Systematic review of benefits and risks of second-line irinotecan monotherapy for advanced colorectal cancer

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This study was performed to obtain a comprehensive overview of the benefits and risks of second-line irinotecan monotherapy for advanced colorectal cancer. The literature was systematically reviewed to identify phase II and phase III trials that investigated the effect of second-line monotherapy with irinotecan. Thirty studies were included in this review: 25 phase II studies including 32 samples and five phase III studies including six samples. A disease control rate of greater than or equal to 50% was found in 23 out of 32 phase II samples, and one out of two phase III samples that reported disease control rate. Median time to progression was 2.7–6.0 months in phase II samples and 3.0–4.3 months in phase III samples. Median overall survival ranged from 6.6 to 16.1 months in phase II samples and 9.1–10.8 months in phase III samples. The most important severe adverse event in both phase II and phase III trials was diarrhea (5–39 and 15–36%, respectively), followed by nausea (1–24 and 5–14%), vomiting (2–22 and 6–14%), and asthenia (0–31 and 4–21%). Treatment-related mortality was 0–2% in phase II samples and 0–5% in phase III samples. Quality-of-life scores in phase II studies were associated with tumor response. In phase III studies, the quality of life while on treatment with irinotecan was similar to that of 5-fluorouracil, but better than supportive care alone. The quality of life on the weekly schedule was similar to the 3-weekly schedule. This study provides a comprehensive overview of the benefits and risks of second-line irinotecan. In general, second-line treatment with irinotecan is beneficial to patients. *Anti-Cancer Drugs* **21:749–758**

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Introduction

Colorectal cancer is one of the three most common adult malignancies worldwide [1]. Approximately 50% of patients with colorectal cancer will ultimately develop incurable locally recurrent or metastatic disease [2]. These patients can be treated with palliative chemotherapy to control symptoms, maintain or improve quality of life (QoL), and prolong survival [3]. Chemotherapeutic options include fluoropyrimidines, oxaliplatin, and irinotecan. First-line treatment consists of a fluoropyrimidine [intravenously 5-fluorouracil (5-FU) or oral fluoropyrimidines] in various combinations and schedules [4]. Combination chemotherapy with 5-FU, leucovorin (LV), and oxaliplatin (FOLFOX) or 5-FU, LV, and irinotecan (FOLFIRI) provides higher response rates, longer progression-free survival and better survival than 5-FU/LV alone. As FOLFOX is a more common choice for first-line treatment, irinotecan is the most likely option for second-line treatment.

Despite these recommendations for second-line palliative chemotherapy, there are uncertainties about the balance between benefits and risks. The potential benefits of irinotecan (control symptoms, maintain or improve QoL, and prolong survival) have to be weighed against the potential risks of treatment-related mortality and morbidity, which consists mainly of neutropenia, nausea, vomiting, diarrhea, and asthenia [5]. This decision could be supported by a comprehensive overview of benefits and risks of second-line irinotecan monotherapy.

A number of reviews, including one from the Cochrane Collaboration, have discussed the use of second-line irinotecan in advanced and metastatic colorectal cancer [6–9]. The Cochrane review used a strict methodology, including only randomized controlled trials, and the search strategy and characteristics of the included studies were presented in detail [8]. On account of the strict inclusion criteria, this review included only six studies reporting on second-line irinotecan. The other three reviews were written by experts in the field and did not report on the search strategy or on the characteristics of the studies that were included [6,7,9].

This review will provide a comprehensive overview of the benefits and risks of second-line treatment with irinotecan, including all available evidence from phase II and phase III studies.

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Methods

Literature search

A literature search was performed in MEDLINE, EMBASE, PubMed, and the Cochrane Controlled Trials Register for studies published between 1990 and April 2007. The search strategy for MEDLINE is shown in Appendix 1. This strategy was modified for the other bibliographic databases. The reference lists of all relevant articles were reviewed for additional studies. Searching took place between January and August 2007. Studies were included if they met the following criteria: (i) phase II or III clinical trial; (ii) patients with locally advanced or metastatic colorectal cancer; (iii) second-line palliative chemotherapy using systemically administered irinotecan monotherapy; (iv) outcome measures include tumor response rate, median time to progression (TTP), median overall survival (OS), severe adverse events, and/or QoL data; and (v) full-length articles in English, Dutch, German, or French language. Within randomized trials, only patients groups (referred to as 'samples' in the results) in whom second-line monotherapy with irinotecan was investigated were included.

Data collection

With regard to the study design, from each sample the phase of the clinical trial and the chemotherapeutic regimen were extracted. As for patient characteristics, data on sex, median age, WHO performance status, tumor site (which could be colon or rectum), involvement of more than one organ, and liver involvement were obtained.

The following outcome data were extracted: tumor response rate, median TTP, median OS, incidence of severe adverse events, and QoL scores. To compare tumor response rates between phase II and III phase studies, response rates of phase II studies (usually computed by including only assessable patients) were recomputed using the intention-to-treat principle, following Zia *et al.* [10]. For our overview, the outcome of interest for tumor response rate was the disease control rate (overall response and stable disease). The incidence of grade 3 or 4 adverse events during the course of chemotherapy and up to 30 days after the last chemotherapy gift was extracted. Treatment with irinotecan can cause a variety of adverse events. Therefore, a selection of severe adverse events (grades 3–4) was made based on incidence and relevance for the patient [11,12]. For alopecia, all grades of adverse events (grades 1–4) were extracted.

