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ORIGINAL ARTICLE

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Phase I/II trial of topotecan given as continuous infusion in combination with oxaliplatin in 5-FU-pretreated patients with colorectal cancer

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Abstract *Background*: Oxaliplatin and topotecan are novel options for a variety of neoplasms. Topotecan has shown fewer side effects and higher efficacy when given as a continuous i.v. infusion compared to single doses, but this regimen has not yet been combined with oxaliplatin. *Patients and methods*: This phase I/II trial was designed to establish the dose-limiting toxicity of a combination of oxaliplatin (85–130 mg/m^2 on day 1) and a continuous infusion of topotecan (initial 0.9 mg/m^2 over 72–120 h). Eligible patients with metastatic colorectal cancer had progressive disease during, or within 12 weeks after, palliative fluoropyrimidine-based chemotherapy or in whom intolerable 5-FU toxicity had developed. *Results*: The study included 21 patients. Subjectively the treatment was well tolerated but haematological toxicity was observed with the initial treatment schedule of oxaliplatin 85 mg/m^2 on day 1 and topotecan 0.9 mg/m^2 on days 1–5. Reducing topotecan to 0.9 mg/m^2 on days 1–3 resulted also in acceptable haematological toxicity. In patients completing three or more therapy cycles, median progression-free survival was 5 months, and 50% had stable disease or showed a partial response. *Conclusion*: The recommended dose of this combination for further testing is oxaliplatin 85 mg/m^2 on day 1 and topotecan 0.9 mg/m^2 per day as a continuous infusion on days 1–3.

Keywords Colorectal cancer · Oxaliplatin · Second-line treatment · Topotecan

Dr. Hubert Szélenyi, born 11 January 1965, died in the prime of life on 29 August 2002. We are deeply saddened by the loss of an excellent physician, accomplished scientist and admirable and warm-hearted friend and colleague. He had essentially designed and developed this study, and we decided to finish it in compliance with his intentions.

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Introduction

Surgical resection is the only potentially curative treatment for colorectal cancer (CRC), but more than 50% of patients with CRC eventually die of metastatic disease. However, patients with metastasized CRC and progressive disease after adjuvant or palliative chemotherapy with 5-fluorouracil (5-FU) and folinic acid (FA) may often profit from additional therapy [7]. With oxaliplatin and irinotecan, effective first-line and second-line treatment options have become available for patients with metastatic CRC.

In clinical trials, oxaliplatin has been shown to be effective and well tolerated both as first-line therapy in combination with 5-FU/FA and as second-line monotherapy [16, 17]. In one phase III multicentre trial, an objective response of 53% was shown for the combination of oxaliplatin/5-FU/FA vs 16% for 5FU/FA alone. Median survival times were 19.9 and 19.4 months, respectively [8].

Topotecan (TPT), a topoisomerase I inhibitor, is a water-soluble semisynthetic analogue of the alkaloid irinotecan (camptothecin, CPT-11). CPT-11 has shown a 10–20% partial response rate as first-line therapy in patients with metastatic rectal cancer and in patients progressing on 5-FU therapy. Like oxaliplatin, it achieves disease stabilization in 50% of patients and 1-year survival rates in responders of up to 38.2%, albeit at the cost of considerable toxicity [5, 20, 23]. The main objective in the development of TPT was to reduce toxicity [3].

In early clinical studies the safety and tolerability of TPT was assessed with various dosing schedules, including single bolus injections of up to 22.5 mg/m^2, daily intravenous (i.v.) infusions with 0.5–4.5 mg/m^2, and continuous i.v. infusion from 24 h to 21 days [6]. Haematological toxicity is the main dose-limiting side effect, and in contrast to the sister compound CPT-11, TPT is not associated with severe diarrhoea [4]. According to these studies, continuous i.v. infusion appears to be more tolerable especially in heavily pretreated patients. The maximum tolerated dose (MTD) for continuous i.v. TPT administered over 72 h ranges from 1.0 to 1.6 mg/m^2 per day [2, 18] and for 120 h from 0.68 to 2.1 mg/m^2 per day [2, 19].

