ACTA ONCOLOGICA, 2016
VOL. 55, NO. 7, 881–885
http://dx.doi.org/10.3109/0284186X.2016.1161825

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ORIGINAL ARTICLE

Experience with S-1 in older Caucasian patients with metastatic colorectal cancer (mCRC): Findings from an observational chart review

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ABSTRACT

Background: An aging population will increase the number of older patients with metastatic colorectal cancer (mCRC). However, there is limited knowledge about treatment in older patients as they are under-represented in clinical trials. The oral fluoropyrimidine S-1 is associated with a lower rate of adverse events than capecitabine and may therefore be a suitable drug for elderly. However, data on the use of S-1 in Caucasian mCRC patients are lacking/scarce. **Material and methods**: In the present study we evaluated safety and the efficacy of S-1 alone or in combination with oxaliplatin (SOx) or irinotecan (IRIS) in older mCRC patients. Patients who received at least one cycle of S-1 (first-line therapy), SOx (mainly first-line therapy) or IRIS (second-line therapy) were included. **Results**: From June 2012 to December 2014, 71 older patients received $\geq$1 cycle of either S-1 ($n = 9$), SOx ($n = 44$) or IRIS ($n = 18$) for mCRC. Median age was 76 years and most patients had a WHO performance status of 0 (32%) or 1 (56%). All patients were evaluable for response and safety. In the SOx group, 18 (41%) and 20 patients (45%) had partial response (PR) and stable disease (SD), respectively (disease control rate 86%). Median progression-free survival (PFS) was 8.5 months and median overall survival (OS) was 18.5 months. In the S-1 group (median age 82 years), PR was 22%, median PFS 6.4 months and median OS 15.8 months. In the IRIS group, PR was 28%, median PFS 7.8 months and the median OS 16.5 months. In general, therapy was well tolerated; main non-hematological toxicities were fatigue and diarrhea. **Conclusion**: S-1 monotherapy, SOx and IRIS were well tolerated for older patients with mCRC and could become alternative regimens in older mCRC patients. These regimens are now further evaluated in the randomized ongoing NORDIC9 trial.

ARTICLE HISTORY
Received 27 January 2016
Revised 22 February 2016
Accepted 28 February 2016
Published online 13 May 2016

The incidence of colorectal cancer (CRC) is strongly related to age, increasing sharply from the age of 50 years and reaching a peak at age >80 years [1]; approximately half of patients diagnosed with CRC are $\geq$70 years of age. Patients receiving first-line combination chemotherapy regimens as part of clinical trials generally have a median overall survival (OS) of over 20 months [2]. However, in unselected populations of patients with metastatic colorectal cancer (mCRC), median OS falls to around half this time [3,4]. The low overall median OS in unselected patients from the general population is at least partly due to shorter survival in older patients, who appear to be 'undertreated' [5,6]. Indeed, while older patients with a good performance status/physical health can be treated with a combination of a fluoropyrimidine with oxaliplatin or irinotecan, 'real-life' clinical studies have shown that monotherapy is often utilized in older patients [7]. Given that older cancer patients are under-represented in standard clinical trials, patients from large studies are therefore not representative of the majority of older patients who are treated in everyday clinical practice.

The third-generation oral fluoropyrimidine S-1 (Teysuno®) is associated with a lower rate of adverse events than capecitabine, particularly hand-foot syndrome (HFS) [8–10]. S-1 is currently approved for several indications including gastric, colorectal, non-small cell lung, breast, pancreatic, biliary tract and head and neck cancer in Japan but only for gastric cancer in the European Union. Study data on the use of S-1 in Caucasian mCRC patients are therefore lacking/scarce. Nevertheless, in the summer of 2012 we began switching patients who were troubled by HFS or gastrointestinal (GI) toxicity from capecitabine to S-1 at our institutions.

In the current observational chart review, the primary aim was to evaluate the safety of S-1 (monotherapy or combination therapy with oxaliplatin (SOx) or irinotecan (IRIS)) in older mCRC patients.

Material and methods

Patients

This was an observational chart review from two Nordic Oncologic Institutions. We included older patients with mCRC who received at least one course of S-1 treatment between June 2012 and December 2014.

