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Compassionate use programme of irinotecan in colorectal cancer patients in the Netherlands

W.W. ten Bokkel Huinink[1*], C.J. van Groeningen[2], E.E. Voest[3], W.G. Peters[4], H.J. Keizer[†5], J.H de Witte[6]

[1]Antoni van Leeuwenhoekhuis, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands, tel.: +31 (0)20-512 29 51, fax: +31 (0)20-512 25 72, e-mail w.t.bokkel@nki.nl, [2]Free University Medical Centre, Amsterdam, the Netherlands, [3]University Medical Centre Utrecht, Utrecht, the Netherlands, [4]Catharina Hospital, Eindhoven, the Netherlands, [5]Leiden University Medical Centre, Leiden, the Netherlands, [6]Aventis Pharma B.V., Hoevelaken, the Netherlands, * corresponding author

ABSTRACT

Background: Irinotecan is an effective treatment for metastatic colorectal cancer. However, its use may be associated with troublesome adverse effects such as delayed diarrhoea, acute cholinergic syndrome and neutropenic infection. The manufacturer decided to release irinotecan for compassionate use in the Netherlands prior to its regulatory approval (June 1998) and first introduction for second-line treatment of metastatic colorectal cancer. In view of the drug's adverse effect profile this was done in a carefully controlled manner.

Methods: Irinotecan was made available to patients with colorectal cancer with elaborate precautions. Treating physicians requesting irinotecan for compassionate use received a protocol, providing recommendations for the proper use and the prevention/management of potentially troublesome adverse events. Limited demographic, toxicity and efficacy data were collected.

Results: Between June 1997 and September 1998, 112 patients were registered for this programme, 103 of whom actually received irinotecan. The percentage of patients experiencing grade 3-4 adverse effects was relatively low: delayed diarrhoea in 17%, nausea and vomiting 17%, acute cholinergic syndrome 6%, febrile neutropenia 4% and neutropenic infection 2%. Five partial tumour responses and a high proportion of patients with 'no change' were noted.

Conclusions: The carefully controlled release of irinotecan for compassionate use with a very detailed protocol for guidance and advice on safety precautions seems to have contributed to the relatively safe use of the drug outside the setting of a formal clinical trial.

INTRODUCTION

Irinotecan (CPT-11, trademark Campto®) is a topoisomerase I inhibitor which interferes with DNA replication and cell division.[1,2] Irinotecan has demonstrated significant antitumour activity with tolerable side effects in various phase II and III clinical trials in 5-fluorouracil (5-FU) pretreated patients with advanced colorectal cancer.[3,4] In randomised phase III studies, irinotecan has shown superior efficacy in terms of response rate, time to progression and survival in comparison with infusional 5-FU/leucovorin[5] or best supportive care.[6] The survival benefit in these trials was achieved without increasing the overall cost of medical care consumption.[7,8] Irinotecan in combination with 5-FU/leucovorin has demonstrated clinical antitumour activity in first-line chemotherapy of metastatic colorectal cancer with overall tumour response rates of 24 to 49%, prolongation of time to tumour progression and increased overall survival compared with 5-FU/leucovorin alone.[4,9,10] Based on available studies, irinotecan has been approved worldwide for both second-line treatment (after 5-FU based regimens) and, in combination with 5-FU/leucovorin, first-line treatment of advanced colorectal cancer.

One of the most common and troublesome side effects encountered during the early clinical development of irinotecan was delayed diarrhoea, which could be severe.[4] Therefore, during the later stages of development, high-dose loperamide was advocated for use in patients with first signs of liquid stools. This intervention has been shown to significantly reduce the incidence of this complication.[11,12] The recommendation to use high-dose loperamide in patients with early signs of delayed diarrhoea is therefore included in the package insert of the currently marketed product.