Results

Literature search

The systematic literature search identified 2905 studies. Figure 1 presents a flow diagram of the ensuing selection process [13].

Thirty studies met all criteria and were included in this review (see Table 1).

In the 25 phase II studies included, 32 relevant samples were identified [5,14–37] and in the five phase III studies, six relevant samples were identified [38–42].

Phase II studies

Description of studies

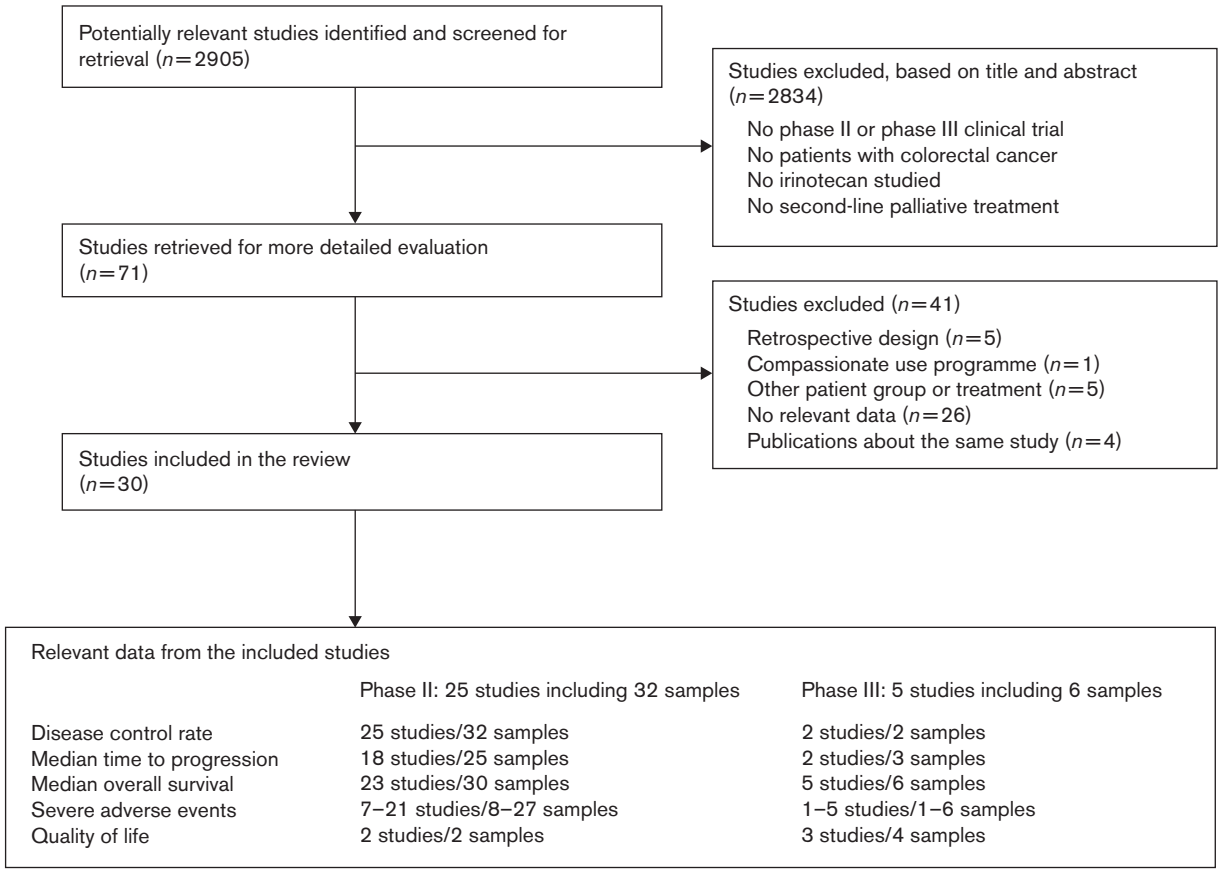
In the 32 samples from the phase II studies a variety of chemotherapeutic regimens were used. In 10 study samples, irinotecan was administered 3-weekly, using a dose of 350 mg/m^2 [5,17,19,20,23,25,29,30,33,35]. In seven study samples, irinotecan was administered weekly for 4 consecutive weeks, using a dose of 125 mg/m^2, followed by a 2-week rest period [15,16,18,22,26,35,37]. The remaining 14 study samples used other regimens, including dose variations on the 3-weekly schedule [21,30] and the weekly schedule [14,18,28,32]. Furthermore, there were changes in the frequency of the schedule to weekly doses without a rest period [27], or to a 2-weekly schedule [34,35,36], and changes in the dose by escalation [5,31], or adapting the dose according to patient characteristics [5,24,34].