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Therapy and treatment regimens

The optimal schedule of S-1 and irinotecan or oxaliplatin has not been well established in Caucasian patients with mCRC [10], but based on data from Asian patients and knowledge from the use of other oral fluoropyrimidines in Caucasian patients with mCRC we used the following doses:

S-1 monotherapy

Standard full dose S-1 monotherapy in Caucasian patients is 30 mg/m^2 orally twice daily on Days 1–14 every three weeks. However, in patients aged 80 years or older we recommended reducing the dose of S-1 to 25 mg/m^2 orally twice daily.

S-1 with oxaliplatin (SOx)

S-1 (25 mg/m^2 orally twice daily on Days 1–14) with oxaliplatin (130 mg/m^2 iv on Day 1) every three weeks.

S-1 with irinotecan (IRIS)

S-1 (25 mg/m^2 orally twice daily on Days 1–14) with irinotecan (200 mg/m^2 iv on Day 1) every three weeks.

In patients with moderate renal impairment (GFR 30–49 ml/min), the dose of S-1 should be reduced (monotherapy to 25 mg/m^2). In patients with GFR $\geq$ 50 ml/min no dose reduction was recommended.

Therapy was continued until a planned number of 6–8 courses, unless disease progression or unacceptable toxicity was registered. For patients who developed grade 4 hematological toxicity or grade 3 non-hematological toxicity it was recommended to reduce the doses of S-1 and oxaliplatin/irinotecan to 75% of the initial starting doses. Prophylactic granulocyte-colony stimulating factor (G-CSF) support was not used in any patients.

Safety evaluation

All patients were as a routine evaluated prospectively for toxicity according to NCI-CTCAE (version 3.0) during each course of therapy. Nadir hematology was evaluated 10–14 days after the first cycle.

Efficacy evaluation

Investigators evaluated response using a computed tomography (CT) scan of the thorax and abdomen after every three cycles (every nine weeks) according to RECIST (version 1.1). In patients given a treatment break without disease progression (PD), a CT scan was performed every three months. Other clinical characteristics were retrieved from patient records and entered into a database (MedLog).

Progression-free survival (PFS) and OS were calculated from the first administration of chemotherapy (for the actual line of therapy) to the first observation of PD or death from any cause with censoring on 1 September 2015. The Kaplan-Meier method was used to estimate the distribution of time to events for PFS and OS.

Results

Patient characteristics

Since June 2012, we treated 71 older mCRC patients with S-1 monotherapy or combination therapy, as first- or later-line therapy. Patient characteristics, separated by regimen, are shown in Table 1.

Combination of S-1 with oxaliplatin

The median age was 75 years (range 67–83 years) in the SOx group and the majority of patients (32% and 52%) had a WHO performance status (PS) of 0 or 1, respectively. Six SOx patients had received prior adjuvant therapy with capecitabine and seven patients had received prior first-line therapy (capecitabine $n = 2$, S-1 $n = 3$, CapIri $n = 1$, FOLFIRI with cetuximab $n = 1$); 37 patients received SOx as first-line therapy. Thirty-three patients received the SOx regimen as initial treatment, but 11 patients started therapy with a combination of oxaliplatin and capecitabine (CapOx) and subsequently switched to SOx after one ($n = 7$) or two ($n = 4$) cycles due to toxicity (GI toxicity $n = 9$, HFS $n = 2$). All 44 patients were evaluable for response and toxicity.

Thirty-two patients (73%) completed at least six cycles of therapy. Other reasons for discontinuing chemotherapy included poor PS/clinical PD (11%), radiological PD (7%), and toxicity/patient's decision (9%). Twenty-seven patients (61%) started with full dose therapy and 17 patients started with reduced dose SOx (prior therapy $n = 8$, poor PS $n = 2$, age $n = 6$, comorbidity $n = 1$). In addition, five patients had dose reduction of S-1, typically after the third or fourth cycle of therapy.

All 44 patients received a total of 251 cycles of oxaliplatin, of which 225 cycles were in combination with S-1. The median relative dose intensities for oxaliplatin and S-1 were 82% and 88%, respectively (Table 1). Three patients received only one cycle of S-1, (patients' decision $n = 2$; death due to febrile neutropenia $n = 1$).