Another relatively frequent side effect of irinotecan was acute cholinergic syndrome, possibly due to inhibition of cholinesterase activity by irinotecan. Symptoms may occur shortly after administration and typically include diarrhoea and various other cholinergic symptoms such as diaphoresis, chills, malaise, dizziness, visual disturbances, lacrimation, salivation, bradycardia and abdominal cramps. Symptoms are usually short lasting and may be treated effectively by the subcutaneous administration of atropine.

Further common toxicities include neutropenia, alopecia, fatigue, and nausea and vomiting. Nausea and vomiting is commonly seen in association with many cytotoxic agents and is usually manageable with routine measures.[4] The combined occurrence of diarrhoea and neutropenia may lead to severe infection and poses a potential safety concern.

Irinotecan was approved for the treatment of colorectal cancer by the regulatory authorities of the Netherlands in June 1998 and was introduced in the Netherlands in September 1998. The recommended dose schedule is 350 mg/m^2, given as an intravenous infusion over 30 to 90 minutes once every three weeks. In view of the lack of an effective second-line treatment regimen for colorectal cancer at the time of introduction, the manufacturer of irinotecan (Rhône-Poulenc Rorer, currently Aventis Pharma and further referred to as Aventis Pharma) decided to make the drug available to colorectal cancer patients in the Netherlands on a compassionate use basis prior to its general introduction onto the market. In view of the specific side-effect profile, it was decided to release irinotecan to patients qualifying for compassionate use with a number of safety precautions. An important feature of this programme was the use of a 'compassionate use protocol', providing recommendations for the proper use of irinotecan and the prevention and management of possible adverse events, in particular delayed diarrhoea, febrile neutropenia and acute cholinergic syndrome.

MATERIALS AND METHODS

Programme design

A compassionate use programme, giving colorectal cancer patients access to irinotecan, was conducted under carefully controlled conditions between June 1997 and February 1999. Oncologists at hospitals throughout the Netherlands were given the opportunity to obtain irinotecan for the treatment of patients meeting the programme's entry criteria. The main motivation to initiate this programme was humanitarian in nature. The programme was aimed at patients who could not be expected to benefit from another therapy or could not enter into an ongoing clinical trial, and gave them access to a potentially beneficial drug treatment. A good benefit/risk ratio should reasonably be expected for each individual patient entering the programme according to the most up-to-date clinical data on irinotecan. A defined set of demographic, toxicity, efficacy and treatment data was collected for each course using a simple case report form (CRF). The clinical data documented in the CRF were monitored by a representative of the sponsor according to standard ICH-GCP guidelines.

Patients

Patients had to meet the following entry criteria:

- Histologically proven adenocarcinoma of colon or rectum, either metastatic or with a nonresectable loco-regional relapse;
- At least one measurable or evaluable metastatic lesion according to WHO criteria;
- Age at least 18 years;
- Having failed a prior 5-FU-containing chemotherapy regimen for metastatic disease;
- Good performance status (WHO grade 0-2) and a life expectancy of more than three months;
- No bowel obstruction or subobstruction at baseline;
- Serum bilirubin ≤1.5 times upper normal limit;
- Serum creatinine ≤150 μmol/l;
- Baseline neutrophil count ≥1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l;
- No inflammatory bowel disease (Crohn's disease, ulcerative colitis);
- No known hypersensitivity to irinotecan or one of the excipients;
- Number of lines of chemotherapy ≤3 (4 if one adjuvant).

Pregnant or breastfeeding women and patients, both male and female, of reproductive potential but not using effective contraception were excluded from participation. Patients qualifying for compassionate use of irinotecan were required to sign a written informed consent stating that they were aware of the fact that irinotecan was not a registered drug and that he/she was not entering a clinical trial. Furthermore, all patients received an information leaflet from their treating physician with instructions on

the use of loperamide should delayed diarrhoea develop following treatment and other precautions against potential serious adverse effects.
At registration, the patient's date of birth, gender, date of informed consent, cancer history (primary tumour site, date of first diagnosis, metastatic spread and date of metastasis diagnosis), prior radiotherapy (yes/no, site), performance status, body weight and body surface area were noted.

