Meier curve of PFS (grey line) and OS (black line) for 29 patients treated with CetIri every other week in combination with sunitinib after PD to CetIri.

Toxicity

Toxicity was modest. CTCAE grades 2 and 3–4 are shown in Table III.

Grade 3 or 4 events included leucopenia (18%), fatigue (18%), diarrhoea (7%), skin toxicity (10%) and nail changes (3%). In addition, one patient had bleeding grade 3 from upper GI-tract and 1 patient was reported to have grade 4 hypomagnesiemia. No patient had an allergic reaction to cetuximab. No patient died due to toxicity.

Discussion

This is the first report on the combination of sunitinib, cetuximab and irinotecan in heavily pre-treated patients with mCRC.

Sunitinib can be delivered either in an intermittent or in a continuous-dosing schedule. Concerns have been raised to the continuous-dosing schedule due to potential accumulation of sunitinib and its products [6]. However, evidence suggests that the activity of sunitinib is diminished in the dosing free intervals in the intermittent-dosing schedules in patients with RCC and GIST tumours [6]. Furthermore, phase II data in patients with RCC [11] and GIST [12] show that the continuous-dosing regimen of single agent sunitinib is tolerable at a starting dose of 37.5 mg. We therefore chose to use a continuous-dosing schedule of sunitinib.

Table 3. Toxicity of SIC.

	Grade		
Toxicity	2	3	4
Skin (%)	14	10	0
Nail (%)	3	3	0
Diarrhoea (%)	22	7	0
Nausea (%)	9	0	0
Vomiting (%)	6	0	0
Fatigue (%)	36	18	0
Leucopenia (%)	7	11	7
Thrombocytopenia (%)	0	0	0
Anaphylactic reaction (%)	0	0	0

A phase I study evaluating sunitinib 37.5 mg in an intermittent-dosing schedule in combination with FOLFIRI in patients with treatment-naïve mCRC showed that this combination was generally well-tolerated. Enrolment in a continuous-dosing schedule of sunitinib in combination with FOLFIRI is planned [13]. In a preclinical study on colon carcinoma xenografts treated with sunitinib, it was shown that several gene products, including amphiregullin, were up-regulated, giving a biological rationale for combining sunitinib with an EGFR-receptor inhibitor [14].

In our institutions, we routinely administer CetIri as a simplified regimen dispensed in only 90 minutes every other week based on pharmacokinetic data [15] as well as reported clinical experiences [4].

None of our heavily pre-treated patients experienced an objective response but 12 patients had stable disease with a median duration of 6.1 months. Furthermore, 13 patients had subjective benefit from the treatment.

In the study by Jonker et al. [16] comparing cetuximab single agent to best supportive care (BSC) in heavily pre-treated patients, the median survival in the BSC arm was 4.6 months, and the proportion surviving at six months was 33%, and 24% had no documented progression at three months. In the present study, where patients were heavily pre-treated, the median survival was 7.4 months. This could be due to selecting bias, but SIC may have postponed progression and death in some patients.

The most frequent adverse events to treatment with sunitinib are fatigue and diarrhoea [11,12,17]. In general, SIC was well-tolerated, however as expected

both fatigue and diarrhoea were among the most often reported severe adverse events in the present study. Furthermore, 18% of patients had grade 3–4 leucopenia; however no patient was lost due to toxicity.

Phase I, II and III studies of sunitinib in combination with irinotecan as well as oxaliplatin based chemotherapy are ongoing in patients with mCRC (www.clinicaltrial.gov) but hardly any data are presently available.

In a phase II study [17], single agent sunitinib was administered at a daily dose of 50 mg in an intermittent dosing schedule (for four consecutive weeks, followed by two weeks off treatment, in repeated six week cycles) in patients with heavily pre-treated mCRC. Single agent sunitinib failed to demonstrate a meaningful response. However, the authors concluded that the mode of action along with an acceptable safety profile could facilitate its incorporation into standard combination regimens for mCRC, particularly in patients less exposed to previous treatment.

We conclude that the combination of a continuous-regimen sunitinib, administered in a starting dose of 25 mg/day, with full dose cetuximab and irinotecan is well tolerated without any unexpected toxicities. The activity of SIC in heavily pre-treated patients with mCRC might be of interest when compared to historical data. However, it should be stressed that this group of patients is highly selected, and therefore SIC has to be tested properly before using it in a daily routine.

Declaration of interest: The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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