Eighteen (41%) and 20 patients (45%) had partial response (PR) and stable disease (SD), respectively resulting in a disease control rate (DCR) of 86%. The median PFS was 8.5 months and the median OS was 18.5 months (Table 2).

Adverse events are summarized in Table 3. The most common non-hematological adverse events were fatigue (80% of patients), neuropathy (70%), diarrhea (48%), and nausea (34%). Adverse events were generally mild in nature with grade 3 fatigue and grade 3/4 diarrhea being observed in 14% and 11% of the patients, respectively. The rate of HFS was very low (7%, all grade 1). Hematological adverse events were rare and only two patients (5%) developed febrile neutropenia.

Combination of S-1 with irinotecan

IRIS was mainly administered as second- or later-line therapy; 15 patients had received prior oxaliplatin-based therapy for metastatic disease, three patients had received prior capecitabine or S-1 but no oxaliplatin (because of preexisting

Table 1. Characteristics for 71 older patients receiving S-1 for mCRC. SOx was received as primary first-line therapy, S-1 was received as first-line therapy and IRIS was received as primary second-line therapy.

Characteristic	SOx	S-1	IRIS
Number	44	9	18
Median age, years (range)	75 (67–83)	82 (78–87)	73 (67–82)
Gender, *n* (%)			
Male	26 (59)	5 (56)	11 (61)
Female	18 (41)	4 (44)	7 (39)
WHO PS, *n* (%)			
0	14 (32)	2 (29)	7 (39)
1	23 (52)	7 (71)	10 (55)
2	7 (16)	0 (0)	1 (6)
No. of patients starting with capecitabine	11	0	0
Number of cycles, median (range)	6 (1–9)	8 (1–9)	6 (3–9)
Patients starting full dose chemotherapy, *n* (%)	27 (61)	9 (100)	15 (83)
S-1 dose intensity, % (IQR)	88 (76–99)	100*	87 (40–103)
Oxaliplatin/irinotecan dose intensity, % (IQR)	82 (76–97)	–	97 (75–100)
Median oxaliplatin cumulative dose, mg (IQR)	629 (446–771)	–	–
Reason for S-1 discontinuation *n* (%)			
Completed at least 6 cycles	32 (73)	6 (67)	10 (56)
Poor PS, clinical PD	5 (11)	1 (11)	1 (6)
PD	3 (7)	0	5 (27)
Toxicity or patients' wish	4 (9)	2 (22)	2 (11)
First-line therapy, *n* (%)	37 (84)	9 (100)	0
Prior adjuvant therapy, *n* (%)	6 (14)	0	4 (22)

*All nine very old patients started and continued with S-1 25 mg/m^2 twice daily.
IQR, interquartile range.

Table 2. Outcome data for 71 older patients receiving S-1 for mCRC.

	SOx	S-1	IRIS
Number of patients	44	9	18
First-line therapy, *n* (%)	37 (84)	9 (100)	0
Complete response (CR)	0	0	0
Partial response (PR), *n* (%)	18 (41)	2 (22)	5 (28)
Stable disease (NC), *n* (%)	20 (45)	6 (67)	9 (50)
Progression (PD), *n* (%)	3 (7)	1 (11)	4 (22)
Not evaluable, *n* (%)	3 (7)	0	0
Median PFS, months (95% CI)	8.5 (7.4–9.6)	6.4 (4.0–9.2)	7.8 (4.0–9.6)
Median OS, months (95% CI)	18.5 (12.3–38.6)	15.8 (6.8–NR)	16.5 (13.3–NR)

Table 3. Toxicity in 71 older patients receiving S-1 regimens for non-resectable mCRC.

Therapy	SOx		S-1		IRIS	
No. of patients	44		9		18	
Toxicity, *n* (%)	Grade					
Non-hematological	Any	3-4	Any	3-4	Any	3-4
Diarrhea	21 (48)	5 (11)	3 (33)	0	10 (56)	2 (11)
Nausea	15 (34)	0	3 (33)	0	8 (44)	0
Vomiting	9 (20)	0	1 (11)	0	3 (17)	0
Fatigue	35 (80)	6 (14)	2 (22)	0	16 (89)	0
HFS	3 (7)	0	0	0	1 (6)	0
Neuropathy	31 (70)	3 (7)	0	0	–	–
Infection/fever	2 (5)	2 (5)	1 (11)	1 (11)	1 (6)	1 (6)
Mucositis	5 (16)	2 (6)	0	0	3 (17)	0
Hematological						
Neutropenia	5 (14)	3 (7)	0	0	4 (28)	3 (17)
Thrombocytopenia	5 (14)	1 (2)	5 (56)	2 (22)	2 (11)	1 (6)
Febrile neutropenia	2 (5)	2 (5)	0	0	1 (6)	1 (6)