Drug treatment
The recommended dose of irinotecan was 350 mg/m^2, given as a 30 to 90 minute intravenous infusion, once every three weeks. If the neutrophil count at day 22 was below 1.5 x 10^9/l, the next course was to be delayed until recovery of the neutrophil count to ≥1.5 x 10^9/l. If recovery was observed at day 35, treatment was to be discontinued.
In patients experiencing severe gastrointestinal adverse events, such as diarrhoea or nausea and vomiting, it was recommended to delay further dosing of irinotecan until full recovery of symptoms, in particular diarrhoea.
Dose adjustments for a subsequent treatment cycle were recommended as follows:

- Same dose, if lowest absolute neutrophil count (ANC) >1.5 x 10^9/l without related fever *and* <grade 4 diarrhoea without need for intravenous rehydration;
- Approximately 20% dose reduction (i.e. from 350 mg/m^2 to 300 mg/m^2, and from 300 mg/m^2 to 250 mg/m^2), if lowest ANC <0.5 x 10^9/l, *or* lowest ANC <1.0 x 10^9/l with concomitant related fever or infections, *or* severe diarrhoea;
- Patient to be withdrawn if the 250 mg/m^2 dose could not be tolerated.

Prophylactic antiemetic treatment according to local guidelines, subcutaneous atropine sulphate (in case of acute cholinergic symptoms), high-dose loperamide (with a curative intent, as soon as first liquid stool occurred), oral broad-spectrum antibiotics (in case of severe diarrhoea) and intravenous broad-spectrum antibiotics (in case of febrile neutropenia) were recommended as concomitant medication. Prophylactic loperamide, other anticancer treatment (except localised radiotherapy) and other investigational agents were prohibited.
Treating physicians were advised to make patients aware of the risk of delayed diarrhoea. Patients should be advised to inform their physician and to start appropriate therapy promptly if signs of liquid stools appeared more than 24 hours after administration of irinotecan.
Physicians were also advised to inform patients about the risks of severe diarrhoea and severe neutropenia and the significance of fever during treatment.

Follow-up
After each cycle of irinotecan, weekly blood cell counts (with differential counts) and, in patients who experienced diarrhoea, serum electrolytes and creatinine were taken. Weekly visits or phone calls were mandatory for all patients during at least the first cycle to check for adverse events and patient compliance with the recommended concomitant medication. Particular attention was to be given to higher-risk patients, i.e. patients older than 65 years, heavily pretreated patients, patients with prior abdominopelvic radiotherapy, performance status 2, or bilirubin >1 upper normal limit, patients whose performance status worsened during therapy and patients with expected poor compliance. Weekly visits were strongly recommended for these patients during the full duration of treatment.
Clinical adverse experiences were to be documented in the CRF, indicating the degree of severity according to the Netherlands Cancer Institute Common Toxicity Criteria (NCI-CTC), date of onset and cessation, outcome and relation to study medication. Serious adverse events (SAE) were to be reported to Aventis Pharma within a 24-hour working day period following their occurrence, followed by the submission of a standard SAE form.
Antitumour efficacy was evaluated according to World Health Organisation (WHO) criteria[13] by the local radiologist every second treatment cycle, using the most accurate, reliable and repeatable methods that are routinely used. Tumour responses were not independently reviewed by an external committee. Tumour responses and disease control, defined as the absence of progression for at least six cycles without deterioration in performance status, weight loss or symptom onset, were noted on the CRF. Treatment was stopped in case of progressive disease, patient's withdrawal, unacceptable adverse events irrespective the duration of treatment, or the absence of clinical benefit after six cycles.

Logistics
Drug supplies for patients meeting all requirements for participation in the programme were despatched to the pharmacy at the centre of the treating physician for two cycles at a time. Supplies for further cycles were provided if treatment was to be continued and only after communication with the supplier.