A total of 1894 patients (range 16–165) were included between 1989 and 2004. Data on sex was reported for 31 out of 32 samples, of which 23 samples included a majority of men (range 51–76%), six samples included a majority of women (range 51–61%), and two samples included equal percentages of men and women. Median age was reported for all samples, except for one sample that reported mean age, which ranged from 53 to 67 years of age. WHO performance status was reported for 30 samples, of which 27 reported on the percentage of patients with a status of 0, 1, or 2. Except for one sample including relatively few patients (50%) with a performance status of 0 or 1, the remaining 26 samples included 73–100% of patients with a status of 0 or 1. Out of 25 samples reporting on disease location, in 21 samples more patients with a tumor in the colon, as opposed to the rectum, were included (54–82%). Involvement of multiple organs, which was reported for 16 out of 32 samples, ranged from 19 to 84%. Twenty-seven out of 28 samples included a majority of patients with liver involvement (53–88%). With regard to earlier treatment, 92–100% of patients had undergone surgery earlier, 0–44% had received radiotherapy earlier, and almost all patients included in these samples had received chemotherapy with fluoropyrimidines earlier, most of them in the palliative setting.

Outcomes

Table 2 presents an overview of disease control rate, median TTP, and median OS. Disease control rate could be computed for all 32 samples, and ranged from 25.9 to 72.6%. Twenty-three samples reported a disease control rate of at least 50%. Median TTP was reported in 25 samples and ranged from 2.7 to 6.0 months. Median OS was reported in 30 samples, which showed a wide range of 6.6–16.1 months. Eleven samples reported a median OS shorter than 9 months, whereas 19 samples reported a median OS of 9 months or longer.

Fig. 1



Flow diagram.

An overview of severe adverse events is provided in Table 3. All samples reported on the incidence of severe adverse events, but five samples reported the incidence of events for each cycle and not for each patient [20,24,25,30]. Therefore, Table 3 presents no data for these five samples, except for alopecia and treatment-related mortality. Most severe adverse events (grades 3–4) were gastrointestinal. The highest incidence was reported for severe diarrhea (5–39%). Nausea (1–24%) and vomiting (2–22%) were also frequently observed, whereas lower incidence rates were observed for anorexia (0–12%), constipation (0–6%), and mucositis (0–3%). With regard to other severe adverse events, severe asthenia was frequently observed (0–31%). Alopecia (grades 1–4) was observed in 32–100% of patients. A treatment-related mortality of 2% was seen in two samples, whereas the other 13 out of 15 samples reported no treatment-related mortality.

QoL was reported in two samples. In the first sample, Van Cutsem *et al.* [19] ($n = 107$) used the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [43], which was filled in at baseline and before each 3-weekly cycle. Questionnaire return rate was not reported. The median Global Health Status improved with successive cycles, probably because of the selection of patients with treatment benefit. In patients who had a partial response, median Global Health Status was 75.9, compared with 63.1 in nonresponders, and 58.3 in patients with progression as a best response. In the second sample, Michael *et al.* [22] ($n = 65$) used the EORTC QLQ-C30 version 2.0, which was filled in every 6 weeks. Questionnaire return rate was 98% at baseline and 93% during treatment. At baseline, there were significant role and physical impairments, with a marked reduction in overall QoL. On treatment, there was a significant improvement in social functioning and pain intensity. There were nonsignificant trends towards improved global QoL score and emotional functioning, reduction of fatigue, and anorexia, and worsening of diarrhea.

Phase III studies

Description of studies

Within the phase III studies that were included, randomized comparisons were made between irinotecan and best supportive care [38], irinotecan and fluorouracil by continuous infusion [39], and weekly irinotecan and