In addition three cases of grade 3 AE (heart failure, syncope, dehydration) were noticed in patients receiving S-1 monotherapy.

neuropathy). Median age was 73 years (range 67–82 years). Ten patients (56%) completed at least six cycles of therapy. Reasons for discontinuing chemotherapy included radiological PD ($n = 5$) and toxicity/patient's wish ($n = 2$). Fifteen patients (83%) started with full dose therapy and three patients started with reduced dose IRIS (reduced dose in previous line $n = 2$, comorbidity $n = 1$). The median relative dose intensities for irinotecan and S-1 were 97% and 87%, respectively (Table 1).

Five (28%) and nine patients (50%) had PR and SD, respectively, resulting in DCR of 78%. The median PFS was 7.8 months and the median OS was 16.5 months.

Adverse events are summarized in Table 3. The most common non-hematological adverse events were fatigue (89%), diarrhea (56%), and nausea (44%). Adverse events were generally mild in nature with grade 3 diarrhea being observed in 11% of patients. The rate of HFS was very low (1 patient grade 1). Hematological adverse events were mild and only one patient (6%) developed febrile neutropenia.

S-1 monotherapy in very old mCRC patients

In the S-1 group (median age 82 years), S-1 was given as first-line therapy. Tolerance was generally good, as most managed to receive the eight planned cycles (Table 3). One patient with a simultaneously grade 3 thrombocytopenia and grade 3 infection had reduced renal function. Patients seemed to benefit from treatment as two patients achieved PR and six patients SD (DCR was 89%), median PFS was 6.4 months and median OS 15.8 months.

Discussion

Very little is known about S-1 in Caucasian patients with mCRC and therefore we present our experience with S-1 in Caucasian patients. The primary aim of our study was to evaluate toxicity and dose intensity but efficacy is also reported even though drawing conclusions on outcome data is difficult in retrospective studies.

Randomized studies in Japanese patients have shown that S-1 is as effective as other fluoropyrimidines (5-FU and capecitabine) when given either as monotherapy or in combination with oxaliplatin [11,12] or irinotecan [13]. In the phase 3 'SOFT' study chemo-naïve patients were randomized to mFOLFOX6 plus bevacizumab or SOx plus bevacizumab [12].

The authors found no difference in efficacy (overall response rate 63% vs. 62%; median PFS 11.5 vs. 11.7 months; median OS 30.9 vs. 29.6 months, respectively), and concluded that SOx plus bevacizumab could become a standard regimen in mCRC.

S-1 has also been evaluated in older patients in Japan. In a phase II study ('BASIC'), 56 patients with a median age of 75 years received S-1 plus bevacizumab as first-line therapy for mCRC [14]. Median OS was 25.0 months and the authors concluded that S-1 plus bevacizumab therapy is effective and well tolerated for older patients with mCRC.

There is no exact determination of when a patient is old, some studies use 65 years as lower limit, other 70 or even 75 years [15]. In our retrospective chart review, we included older patients close to 70 years with mCRC, many of which were considered not candidate for standard combination therapy with targeted therapy. Aging is an individual process of declining function of several organs, such as kidney, heart, lung and bone marrow, and the physiological status of the patient is thus not always reflected in the chronological age. To optimize the selection of treatment for older patients some kind of geriatric assessment screening tools is recommended when treating older cancer patients [16,17].

In the first-line setting with SOx we observed a response rate of 41%, DCR of 86%, median PFS of 8.5 months and median OS of 18.5 months, data which are in line with what would be expected in older mCRC patients treated with chemotherapy [18,19]. Our findings indicate that the SOx regimen is well tolerated even in older patients with a low rate of clinical adverse events similar to what would be expected with other fluoropyrimidine-oxaliplatin-based combinations, albeit with a much lower rate of HFS [20]. The rate of hematological adverse events also appears to be lower with SOx compared with other fluoropyrimidine-oxaliplatin combinations.