TPT as a single agent has demonstrated only minor activity in CRC in clinical studies [6]. However, preclinical data suggest that administration over extended periods of time may not only reduce toxicity, but also increase the efficacy of TPT [13]. Furthermore, preclinical and early clinical studies have demonstrated a synergistic effect of TPT in combination with oxaliplatin [9, 22].

The objective of this trial was to test the feasibility of TPT–oxaliplatin combination therapy in escalating doses with TPT being administered as continuous i.v. infusion, and to determine the MTD and the dose-limiting toxicities (DLT) of this regimen. A secondary objective was to describe potential antitumour activity of this combination in patients with CRC failing 5-FU-based treatment.

Patients and methods

Patient selection. This trial was designed in 1998, and all patients were included between 1998 and 2000 at the Campus Benjamin Franklin of the Charité Berlin. Patients with histologically confirmed metastatic or locally recurrent CRC who had at least one index lesion suitable for two-dimensional measurement in computed tomography scans were candidates for this study if they had developed progressive disease during, or within 12 weeks after,palliative fluoropyrimidine-based chemotherapy, or if they had experienced intolerable 5-FU-specific toxicity during a previous treatment. Further inclusion criteria were an age of at least 18 years, a performance status (ECOG) of 0–2, and hepatic, renal and haematological parameters within predetermined baseline limits.

Exclusion criteria were prior chemotherapy with oxaliplatin or a camptothecin derivative, previous malignancy with the exceptions of excised cervical carcinoma in situ or basal/squamous cell skin carcinoma, peripheral neuropathy higher than grade 2, clinical evidence for CNS metastases, pregnancy or child-bearing potential, concomitant and uncontrolled nonmalignant disease including active infection.

All patients were required to provide written informed consent before entry into the study. This trial was conducted in accordance with the Declaration of Helsinki and good clinical practice, including approval from the institutional Ethics Committee.

Treatment plan. The plan for this trial was to administer TPT and oxaliplatin in increasing doses as detailed in Table 1. Dose level 1 consisted of oxaliplatin 85 mg/m^2 administered as a 2-h infusion on day 1 followed by TPT 0.9 mg/m^2 per day given as a continuous i.v. infusion on days 1–5. Depending on toxicity, it was planned to increase the dose of oxaliplatin to levels 2 and 3, each including six patients until DLT had been reached.

Treatment courses were repeated on day 22 for a total of six courses unless there was prior evidence of progressive disease. Concomitant medication routinely given before cytotoxic drug administration included 5 mg of the selective serotonin receptor antagonist tropisetron as an antiemetic.

Pretreatment and follow-up evaluations. Before chemotherapy was initiated, all patients were assessed by physical examination, routine haematology and biochemistry analyses, and CT scans to define the extent of the disease. Complete blood cell counts were obtained twice weekly during chemotherapy, and serum chemistry analyses were repeated before each therapy course. Subjective symptoms, physical examination results, and all adverse reactions were recorded prior to each treatment cycle. Tumour size was measured by CT scan after cycles 2, 4 and 6.

Evaluation of toxicity. All toxicities were graded using version 1 of the National Cancer Institute Common Toxicity Criteria (NCI CTC). The DLTs were defined as grade 3 or 4 toxicities except for alopecia. The DLT for leucopenia was grade 4. In case of DLT, the treatment was to be discontinued until recovery to grade 1 or less and, if clinically indicated, resumed for the subsequent cycle at the next lower dose level than that causing the DLT.

It was planned to enter six patients in each dose level. Escalation to the next dose level depended on the evaluation results of at least one treatment cycle in each of the six patients included at the current dose level. If fewer than three of the six patients at a given dose level

Table 1 Proposed treatment schedule

Dose level	TPT		Oxaliplatin (mg/m^2)
	Dose (mg/m^{2}per day)	Infusion duration (h)	
−1	0.6	72	65
0	0.9	72	85
I	0.9	120	85
2	0.9	120	115
3	0.9	120	130

experienced a DLT, the subsequent six patients were to be entered into the next higher dose level.