Table 1 Study characteristics

Study	*n*	Chemotherapeutic regimen	Sex (male/female, %)	Age median (range)	WHO status %			Tumor site colon (vs. rectum, %)	More than 1 organ involved (%)	Liver involved (%)
					0	1	2			
Phase II studies										
Shimada *et al.* [14]	67	A: 100 mg/m^2 weekly (n=31) B: 150 mg/m^2 every 2 weeks (n=32)	59/41	57 (24–72)	38	35	22	–	–	63
Rothenberg *et al.* [15]	48	150 mg/m^2 (n=9) and 125 mg/m^2 (n=39) every week for 4 weeks, 2-week rest	54/46	63 (29–78)	60	38	2	–	–	67
Pitot *et al.* [16]	90	125 mg/m^2 every week for 4 weeks, 2-week rest	64/36	63 (32–82)	38	48	14	74	–	–
Rougier *et al.* [17]	165	350 mg/m^2 every 3 weeks	56/44	60	52	35	13	73	69	79
Rothenberg *et al.* [18]	64	125 mg/m^2 every week for 4 weeks, 2-week rest	50/50	61 (42–84)	59	33	8	–	84	80
	102	100 mg/m^2 every week for 4 weeks, 2-week rest	49/51	64 (25–84)	44	51	5	–	79	72
Van Cutsem *et al.* [19]	107	350 mg/m^2 every 3 weeks	59/41	58 (28–72)	Median 1	(0–2)		68	–	–
Ratanatharathorn *et al.* [20]	16	350 mg/m^2 every 3 weeks	69/31	56 (41–68)	88	13	0	69	44	33
Ulrich-Pur *et al.* [21]	38	175 mg/m^2 on days 1 and 10 every 3 weeks	76/24	65 (31–75)	24	63	13	58	76	74
Michael *et al.* [22]	65	125 mg/m^2 every week for 4 weeks, 2-week rest	51/49	56	8	77	15	68	71	75
See *et al.* [23]	33	350 mg/m^2 every 3 weeks	73/27	58 (39–70)	–	–	–	55	–	–
Tsavaris *et al.* [24]	90	350 mg/m^2 every 3 weeks (WHO 0) or 250 mg/m^2 every 3 weeks (WHO 1)	61/39	66 (42–70)	49	51	0	–	–	79
Antón *et al.* [25]	60	350 mg/m^2 every 3 weeks	62/38	58 (37–70)	53	42	5	67	38	73
Cassinello *et al.* [26]	69	125 mg/m^2 every week for 4 weeks, 2-week rest	49/51	63 (37–79)	45	49	6	57	36	71
Cerea *et al.* [27]	16	125 mg/m^{2}weekly	44/56	63 (42–74)	Median 0	(0–1)		–	–	76
Karaoğlu *et al.* [28]	36	100 mg/m^2 every week for 4 weeks, 2-week rest	61/39	53 (33–72)	Median 0	(0–2)		66	19	61
Méndez *et al.* [29]	115	350 mg/m^2 every 3 weeks	62/38	61 (32–75)	40	55	5	64	36	73
Tsavaris *et al.* [30]	60	350 mg/m^2 every 3 weeks	57/43	64 (48–70)	60	40	0	32	–	78
	60	175 mg/m^2 on days 1 and 10 every 3 weeks	60/40	62 (46–70)	65	35	0	35	–	82
Viéitez *et al.* [31]	35	250 mg/m^2 every 3 weeks, increased by 50 mg/m^{2}in each cycle	63/37	63 (42–75)	5	45	48	–	46	–
Benavides *et al.* [32]	34	100 mg/m^2 every week for 4 weeks, 2-week rest	38/62	60 (34–75)	0	71	29	68	26	53
Hartmann *et al.* [33]	50	350 mg/m^2 every 3 weeks	42/58	59 (39–77)	40	56	4	46	52	88
Saigi *et al.* [34]	45	200 mg/m^2 every 2 weeks (high risk)	58/42	64 (31–77)	–	–	–	56	–	67
	51	250 mg/m^2 every 2 weeks (low risk)	69/31	65 (31–79)	100	0	0	82	–	87
Schoemaker *et al.* [35]	41	350 mg/m^2 every 3 weeks	56/44	60 (28–75)	29	68	2	54	29	85
	37	125 mg/m^2 every week for 4 weeks, 2-week rest	46/54	58 (41–71)	35	54	11	65	46	84
	46	250 mg/m^2 every 2 weeks	59/41	62 (35–74)	46	52	2	59	35	72
García-Girón *et al.* [36]	63	250 mg/m^2 every 2 weeks	-/-	Mean: 63 (41–75)	46	48	6	60	–	66
Van Cutsem *et al.* [5]	36	350 mg/m^2 every 3 weeks	50/50	60 (29–71)	50	44	6	64	–	70
	62	250 mg/m^2 every 3 weeks (increasing to 350 and 500 mg/m^2)	71/29	59 (33–70)	60	36	5	66	–	79
	66	500 mg/m^2, 350 mg/m^2, or 250 mg/m^2, based on toxicity risk factors	62/38	60 (30–70)	46	53	2	67	–	80
Graeven *et al.* [37]	27	125 mg/m^2 every week for 4 weeks, 2-week rest	74/26	67 (53–78)	37	56	7	48	–	74
Phase III studies										
Cunningham *et al.* [38]	189	350 mg/m^2 every 3 weeks	68/32	59 (22–75)	47	39	14	53	57	80
Rougier *et al.* [39]	127	350 mg/m^2 every 3 weeks	57/43	58 (30–75)	57	35	8	56	52	79
Aravantinos *et al.* [40]	62	350 mg/m^2 every 3 weeks	65/35	63 (23–75)	53	36	11	79	66	69
Fuchs *et al.* [41]	95	125 mg/m^2 every week for 4 weeks, 2-week rest	62/38	<70:66%[a]	48	46	5	78	44	73
	196	350 mg/m^2 every 3 weeks	58/42	≥ 70:34%[a]	43	45	11	76	54	70
Chau *et al.* [42]	339	350 mg/m^2 every 3 weeks	59/41	62 (29–80)	27	61	12	62	–	73

–, data not reported.
[a]Owing to stratification by age, both samples contained equal percentages of patients <70 vs. ≥ 70.

3-weekly irinotecan [41]. Furthermore, one sample presented a selection of patients from Greece from a large international phase III study evaluating the benefit of adding granulocyte colony-stimulating factor to irinotecan [40]. In the remaining sample, the patients who achieved an objective response or disease stabilization after 24 weeks of irinotecan were randomized to either stop or continue irinotecan [42].

In these six samples from phase III studies, only the 3-weekly regimens (five samples) and the weekly regimen (one sample) were used. A total of 1008 patients (range 62–339) were included between 1995 and 2003. All samples included a majority of men (range 57–68%) and median age, which was reported in four samples, ranged from 58 to 63 years of age. Furthermore, 86–94% of patients had a WHO performance status of 0 or 1. In all six samples, the disease was more often located in the colon, as opposed to the rectum (53–79%). Next, 44–66% of patients had multiple organ involvement and 69–80% had liver involvement. With regard to earlier treatment, 91–99% of patients had undergone surgery earlier, 8–28% had received radiotherapy earlier, and almost all patients had received chemotherapy earlier with fluoropyrimidines, most of them in the palliative setting.