The use of the combination of capecitabine and irinotecan has been associated with some concerns primarily due to an increased risk of toxicity, primarily GI toxicity compared to FOLFORI [21]. The IRIS regimen with irinotecan given at a dose of 200 mg/m^2 were in general well tolerated with 11% experiencing grade 3/4 diarrhea which is comparable to the incidence of diarrhea to the FOLFIRI-regimen [21]. Furthermore data was comparable to other second-line settings [22].

At present, the most commonly used monotherapy dose of S-1 in fit Caucasians is 30 mg/m^2 twice daily on Days 1–14 every three weeks [9] whereas the dose of S-1 is generally reduced to 25 mg/m^2 twice daily on Days 1–14 every three weeks when given in combination with oxaliplatin or irinotecan. While there is generally a consensus on the most appropriate dose of oxaliplatin to use (i.e. 130 mg/m^2) when administered every three weeks with S-1 or capecitabine [9,10,23,24], the dosing schedules of IRIS or CapIri have been the subject of much debate over the years. Capecitabine 2000 mg/m^2 on Days 1–14 with irinotecan 250 mg/m^2 on Day 1 every three weeks is probably the most commonly recommended schedule but other [18,25] recommend a lower dose of irinotecan (200 mg/m^2 or even 160 mg/m^2 on Day 1 every three weeks) and sometimes even lower doses of capecitabine (1600 mg/m^2 on Days 1–14 every three weeks) in order to limit GI toxicity. Based on these facts and knowledge gained from Asian studies with irinotecan [13] we recommend S-1 25 mg/m^2 orally twice daily on Days 1–14 with IRIS 200 mg/m^2 iv on Day 1 every three weeks in fit patients. The optimal dosing for patients aged >80, balancing response and side effects is not known. However, our preliminary results in this population shows that a monotherapy schedule with 25 mg/m^2 is tolerable with promising activity.

Nevertheless, the debate regarding the most appropriate dosing of fluoropyrimidine-based therapy for 'older' patients with mCRC is ongoing. In the FOCUS2 trial of various reduced dose chemotherapy options in patients considered unfit for full dose regimens, despite permissive entry criteria and no upper age limit, the median age was only 64 years and a retrospective survey showed that almost twice as many patients had been treated off-trial during the same period, frequently using reduced dose or single agent schedules [19]. The most common reasons for non-inclusion were physicians' concerns about the adverse effects of standard dose treatments and patients' wishes to avoid toxic effects. In clinical practice many oncologists use either full dose monotherapy (with subsequent toxicity driven dose reductions) or upfront reduced dose combination therapy in older/frail patients without much evidence for any of these two strategies.

Therefore we will compare these two strategies administered every three weeks in the ongoing NORDIC9, a Nordic multicenter randomized trial comparing a full dose monotherapy strategy (S-1 30 mg/m^2 twice daily Days 1–14 followed by irinotecan 250 mg/m^2 at the time of progression) to reduced dose combination therapy strategy (S-1 20 mg/m^2 twice daily Days 1–14 and oxaliplatin 100 mg/m^2 followed by S-1 and irinotecan 180 mg/m^2 at the time of progression). The study aims to recruit 150 older ($\geq$70 years) mCRC patients who are not candidates for full dose standard combination therapy. Patients will be included based on routine disease characteristics but also geriatric assessments with G8, VES-13, simple physical test [16,17] and quality of life will be registered at baseline.

In conclusion, S-1 monotherapy, SOx and IRIS regimens had comparable efficacy to standard regimens in mCRC, were well tolerated for older patients and could become alternative regimens in those who are not candidates for full dose intense combination therapy. These regimens will be evaluated further in the randomized NORDIC9 trial.

Disclosure statement

Per Pfeiffer: advisory boards, symposia, or lectures for Amgen, Bayer, Celgene, Merck-Serono, MSD, Nordic Drugs, Roche, Sanofi, Taiho.

Halfdan Sorbye: advisory board, honoraria or research grants from Ipsen, Novartis, Pfizer, Amgen, Bayer, Celgene, Merck-Serono, Nordic Drugs, Roche.

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