Assessment of response. The response was assessed according to WHO criteria. A complete response (CR) required the complete disappearance of all objective evidence of disease on two separate measurements at least 4 weeks apart. A partial response (PR) was defined as more than 50% reduction in the sum of the products of the largest perpendicular diameters of lesions measurable in two-dimensions, without any progression of any lesion by more than 25% or the appearance of any new lesion, confirmed on two separate measurements 4 weeks apart. Progressive disease (PD) was defined as the enlargement of any existing measurable lesion by more than 25% or the development of new metastatic lesions. Stable disease (SD) was assumed when any measurable lesion did not meet the criteria for CR, PR or PD.

Secondary assessments included the duration of response (measured from the onset of the best response to the date of disease progression), time to progression (from initiation of treatment) and overall survival.

Results

Patient characteristics

Between December 1998 and October 2000, a total of 21 patients (12 male, 9 female) were entered into this trial at a single institution. All patients were assessable for toxicity and response. The demographic data, sites of primary tumour, sites of metastases, and prior therapies are listed in Table 2. The patients received a total of 65 cycles of therapy (range 1–6, median 4). Their ages were between 49 and 78 years with a median of 65 years. The primary cancer site was colon in 16 and rectum in 5 patients, and 90% of patients had more than three metastatic sites.

All patients had previously received at least one cycle of a 5-FU-containing chemotherapy, and 16 (76%) had shown PD during therapy with 5-FU, 3 had completed 5-FU treatment and developed PD 3–7 months later, and 2 had a relapse within 6 months after adjuvant 5-FU therapy and were included in this study because of a known history of 5-FU toxicity. For patients with progressive disease the interval between discontinuing fluoropyrimidine-based chemotherapy and the beginning of the trial was at least 24 days.

Table 2 Patient characteristics. The data are presented as number and percent of patients, except age in years

	n	%
Gender		
Male	12	57
Female	9	43
Age (years)		
Median	65	
Range	49–78	
WHO performance status		
0	1	5
1	12	57
2	8	38
Primary cancer site		
Colon	16	76
Rectum	5	24
Metastatic sites		
Liver	16	76
Lung	7	33
Local relapse	6	28
Other	6	28
Pretreatments		
5-FU/FA	20	95
5-FU/mitomycin C	1	5
Radiation	2	10
Panorex/Il-2	1	5
Interval (weeks) after 5-FU treatment		
3–4	13	62
4–8	3	14
>8	5	24

Treatment

Five patients received dose level 1, consisting of oxaliplatin 85 mg/m^2 on day 1 and continuous i.v. TPT 0.9 mg/m^2 per day administered over 120 h (days 1–5). Four of these patients experienced severe thrombocytopenia exceeding grade 3. One patient developed neutropenic fever and died of sepsis although specific therapy was introduced immediately.

Because of this nontolerable haematological toxicity at the first dose level, we amended the protocol to continue with a reduced dose (level 0) in which TPT was administered over 72 h instead of 120 h. A total of 18 patients received at least one cycle of this dose level, and a total of 57 cycles were administered.

In three patients, prolonged thrombocytopenia required an additional dose reduction to oxaliplatin 65 mg/m^2 and TPT 0.6 mg/m^2, designated level −1. In one of these patients, thrombocytopenia persisted even after dose reduction to level −1, and the therapy was continued with oxaliplatin only.

Toxicity

Hematological toxicity. The frequency of severe haematological adverse events in dose level 1 was intolerable, with four of five patients developing grade 3 or 4 toxicity. Two patients had one episode of neutropenic fever and one patient died of uncontrollable septic disease during neutropenia. Toxicity analysis of this dose level 1 showed a late onset of neutropenia and thrombocytopenia after day 22 (data not shown). In three patients, therapy was continued at the reduced level 0. Dose reduction of TPT to level 0 lowered the toxicity,

Table 3 Dose levels and toxicity

	Dose level		
	1	0	−1
Total number of cycles	8	46	7
Thrombocytopenia			
Grade 3	1 (12%)	3 (6%)	0 (–)
Grade 4	2 (25%)	2 (4%)	0 (–)
Neutropenia			
Grade 3	1 (12%)	2 (4%)	0 (–)
Grade 4	2 (25%)	1 (2%)	0 (–)
Neutropenic fever	2 (25%)	1 (2%)	0 (–)
Diarrhea			
Grade 3	2 (25%)	0 (–)	0 (–)
Grade 4	0 (–)	0 (–)	0 (–)

but in three patients thrombocytopenia of grade 3 was still observed. In subsequent cycles, doses of oxaliplatin and TPT were further reduced to level −1 for these patients. At this level, no haematological toxicity exceeding grade 2 was observed (Table 3).