Outcomes

Disease control rate, which could be computed in two phase III samples, was 42.4 and 54.9%, respectively. Median TTP was reported in three samples and ranged from 3.0 to 4.3 months. All six samples reported a median OS of more than 9 months (range 9.1–10.8).

Severe adverse events (grades 3–4) were reported for all six samples. Most of the reported severe adverse events were gastrointestinal, including diarrhea (15–36%), nausea (5–14%), and vomiting (6–14%). Furthermore, severe asthenia was observed in 4–21% of patients. One sample reported that 86% of patients experienced some grade of alopecia. Treatment-related mortality ranged from 0 to 5%.

QoL was reported in four samples. Cunningham *et al.* [38] ($n = 189$) used the EORTC QLQ C-30, which was filled in at baseline, at 3 weeks, 6 weeks, and then every 6 weeks. After discontinuation of treatment in the irinotecan group, the patients continued to fill in the QLQ–C30 questionnaires every 6 weeks as in the supportive-care group. Questionnaire return rate at baseline was approximately 80% in both groups and decreased during the study to approximately 50%. Questionnaire return rate decreased more rapidly in the supportive-care group, which the investigators attributed to earlier deterioration in the patients. All significant differences were in the favor of the irinotecan group, except for diarrhea score. In the sample of Rougier *et al.* [39] ($n = 127$) the EORTC QLQ-C30 was filled in at baseline, at 3 weeks, and at 6 weeks, then every two visits up to 1 year. After the treatment was stopped the questionnaire was filled in every 6 weeks in both the groups. The questionnaire return rate was similar in both the groups: 67% in the irinotecan group and 70% in the fluorouracil group. QoL scores were also similar in both the groups. In the two samples of Fuchs *et al.* [41] ($n = 95$ and $n = 196$) the EORTC QLQ-C30 version 2.0 was filled in at baseline, every 6 weeks during treatment and at treatment discontinuation. Questionnaire return rate was similar in the two groups: 81% in the weekly irinotecan group and 86% in the every-3-weeks irinotecan group. There were no significant differences in the QoL scores between the treatment groups.

Discussion

Our study provides a comprehensive overview of the benefits and risks of second-line irinotecan. A disease control rate of at least 50% was reported in 23 out of 32 phase II samples and one out of two phase III samples. Median TTP was 2.7–6.0 months in phase II samples and 3.0–4.3 months in phase III samples. Median OS was 6.6–16.1 months in phase II samples and 9.1–10.8 months in phase III samples. The most important severe adverse event in both phase II and phase III studies was diarrhea, followed by nausea, vomiting, asthenia, and alopecia (grades 1–4). Treatment-related mortality was 0–2% in phase II samples and 0–5% in phase III samples. QoL scores in phase II studies were in accordance with tumor response: highest scores were observed for patients with an objective response, followed by patients with stable disease, followed by patients with progressive disease. Randomized phase III studies showed that QoL on treatment with irinotecan was similar to 5-FU, but better than supportive care alone. In addition, a similar QoL was observed for the weekly and 3-weekly irinotecan schedule.

In this review, extensive search was undertaken by using a highly sensitive search strategy in multiple databases, followed by an additional search of the reference lists. Sufficient studies were available to provide an overview of the benefits and risks of irinotecan, but there is a possibility of a publication bias, as studies finding a lack of benefit or a high incidence of severe adverse events may have been abandoned by scientists or rejected by editors.

The available data originate from a variety of phase II and phase III studies. Differences in study design may hamper the comparability of studies. An important factor in the study design is the phase of the clinical trial. In this review, the phase III studies that were included reported higher treatment-related mortality than the included phase II studies. A plausible explanation would be the selection of patients with good prognostic factors for phase II studies, but no obvious differences were observed in this review between the patients included in phase II and phase III studies regarding sex, median age, WHO performance status, tumor site, involvement of more than one organ, liver involvement, and pretreatment. A second factor in the study design is the regimen of irinotecan used. Two of the studies that were included, a randomized phase II study [35] and a randomized phase III study [41], compared the weekly and the 3-weekly regimen. Similar disease control rates, median TTP, and median OS were found. However, a higher incidence of severe diarrhea was reported with the weekly regimen compared with the 3-weekly regimen in both the phase II study, which reported the incidence in percentage of cycles, and the phase III study (36 vs. 19%, respectively; $P = 0.002$). In this review also higher incidence of severe

Table 2 Disease control rate, median time to progression, and median overall survival