RESULTS

A total of 112 patients were registered by physicians from 40 different hospitals throughout the Netherlands. Main patient characteristics at registration are depicted in *table 1*. All patients had received prior chemotherapy, mostly a 5FU/leucovorin-based regimen or a raltitrexed (Tomudex®)-based regimen. Just over 20% of patients had also received prior radiotherapy, mostly in the pelvic region.

Treatment was initiated between June 1997 and September 1998. The last treatment course was given on 29 September 1999. Five patients did not receive irinotecan although they were registered and for another four patients largely incomplete data were obtained. The 103 patients who were actually treated with irinotecan and for whom adequate data is available received a total of 553 courses (median: 4 courses; range: 1-21 courses). These 103 patients and 553 courses were used as the denominator for the calculation of incidence and rate figures in the remainder of this paper unless otherwise indicated.

Of the courses given, 75% were within 21 days of the preceding drug administration. However, a significant number of courses had to be delayed by one to nine (22% of courses) or more than nine days (3% of courses). The median relative dose intensity was calculated at 95.5% (range: 16.7-105.2%).

Most of the common toxicities, reported in association with the use of irinotecan in clinical studies, were also reported for patients participating in the compassionate use programme. The most frequently reported clinical adverse experiences were acute cholinergic syndrome, delayed diarrhoea, and nausea/vomiting, mostly of grade 1 or 2 (*table 2*, on the next page). Grade 4 toxicity was associated with only 2.9% (16/553) of courses and included neutropenia (1.6%), delayed diarrhoea (0.7%), febrile neutropenia (0.2%), nausea/vomiting (0.2%) and other toxicities (0.2%). A 'possible' or 'probable' relationship to irinotecan treatment was reported for the majority of adverse events that are considered typical for irinotecan. The number of patients with maximum grade 3-4 was relatively small: neutropenia 21.4%, delayed diarrhoea 17.4%, nausea and vomiting 17.4%, acute cholinergic syndrome 5.8%, febrile neutropenia 3.9% and neutropenic infection 1.9% (*table 3*). Grade 4 toxicity was reported as the maximum grade in 16 patients, nine of whom suffered grade 4 neutropenia. The proportion of patients with grade 3 or 4 delayed diarrhoea was somewhat higher among those who had received prior pelvic radiotherapy (*table 4*), but no statistical significance for the association between prior pelvic radiotherapy and delayed diarrhoea was achieved (p=0.09; exact p value, Fisher's test).

Of the 103 patients, 90 were evaluable for response. Sixty-eight percent (61/90) of these evaluable patients had either a partial response (5.6%), a minor response (13.3%) or no change/stable disease (48.9%) as their best overall response (*table 5*). The median duration of response was 36.4 weeks in patients experiencing a partial response and 25.0 weeks in patients experiencing a minor response. The median duration of disease stabilisation was 23.4 weeks.

Table 1
Demographic data and patient characteristics at entry

VARIABLE	NUMBER	TOTAL (%)
Male/female	77/35	68.8/31.3
Mean age, years (range)	57.5 (25-76)	
Performance status		
0	51	45.5
1	52	46.4
2	8	7.1
3	1	0.9
Primary tumour site		
Colon	75	67.0
Rectum	29	25.9
Colorectal (not specified)	8	7.1
Metastatic tumour sites (all sites)		
Liver	71	
Abdominal lymph nodes	31	
Lung	28	
Peritoneum	17	
Other	25	
Missing data (no. of patients)	17	
Prior chemotherapy		
No	-	-
Yes	112	100
Prior radiotherapy		
No	76	67.9
Yes	25	22.3
Pelvis	19	17.0
Other	10*	8.9
Missing data	11	9.8

* *Five patients had received prior pelvic and non-pelvic radiotherapy.*

Table 3
Maximum grade toxicity per patient (n=103)