The toxicity analysis of 54 cycles at dose level 0 is summarized in Fig. 1. Figure 1a,b shows the median and range of the granulocyte count during and after study treatment. The nadir for neutropenia and anaemia was between days 8 and 10. A second nadir for neutropenia was found between days 22 and 24. Figure 1c shows the time course of the thrombocyte count with a nadir between days 8 and 18.

Table 4 shows the correlation between time since last 5-FU treatment and haematological toxicity. None of

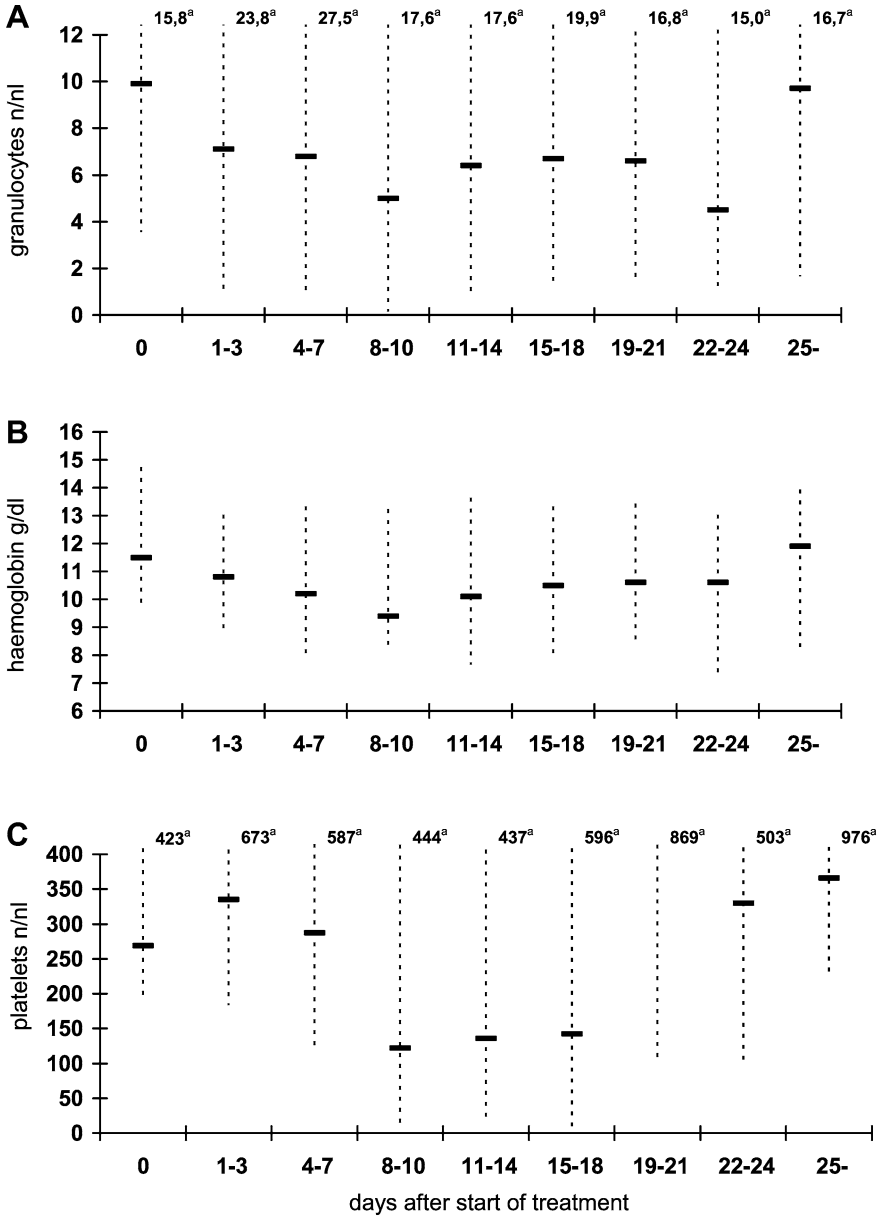

Fig. 1 Haematological toxicity of 54 treatment cycles with a reduced dosage schedule (level 0) of oxaliplatin 85 mg/m^2 on day 1 and continuous i.v. TPT 0.9 mg/m^2 per day administered over 72 h. *Bars* indicate mean values and, *dotted lines* the range between minimum and maximum values. **a** Where the maximum values exceed the graph range, the numerical values are given

Table 4 Toxicity and interval after 5-FU treatment

	Dose level 1			Dose level 0		
Interval (months)	1	2	>3	1	2	>3
Patients	4	–	1	10	3	5
Cycles	7	–	1	23	13	21
Toxicity grade 3 or more	4	–	0	7	0	0
Frequency	100%	–	0%	70%	0%	0%

the eight patients who had a therapy-free interval of more than 1 month before entering this study experienced haematological toxicity higher than grade 2 compared to 70% of the patients with a shorter interval. In dose level 1 there was only one patient out of five with an interval longer than 1 month. In contrast to the other four, this patient did not experience toxicity higher than grade 2.

Nonhaematological toxicity. Three patients suffered from diarrhoea grade 2 and 3. Diarrhea occurred after the first and up to the third treatment cycle. After reconstitution none of the three patients developed diarrhoea again in subsequent treatment cycles. Most patients did not suffer from vomiting at any time, but in one it was rated as grade 3. Other related toxicities were also mild. Alopecia was observed in most patients, especially in those who had discontinued 5-FU-based therapy within 1 month before the start of the study therapy. One patient suffered from paraesthesia grade 1 and another from mucositis grade 3 after the second cycle. In both patients it was possible to continue therapy, and during the subsequent four cycles at the same dose level, these toxicities did not recur.