Study	*n*	Tumor response					Median TTP (months)	Median OS (months)
		OR (%)	SD (%)	PD (%)	Not eligible/not assessable (%)	Disease control rate (%)[a]		
Phase II studies								
Shimada *et al.* [14]	67	25.4	28.4	25.4	20.9	53.8	–	9.3
Rothenberg *et al.* [15]	48	20.8	31.3	37.5	10.4	52.1	–	10.4
Pitot *et al.* [16]	90	13.3	57.8	26.7	2.2	71.1	–	8.3
Rougier *et al.* [17]	165	13.9	26.7	29.1	30.3	40.6	4.2	10
Rothenberg *et al.* [18]	64	14.1	43.8	–	–	57.9	5.1	10.6
	102	8.8	38.2	–	–	47	3.3	9.3
Van Cutsem *et al.* [19]	107	12.1	39.3	32.7	15.9	51.4	3.9	10.4
Ratanatharathorn *et al.* [20]	16	6.3	43.8	50.0	0	50.1	2.7	16.1
Ulrich-Pur *et al.* [21]	38	21.1	50.0	28.9	0	71.1	–	–
Michael *et al.* [22]	65	7.7	35.4	27.7	29.2	43.1	–	7.2
See *et al.* [23]	33	21.2	27.3	42.4	9.1	48.5	–	9.5
Tsavaris *et al.* [24]	90	20.0	43.3	36.7	0	63.3	3.2	6.6
Antón *et al.* [25]	60	13.3	41.7	38.3	6.7	55	4.4	10.5
Cassinello *et al.* [26]	69	17.4	27.5	52.2	2.9	44.9	5.2	13.3
Cerea *et al.* [27]	16	12.5	31.3	56.3	0	43.8	4	–
Karaoğlu *et al.* [28]	36	13.9	36.1	–	–	50	4	12
Méndez *et al.* [29]	115	18.3	36.5	33.0	12.2	54.8	4.8	13.6
Tsavaris *et al.* [30]	60	21.7	35.0	43.3	0	56.7	4.5	7
	60	25.0	36.7	38.3	0	61.7	6	9
Viéitez *et al.* [31]	35	8.6	51.4	40.0	0	60	3	8
Benavides *et al.* [32]	34	20.6	38.2	41.2	0	58.8	5.5	8.3
Hartmann *et al.* [33]	50	12.0	46.0	32.0	10.0	58	3.0	7.9
Saigi *et al.* [34]	45	8.9	33.3	44.4	13.3	42.2	3.2	7.1
	51	15.7	56.9	25.5	2.0	72.6	5.3	11.7
Schoemaker *et al.* [35]	41	7.3	43.9	46.3	2.4	51.2	2.7	9.4
	37	5.4	62.2	18.9	13.5	67.6	3.5	7.1
	46	10.9	54.3	32.6	2.2	65.2	3.8	8.6
García-Girón *et al.* [36]	63	17.5	46.0	23.8	12.7	63.5	4.5	8.8
Van Cutsem *et al.* [5]	36	8.3	50.0	27.8	13.9	58.3	4.1	12.5
	62	12.9	41.0	29.0	17.7	53.9	4.2	12.1
	66	9.1	36.4	48.5	6.1	45.5	3.0	10.9
Graeven *et al.* [37]	27	11.1	14.8	48.1	25.9	25.9	–	10.7
Phase III studies								
Cunningham *et al.* [38]	189	–	–	–	–	–	–	9.2
Rougier *et al.* [39]	127	4.7	–	36.2	–	–	–	10.8
Aravantinos *et al.* [40]	62	6.5	48.4	32.3	12.9	54.9	4.3	9.6
Fuchs *et al.* [41]	95	–	–	–	–	–	4.0	9.9
	196	–	–	–	–	–	3.0	9.9
Chau *et al.* [42]	339	9.4	33.0	57.5	0	42.4	–	9.1

–, data not reported.
OR, overall response; OS, overall survival; PD, progressive disease; SD, stable disease, TTP, time to progression.
[a]The outcome of interest for tumor response is disease control rate, which is computed by combining the overall response and stable disease.

diarrhea was seen in the weekly regimen compared with the 3-weekly regimen, in both phase II (27.1 vs. 22.2%) and phase III studies (36.2 vs. 18.7%).

When extending the results of our review to patients with colorectal cancer who are eligible for second-line irinotecan as encountered in daily clinical practice, there are a number of limitations. First, because of selective recruitment of patients for clinical trials, trial participants may have more favorable prognostic factors than the nonparticipants [44]. Meanwhile, a compassionate use program in 40 hospitals in The Netherlands including 112 patients showed results that are comparable with the results of this review [45]. In addition, a retrospective chart review in one institution among all nontrial patients treated with irinotecan showed that toxicity rates in nontrial patients were not statistically different from the rates reported in published clinical trials [46]. Second, not all patients included in the clinical trials received irinotecan as second-line treatment; in some of the samples irinotecan was administered as first-line treatment (after an adjuvant treatment including fluoropyrimidines) or as third-line or fourth-line treatment.

This review focused on irinotecan monotherapy, whereas during the last decade a number of targeted agents have been developed. The addition of these targeted agents to irinotecan monotherapy may improve efficacy. A retrospective evaluation on bevacizumab and a phase III trial on cetuximab has shown that the addition of either of these targeted agents to irinotecan improves efficacy, with a tolerable safety profile [47,48]. Second, panitumumab has been investigated in the first-line setting and in patients refractory to standard chemotherapy, but no trials in the second-line setting have been published yet.