CLINICAL ADVERSE EXPERIENCE	MAXIMUM GRADE (NO. OF PATIENTS)*				
	0	1	2	3	4
Acute cholinergic syndrome	39	39	19	6	-
Delayed diarrhoea	25	35	25	14	4
Nausea/vomiting	25	30	30	17	1
Neutropenia	72	4	5	13	9
Febrile neutropenia	98	-	1	3	1
Infection with neutropenia	101	-	-	2	-
Other	10	7	47	38	1

* *Grading: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening.*

Table 4
Prior radiotherapy at a pelvic site and the occurrence of delayed diarrhoea

PRIOR RADIOTHERAPY AT PELVIC SITE (N=103)	NO. OF PATIENTS WITH DELAYED DIARRHOEA GRADE 3 OR 4	
	YES	NO
Yes (n=19)	6	13
No (n=84)	12	72

Table 2
Clinical adverse experiences with grading and relation to study medication by course (n=553)

CLINICAL ADVERSE EXPERIENCE	RELATION TO STUDY MEDICATION	NO. OF COURSES WITH GRADE*					TOTAL
		0	1	2	3	4	
Acute cholinergic syndrome	No	378	-	-	-	-	378
	Possible	-	1	-	1	-	2
	Probable	-	138	30	5	-	173
	Total	*378*	*139*	*30*	*6*	-	*553*
Delayed diarrhoea	No	339	-	-	-	-	339
	Remote	-	2	3	-	-	5
	Possible	-	10	1	-	-	11
	Probable	-	123	54	16	4	197
	Not reported	-	1	-	-	-	1
	Total	*339*	*136*	*58*	*16*	*4*	*553*
Nausea/vomiting	No	324	1	2	-	-	327
	Remote	-	2	4	1	-	7
	Possible	-	14	2	-	-	16
	Probable	-	114	62	24	1	201
	Not reported	-	2	-	-	-	2
	Total	*324*	*133*	*70*	*25*	*1*	*553*
Neutropenia	No	472	-	-	-	-	472
	Remote	-	-	1	-	-	1
	Possible	-	-	-	3	1	4
	Probable	-	16	24	28	8	76
	Total	*472*	*16*	*25*	*31*	*9*	*553*
Febrile neutropenia	No	547	-	-	-	-	547
	Probable	-	-	1	4	1	6
	Total	*547*	-	*1*	*4*	*1*	*553*
Infection with neutropenia	No	551	-	-	-	-	551
	Probable	-	-	-	2	-	2
	Total	*551*	-	-	*2*	-	*553*
Other[&]	No	73	115	72	27	-	287
	Remote	-	36	23	8	-	67
	Possible	-	91	56	13	-	160
	Probable	-	209	366	45	1	621
	Not reported	-	6	11	3	-	20
	Total[#]	*73*	*457*	*528*	*96*	*1*	*1155*

[*] *Grading: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening.* [&] *Other adverse clinical experiences include: abdominal pain, alopecia, anorexia, asthenia, chest pain, coughing, fatigue, febris, ileus/volvulus, leucopenia, malaise, oral mucositis, weakness (grade 3 and 4 only and in alphabetical order).*
[#] *Some patients had multiple 'other' adverse experiences; therefore, this total number does not equal the number of cycles given.*

The Kaplan-Meier curves for overall survival and progression-free survival (*figure 1*) illustrate that virtually all patients had disease progression within 15 months of enrolment in the compassionate use programme. The median time to progression was 101 (95% CI: 84-126) days. At 18 months, over 95% of patients receiving irinotecan treatment had died. Median survival was 275 (95% CI: 216-314) days and the one-year survival rate 34.9%.