Efficacy

Eight patients (40%) received only one or two cycles of oxaliplatin and TPT. Of these patients, one died after uncontrollable septic complications during therapy-induced neutropenia, and another died after a surgical intervention. In the other six patients, the therapy was discontinued because of tumour progression. The remaining 13 patients received three to six therapy cycles (median five). Six patients showed PD after three to five cycles. Three patients who received six cycles achieved SD, two a mixed response, and one patient had a PR after four cycles. No CR was observed. The median time to progression for all patients was 5 months (range 3–11 months).

Evaluation of efficacy was restricted by the small number of patients, of whom only 60% received more then two cycles of chemotherapy. The major reason for discontinuation was tumour progression, especially in patients with bulky disease or a WHO performance status below 1. Patients who received more than two cycles

Table 5 Recent experiences with the combination of oxaliplatin and TPT

Proposed dose escalation			Recommended dose			Types of cancer	No. of patients	Main DLT	Reference
Oxaliplatin (mg/m^2)	TPT (mg/m^2)	Cycle (days)	Oxaliplatin (mg/m^2)	TPT (mg/m^2)	Cycle (days)				
65–85, days 1 and 15	0.2–0.3, days 1–14, continuous infusion	–	85, days 1 and 15	0.4, days 1–14 continuous infusion	–	Ovarian cancer	16	No grade 4	15
85–110, day 1	0.5–1.25, days 1–5	21	110, day 1	1.0, days 1–5	21	Advanced cancers	34	Haematological	11
85, day 1	0.5–1.5, days 2–5	21	85, day 1	1.25, days 2–5	21	Advanced cancers	18	Haematological, gastrointestinal	22
85–110, day 1	0.5–1.5, days 1–5	21	85, day 1	0.5–0.75, days 1–5	21	Hepatocellular carcinoma	13	Thrombocytopenia	1

of chemotherapy had a median time to progression of 5 months. Of these, 50% showed PD before completing six cycles, whereas the remaining 50% had a SD or PR.