Another factor associated with the outcome of irinotecan is the genetic variation of proteins involved in irinotecan metabolism. These variations are important when

Table 3 Severe adverse events (grades 3–4)

Study	n	Nausea (*n*, %)	Vomiting (*n*, %)	Nausea and/or vomiting (*n*, %)	Diarrhea (*n*, %)	Constipation (*n*, %)	Anorexia (*n*, %)	Mucositis/ stomatitis (*n*, %)	Asthenia/ fatigue (*n*, %)	Alopecia (grades 1–4) (*n*, %)	Treatment-related mortality (*n*, %)
Phase II studies											
Shimada *et al.* [14]	67	–	–	8 (13)	8 (13	–	–	–	–	39 (62)	–
Rothenberg *et al.* [15]	48	5 (10)	8 (17)	–	18 (38)	–	–	–	3 (6)	–	–
Pitot *et al.* [16]	90	22 (24)	14 (16)	–	33 (36)	1 (1)	11 (12)	2 (2)	9 (7)	63 (70)	–
Rougier *et al.* [17]	165	–	–	36 (22)	64 (39)	–	–	0 (0)	–	128 (88)	–
Rothenberg *et al.* [18]	64	–	14 (22)	–	21 (33)	–	–	–	10 (16)	36 (56)	0 (0)
	102	–	2 (2)	–	24 (24)	–	–	–	17 (17)	57 (56)	0 (0)
Van Cutsem *et al.* [19]	107	–	–	20 (19)	28 (26)	0 (0)	3 (3)	2 (2)	9 (8)	97 (91)	0 (0)
Ratanatharathorn *et al.* [20]	16	×	×	×	×	×	×	×	×	×	0 (0)
Ulrich-Pur *et al.* [21]	38	–	–	0 (0)	2 (5)	0 (0)	0 (0)	–	0 (0)	24 (63)	–
Michael *et al.* [22]	65	–	–	14 (21)	17 (26)	–	–	–	10 (15)	–	0 (0)
See *et al.* [23]	33	–	5 (17)	–	2 (7)	–	–	–	–	30 (100)	–
Tsavaris *et al.* [24]	90	×	×	×	×	×	×	×	×	90 (100)	0 (0)
Antón *et al.* [25]	60	×	×	×	×	×	×	×	×	50 (80)	–
Cassinello *et al.* [26]	69	1 (1)	7 (10)	–	10 (15)	1 (1)	1(1)	–	1 (1)	–	–
Cerea *et al.* [27]	16	–	–	0 (0)	6 (38)	–	–	–	–	–	–
Karaoğlu *et al.* [28]	36	8 (22)	3 (8)	–	10 (28)	2 (6)	1 (3)	0 (0)	–	14 (39)	0 (0)
Méndez *et al.* [29]	115	–	–	12 (10)	22 (19)	3 (3)	–	1 (1)	3 (3)	–	2 (2)
Tsavaris *et al.* [30]	60	×	×	×	×	×	×	×	×	×	–
	60	×	×	×	×	×	×	×	×	×	–
Viéitez *et al.* [31]	35	–	–	2 (6)	6 (17)	–	–	0 (0)	–	11 (32)	–
Benavides *et al.* [32]	34	2 (6)	2 (6)	–	10 (29)	–	–	1 (3)	–	–	–
Hartmann *et al.* [33]	50	2 (4)	4 (8	–	12 (24)	2 (4)	–	1 (2)	1 (2)	–	–
Saigi *et al.* [34]	45	2 (4)	3 (7)	–	8 (18)	–	–	0 (0)	14 (31)	–	0 (0)
	51	4 (8)	1 (2)	–	7 (14)	–	–	1 (2)	4 (8)	–	0 (0)
Schoemaker *et al.* [35]	41	6 (15)	4 (10)	–	4 (10)	–	0 (0)	–	3 (7)	29 (71)	–
	37	2 (5)	1 (3)	–	9 (24)	–	0 (0)	–	1 (3)	16 (43)	–
	46	4 (9)	4 (9)	–	6 (13)	–	0 (0)	–	2 (4)	31 (67)	–
García-Girón *et al.* [36]	63	6 (10)	7 (11)	–	12 (19)	–	–	1 (2)	–	–	0 (0)
Van Cutsem *et al.* [5]	36	4 (11)	5 (14)	–	11 (31)	–	–	–	3 (8)	–	0 (0)
	62	7 (11)	10 (16)	–	13 (21)	–	–	–	7 (11)	–	1 (2)
	66	7 (11)	6 (9)	–	18 (27)	–	–	–	8 (12)	–	0 (0)
Graeven *et al.* [37]	27	2 (7)	1 (4)	–	5 (19)	1 (4)	0 (0)	0 (0)	–	17 (63)	0 (0)
Phase III studies											
Cunningham *et al.* [38]	189	26 (14)	26 (14)	–	42 (22)	19 (10)	9 (5)	4 (2)	28 (15)	–	2 (1)
Rougier *et al.* [39]	127	14 (11)	18 (14)	–	28 (22)	10 (8)	7 (6)	3 (2)	17 (13)	–	0 (0)
Aravantinos *et al.* [40]	62	–	–	0 (0)	9 (15)	–	–	–	2 (4)	53 (86)	2 (3)
Fuchs *et al.* [41]	95	5 (5)	6 (6)	–	34 (36)	1 (1)	1 (1)	–	11 (12)	–	5 (5)
	196	20 (11)	24 (13)	–	36 (19)	0 (0)	6 (3)	–	21 (11)	–	3 (2)
Chau *et al.* [42]	339	–	–	18 (5)	53 (16)	–	–	–	72 (21)	–	–

–, data not reported.
×, incidence of severe adverse events reported for each cycle and not for each patient.

comparing populations with different races. In particular, polymorphisms affecting UGT1A1 expression or activity are being investigated. The evidence is currently insufficient to recommend the routine use of UGT1A1 genotyping [49].