Table 5
Best overall tumour response in evaluable patients (n=90) treated with irinotecan

RESPONSE	NO. OF PATIENTS	%
Complete response	-	-
Partial response	5	5.6
Minor response	12	13.3
No change/stable disease	44	48.9
Progressive disease	29	32.2
Total evaluable	90	100
Not evaluable	13	-

DISCUSSION

Given their nature, compassionate use programmes cannot substitute for prospective clinical research. Clinical trials are essential for assessing the efficacy and tolerability of a new drug before market availability. However, restrictive eligibility criteria in formal clinical trials exclude a significant proportion of advanced colorectal cancer patients with poor prognosis. Study populations with age restrictions, performance status limitations, normal major organ function, prior treatment limitations and disease measur-

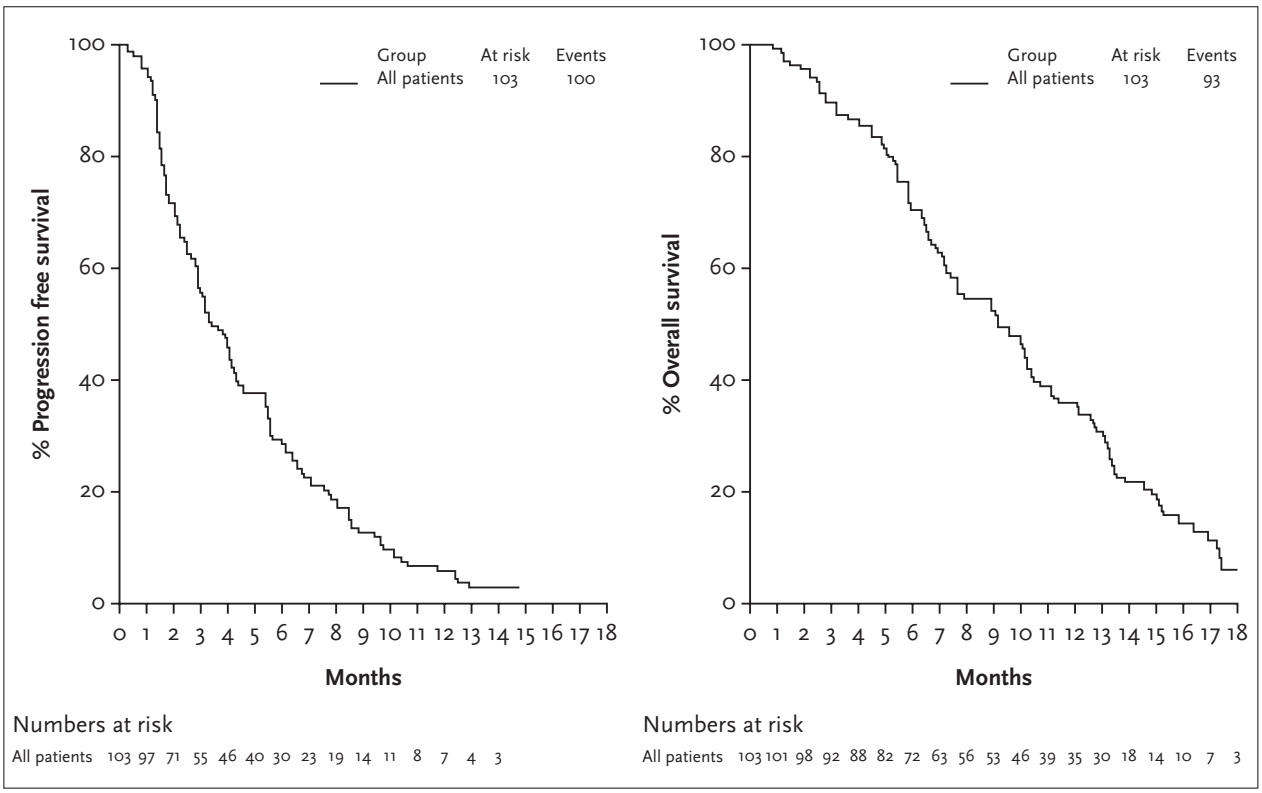

Figure 1
Kaplan-Meier curve for progression-free survival (left panel) and overall survival (right panel) among the group of patients (n=103) receiving compassionate irinotecan treatment

ability requirements allow valid data, yet are not always fully representative of the situation that prevails in routine clinical practice. Therefore, compassionate use programmes offer the opportunity to gather additional safety and efficacy data when used in unselected patients, under prescription and surveillance conditions similar to those of routine oncology practice when a new active agent is initially available to prescribing physicians.[14,15]