Discussion

The objective of polychemotherapy for cancer is to combine cytotoxic agents with different mechanisms of action and resistance in order to potentially achieve a synergistic antitumour effect with reduced toxicity. TPT is a new inhibitor of the nuclear enzyme topoisomerase I, which is necessary for DNA replication. Results from pharmacokinetic studies show a quantitative dose–effect relationship, no accumulation of drug, low plasma protein binding and a high tissue uptake [14]. The efficacy of TPT at various concentrations and in various administration schedules has been evaluated in preclinical and clinical studies [4].

The rationale for this study was based on the observation that platinum-induced DNA crosslinking leads to induction of topoisomerase I. Inhibition of this enzyme therefore delays or blocks repair mechanisms in the tumour cell [9, 10]. Thus, the combination of platinum derivatives with topoisomerase I inhibitors may have therapeutic relevance. In addition, there are experimental indications for increased efficacy of TPT when it is given as a continuous i.v. infusion, which amounts to maintaining a constant pressure on the resistance and repair potential of the damaged tumour cell [12]. We therefore decided to investigate oxaliplatin in combination with continuously administered TPT.

No prior experience has been published concerning the toxicity of oxaliplatin combined with continuous i.v. TPT. Usually TPT is administered in doses of up to 2.1 mg/m^2 per day when given over 120 h. Planning a dose escalation study, we assumed that 0.9 mg/m^2 TPT per day over 120 h [19], combined with 85 mg/m^2 oxaliplatin would not be associated with excessive toxicity as these doses correspond to less than half the known MTD of TPT in combination with two-thirds of the oxaliplatin dose for monotherapy. Subjectively, the treatment was well tolerated, and nonhaematological toxicity was minor. However, at the first dose level, we observed haematological toxicity of grade 4 in 80% of patients. This prompted us to reduce the dose of TPT by administering it over only 72 h instead of 120 h, which reduced haematological toxicity considerably to a tolerable level. Toxicity analysis of this reduced schedule showed that the nadir for granulocytes and red blood cells was between days 8 and 10. The nadir for thrombocytes was between days 8 and 18. The schedule was designed to repeat each cycle on day 22. Complete reconstitution of platelets was achieved on days 19–21 and of leucocytes on days 19–21 in 68% of treatment cycles, so the majority of patients were able to adhere to the planned schedule.

Further analysis of our data revealed that there was a strong relationship between haematological toxicity and time since the last 5-FU treatment. Independently of the dose level, none of those patients with an interval between therapies of more than 1 month had haematological toxicity exceeding grade 2, in contrast to 70% of the patients with an interval of only 1 month. Due to the small number of patients in this study, the significance of this observation cannot be stated. However, it demonstrates that the length of the interval between therapies may be an important factor in predicting adverse effects, and the original dosage schedule of level 1 may be well tolerated in a patient population selected for a longer therapy-free interval.

In summary, this trial demonstrated that oxaliplatin at a dose of 85 mg/m^2 on day 1 plus TPT at a dose of 0.9 mg/m^2 per day by continuous i.v. infusion for 72 h is safe in patients with advanced CRC after failure of 5-FU-based first-line treatment, and it achieves at least disease stabilization in about half of the patients who receive more than three therapy cycles. This dosage schedule may serve as a guide for future clinical studies on this combination chemotherapy, and also for the treatment of other neoplasms that have shown sensitivity to these substances, such as ovarian carcinoma.

In comparison with other trials using the combination of oxaliplatin and TPT, the usual dose of oxaliplatin was 85 mg/m^2 (Table 5). TPT was given over 4–5 days at a dose from 0.5 to 1.25 mg/m^2 as a 30-min daily infusion. In one study in patients with hepatocellular carcinoma, the cumulative dose was lower than that in our trial. This may be in part explained by a known delayed secretion of TPT in patients with hepatic dysfunction [21]. On the other hand our cumulative dose of TPT was lower than in two other trials in which TPT was given as a daily 30-min infusion [11, 22]. Considering the heterogeneity of the patients groups, this may indicate a higher toxicity for an equivalent TPT dose when given as continuous i.v. infusion.

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