In conclusion, for irinotecan in second line, an extensive search was undertaken. Thirty relevant studies were found. The results in general reflect more than acceptable disease control rates, median TTP, and OS durations, whereas in a randomized phase III study OS and QoL with

irinotecan were superior to best supportive care alone. Therefore, in general, second-line treatment with irinotecan is beneficial to the patient. However, decision making for individual patients may be influenced by medical factors and personal preferences. As only aggregated data were available in this review, it was not possible to identify those patients who were most likely to benefit from the treatment with irinotecan. This information could only be obtained by conducting a meta-analysis of individual patient data. Furthermore, the results from this review can be used as reference values for the design of future clinical studies on second-line schedules with new agents.

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Appendix
Medline search strategy

(1) Explode 'COLORECTAL-NEOPLASMS' (searched Colorectal Neoplasms)/all subheadings
(2) 'RECTAL NEOPLASMS'/all subheadings
(3) Explode 'SIGMOID-NEOPLASMS' (searched Sigmoid Neoplasms)/all subheadings
(4) CARCINOMA* near (COLORECTAL or COLON* or RECT* or INTESTIN* or LARGE BOWEL or BOWEL)
(5) NEOPLASIA* near (COLORECTAL or COLON* or RECT* or INTESTIN* or LARGE BOWEL or BOWEL)
(6) NEOPLASM* near (COLORECTAL or COLON* or RECT* or INTESTIN* or LARGE BOWEL or BOWEL)
(7) ADENOCARCINOMA* near (COLORECTAL or COLON* or RECT* or INTESTIN* or LARGE BOWEL or BOWEL)
(8) CANCER* near (COLORECTAL or COLON* or RECT* or INTESTIN* or LARGE BOWEL or BOWEL)
(9) Tumour* near (COLORECTAL or COLON* or RECT* or INTESTIN* or LARGE BOWEL or BOWEL)
(10) Tumour* near (COLORECTAL or COLON* or RECT* or INTESTIN* or LARGE BOWEL or BOWEL)
(11) #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
(12) CAMPTOTHECIN
(13) Irinotecan
(14) CPT-11
(15) CPT11
(16) CPT 11
(17) #12 or #13 or #14 or #15 or #16
(18) RANDOMIZED-CONTROLLED-TRIAL in PT
(19) 'Randomized-Controlled-Trials'/all SUBHEADINGS in MIME.MJME.PT
(20) CONTROLLED-CLINICAL-TRIAL in PT
(21) 'Controlled-Clinical-Trial'/WITHOUT SUBHEADINGS in MIME.MJME.PT
(22) CLINICAL-TRIAL in PT
(23) 'Clinical-Trial'/WITHOUT SUBHEADINGS in MIME.MJME.PT
(24) 'Clinical-Trial-Phase-II'/WITHOUT SUBHEADINGS in MIME.MJME.PT
(25) 'Clinical-Trial-Phase-III'/WITHOUT SUBHEADINGS in MIME.MJME.PT
(26) 'Clinical-Trial-Phase-IV'/WITHOUT SUBHEADINGS in MIME.MJME.PT
(27) explode CLINICAL-TRIALS/all subheadings
(28) (clin* near trial*) in TI
(29) (clin* near trial*) in AB
(30) (singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
(31) (#30 in TI) or (#30 in AB)
(32) 'Single-Blind-Method'/WITHOUT SUBHEADINGS in MIME.MJME.PT

(33) 'Double-Blind-Method'/WITHOUT SUBHEADINGS in MIME.MJME.PT
(34) PLACEBOS
(35) placebo* in TI
(36) placebo* in AB
(37) random* in TI
(38) random* in AB
(39) RESEARCH-DESIGN
(40) COMPARATIVE-STUDY in PT
(41) explode EVALUATION-STUDIES/all subheadings
(42) FOLLOW-UP-STUDIES
(43) PROSPECTIVE-STUDIES
(44) control* or prospectiv* or volunteer*
(45) (#44 in TI) or (#44 in AB)
(46) 'Multicenter-Studies'/all SUBHEADINGS
(47) 'Intervention-Studies'/WITHOUT SUBHEADINGS
(48) 'Cohort-Studies'/WITHOUT SUBHEADINGS
(49) 'Case-Control-Studies'/WITHOUT SUBHEADINGS in MIME.MJME.PT
(50) 'Cross-Over-Studies'/WITHOUT SUBHEADINGS in MIME.MJME.PT
(51) 'Longitudinal-Studies'/WITHOUT SUBHEADINGS in MIME.MJME.PT
(52) 'Risk-Factors'/WITHOUT SUBHEADINGS in MIME.MJME.PT
(53) 'Treatment-Outcome'/WITHOUT SUBHEADINGS in MIME.MJME.PT
(54) #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53
(55) (TG = ANIMALS) not ((TG = HUMANS) and (TG = ANIMALS))
(56) #54 not #55
(57) #11 and #17 and #56.