The carefully controlled release of irinotecan for compassionate use in patients with colorectal cancer in the Netherlands may be regarded a successful effort to make this new agent available to patients whose treatment options were exhausted. At the time this programme was launched, several large studies had already demonstrated the clinical benefits of irinotecan as second-line treatment for patients with advanced colorectal cancer.[3] However, the use of irinotecan had also been shown to be associated with several typical and troublesome side effects.[3] Delayed diarrhoea, (febrile) neutropenia, severe infection and acute cholinergic syndrome were considered to constitute significant risks of the drug in the compassionate use setting. In this setting, many treating physicians were likely to have very limited or no previous experience with the new drug. Therefore, the release of irinotecan for compassionate use occurred under the guidance of a 'protocol', which was aimed at the prevention, and adequate management of severe toxicities that might occur in association with irinotecan.

Analysis of adverse experiences as reported on the CRFs seems to confirm the success of this 'protocolised' compassionate use programme. The number of patients with maximum grade 3-4 for the most important toxicities of irinotecan (17.4% for delayed diarrhoea, 5.8% for acute cholinergic syndrome, and 3.9 and 21.4% for febrile neutropenia and neutropenia, respectively) was relatively low compared with published data from phase II and III clinical trials. A recent review of clinical studies with irinotecan[4] reported that severe cholinergic syndrome may occur in 9% of patients, grade 3 or 4 neutropenia in 23 to 44% of patients and delayed diarrhoea in up to 87% of treated patients. If managed according to recommendations very similar to those advised in the current compassionate use programme, grade 3 or 4 diarrhoea occurred in only 34% of patients, according to the same review.

A remarkable finding in the compassionate use cohort is the low incidence of severe infections with neutropenia. Only two courses with grade 3 infection and none with grade 4 infection were reported. This may be interpreted as an indication of the success of the specific precautions

that were aimed at preventing infection in a setting where neutropenia and diarrhoea are common adverse effects of treatment. Apparently, physicians treating patients in the compassionate use programme were well aware that severe neutropenia as well as other adverse effects could occur and, most likely, followed the recommendations and guidance for the proper use of irinotecan closely. Similarly, the high proportion of 'possible' and 'probable' relations in the physician-reported relation to medication for acute cholinergic syndrome, delayed diarrhoea, and nausea/vomiting suggests that physicians were well aware that these adverse events could occur in association with irinotecan treatment. Also the patients seem to have complied well with the instructions and guidelines given to them regarding delayed diarrhoea and other possible complications.

The data collected during this programme allow some further comparisons with regard to the safety and efficacy of irinotecan in clinical trials. A recently published multivariate analysis of irinotecan-induced toxicity in 416 patients has identified prior abdominopelvic radiotherapy as one of several predictive factors for a high risk of grade 3 or 4 delayed diarrhoea.[16] The data on delayed diarrhoea in the current cohort seem to show a trend for an association between prior radiotherapy at a pelvic site and an increased likelihood of delayed diarrhoea. It should be noted, however, that the total number of patients in the current cohort and the proportion of patients with prior pelvic radiotherapy are small.

In second-line chemotherapy of metastatic colorectal cancer (after prior exposure to a 5-FU-based regimen), irinotecan has demonstrated overall response rates (CR+PR) in the range of 11 to 17% at different dose schedules.[4] All patients receiving irinotecan in the current programme had received prior chemotherapy, and were likely to be heavily pretreated at the time of entry into the programme. This may be an explanation for the comparatively low overall response rate (5.6%, 5 PR) observed in the current cohort compared with the study populations usually included in first- and second-line phase II and phase III trials.

A remarkable feature of anticancer camptothecins, including irinotecan, is the high proportion of patients with long-lasting disease stabilisation, which has been observed in most clinical studies with this class of agents. In first- and second-line clinical trials of metastatic colorectal cancer, the percentage of patients with 'no change' ranged from 38 to 52%.[4] The percentage of patients with 'no change/stable disease' (48.9%) in the current compassionate use programme is at the higher end of this range and confirms the general observation of frequent disease stabilisation by camptothecins, even in a heavily pretreated patient population.

Two phase III trials of second-line treatment of metastatic colorectal cancer have shown survival benefits for irinotecan, 350 mg/m^2 as a 90-minute intravenous infusion once every three weeks, in comparison with either best supportive care or high-dose infusional 5-FU.[5,6] Median survival of irinotecan-treated patients in these trials was 9.2 and 10.8 months, respectively. One-year survival rates were 36 and 45%, respectively. Despite the relative low overall response rates observed, the comparative survival figures from the compassionate use cohort (approx. nine months median survival and 35% one-year survival) appear to be in line with the results of these trials. In one of the second-line phase III studies, best supportive care was associated with a median survival of only 6.5 months and 14% one-year survival.[6] Whether or not these data suggest a clinical benefit for irinotecan in the compassionate use setting is difficult to discern due to methodological complications such as the comparison with a historic control group and the nontrial setting in which the compassionate use data have been collected.

In conclusion, the controlled release of irinotecan in a compassionate use setting in the Netherlands prior to registration may be regarded a successful initiative, giving over 100 patients with advanced colorectal cancer access to a nonregistered drug with potential benefit for the treatment of their disease. Elaborate 'protocolised' precautions by the manufacturer of irinotecan aimed at the prevention and management of potential serious toxicities seem to have contributed to the relatively safe use of the drug outside the setting of a formal clinical trial.

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PARTICIPATING HOSPITALS

University Medical Centre St Radboud, Nijmegen; Antoni van Leeuwenhoek Hospital, Amsterdam; St. Jansdal Hospital, Harderwijk; Reinier de Graaf Gasthuis, Delft; Medical Spectrum Twente, Enschede; Gooi-Noord Hospital, Blaricum; University Medical Centrum, Amsterdam; Nij Smellinghe Hospital, Drachten; Catharina Hospital, Eindhoven; Red Cross Hospital, The Hague; Atrium Medical Centre, Brunssum; Free University Hospital, Amsterdam; Eemland Hospital, Amersfoort; Leiden

University Medical Centre, Leiden; Isala Clinics, location Sophia, Zwolle; St. Joseph Hospital, Veldhoven; Diakonessenhuis, Eindhoven; University Medical Centre, Utrecht; Martini Hospital, Groningen; Rijnstate Hospital, Arnhem; University Hospital Maastricht; Amstelveen Hospital, Amstelveen; Onze Lieve Vrouwe Gasthuis, Amsterdam; St. Elisabeth Hospital, Tilburg; St. Antonius Hospital, Nieuwegein; Slotervaart Hospital, Amsterdam; De Baronie Hospital, Breda; St. Franciscus Hospital, Roosendaal; Canisius-Wilhelmina Hospital, Nijmegen; Deventer Hospital, Deventer; Leeuwarden Medical Centre, location Zuid, Leeuwarden; Twenteborg Hospital, Almelo; Walcheren Hospital, Vlissingen; Ziekenhuiscentrum Apeldoorn, Apeldoorn; Rijnland Hospital, location St. Elisabeth, Leiderdorp; St. Anna Hospital, Geldrop; Diakonessenhuis Voorburg, Voorburg; Bosch Medicentrum, Den Bosch; De Heel Hospital, Zaandam; Laurentius Hospital, Roermond.

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