EUROPEAN JOURNAL OF CANCER 42 (2006) 835–845

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Review

Quality of life versus prolongation of life in patients treated with chemotherapy in advanced colorectal cancer: A review of randomized controlled clinical trials

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ARTICLE INFO

Article history:
Received 26 September 2005
Accepted 4 October 2005
Available online 14 February 2006

Keywords:
Review
Quality of life
Toxicity
Survival gain
Chemotherapy
Advanced colorectal cancer

ABSTRACT

Oncologists disagree if chemotherapy in advanced cancer can improve quality of life (QoL), to prolong duration of life, or both. The objective of this study was to clarify the main treatment intention of palliative chemotherapy (PCT): the prolongation of life (PoL); or QoL. Randomized controlled clinical trials of PCT in advanced colorectal cancer that included HRQoL assessment were selected from PubMed and reviewed. Authors' conclusions were based on both PoL- and QoL-related outcomes. However, if PoL and QoL outcomes of the experimental arm were opposite, which was the case in 13 out of 28 trials, the authors generally based their conclusion on PoL outcomes. Authors' conclusions focused mainly on PoL-related outcomes, while QoL-related outcomes were of overriding importance in only 1/28 case. QoL can therefore not be considered as the main outcome of PCT. The review shows that in the context of chemotherapy in advanced colorectal cancer, 'palliative' refers to a life-prolonging intention, whereas within palliative care it refers to an improvement in QoL.

1. Introduction

According to a paper by Porszolt and Tannock of more than 10 years ago, the critical endpoint of anticancer therapies when applied in incurable situations is relief of suffering rather than prolongation of existence.[1] In a recently published report, the Dutch Health Council defined palliative chemotherapy (PCT) as 'therapy for patients with metastatic cancer... whose functional status or quality of life (QoL) has decreased'.[2] Accordingly, the goal of PCT is defined as increasing QoL and, if possible, prolonging life with preservation of QoL.

However, many oncologists nowadays disagree about this emphasis on QoL improvement by PCT; according to them, PCT is mainly meant to prolong life. They argue that firstly, patients attach great importance to a survival gain of sometimes only a few weeks or months,[3] and secondly, if improvement of QoL would be the main goal, the use of often burdensome PCT in asymptomatic patients would be

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doi:10.1016/j.ejca.2005.10.026

unjustifiable.[4] This discussion shows a lack of clarity about the indication and effectiveness of PCT. PCT treatment can be important in the last months of someone's life, but because of its often-burdensome character, its efficacy and side effects always need to be weighed and alternative options without PCT, sometimes called 'best supportive care', should also be considered. We decided to study the main emphasis in the weighing of these two outcomes, QoL or prolongation of life (PoL), in each of the articles we studied for this paper.

In order to clarify the definitions and corresponding emphases of palliative chemotherapy, we analyzed scientific articles about PCT that took QoL assessments into account. We analyzed the main emphasis of each single article by studying the design and interpretation of the results in the conclusion(s) of the authors.

Originally, the adjective 'palliative' seems to refer to QoL rather than PoL, but we expected the focus of PCT in specific cases to lie on PoL. We formulated two hypotheses. The first hypothesis implied that the later the treatment phase (first-, second-, or third-line PCT) and shorter the life expectancy of the patients who participated, the more emphasis authors would place on QoL-related outcomes in their conclusions, as opposed to an earlier treatment phase, where the authors would place more emphasis on PoL-related outcomes. The second hypothesis implied that trials designed to test ways of administration, like oral versus parenteral medication, and more versus less frequent infusion schedules, would focus more on QoL-related outcomes and convenience of administration as opposed to trials investigating the efficacy of an added drug or single new drug, which would focus more on PoL-related outcomes.

2. Patients and methods

Randomized controlled phase III clinical trials (RCTs) concerning the effectiveness of palliative chemotherapeutics were studied. To test our two hypotheses – whether the emphasis in the weighing of PoL-related and QoL-related outcomes was different for first-compared to second-line chemotherapy (I) and for trials investigating 'administration' versus 'the activity of an added drug' (II) – RCTs in patients with advanced colorectal cancer (CRC) were studied. Choosing one tumour type enabled the comparison between different kinds of trials. Furthermore, CRC has a high incidence, is relatively chemo-sensitive, and several lines of chemotherapy are applied during the course of the disease.

2.1. *Selection*

We analyzed RCTs that included a health-related (HR) QoL assessment in patients with advanced CRC by comparing palliative chemotherapy regimens from a previous systematic review by Efficace et al.[5] They performed a literature study with the following search criteria {(colon OR colorectal OR rectum OR rectal) AND (cancer OR carcinoma OR hepatic metastases OR liver metastases OR neoplasm) AND (quality of life OR HRQoL OR QoL OR health-related quality of life OR health status OR patient-reported outcome)} and selected 31 trials on colorectal cancer, performed between 1980 and March 2003, from PubMed. We excluded seven trials from the original Efficace selection for our study because these did not concern PCT treatments and we updated the Efficace study to August 2004, using the same search strategy and adding four more trials.

2.2. *Evaluation*

In order to test the first hypothesis, trials were categorized into first- and second-line treatment. In order to explore the second hypothesis, trials were also subdivided into the categories 'ways of drug administration', 'added drug', and the rest grouped as 'single drug'. For each trial we listed the study design, QoL-, toxicity-, and PoL-related outcomes as considered in the papers. Only significant differences between the experimental and control arm were taken into account. We summarized QoL-, toxicity-, and PoL-related outcomes as better (+), equal (=) or worse (−) in the experimental than in the control arm. To summarize the QoL outcomes, we valued QoL scores higher than functional scores, and functional scores again higher than symptom scores.[6] So if QoL scores were not significantly different between the two arms except for one or two symptoms (those often also were scored within toxicity), we would still give an (=) sign for the total QoL assessment. We considered OS (overall survival), PFS (progression-free survival), FFS (failure-free survival), TTP (time to (disease) progression) as PoL outcomes.[7] RR (response rate) was not considered as a surrogate for PoL.

In the analysis, we took QoL and toxicity together, because an increase in toxicity (−) is supposed to be related to a decrease in QoL (−), and a decrease in toxicity (+) would increase QoL (+). In our study aims, these two parameters are therefore closely related. To elucidate the basis for the authors' conclusions in the RCTs, toxicity scores were taken together with QoL scores, considered as a counterpart of PoL; toxicity and QoL items were therefore taken together. If the outcomes of toxicity and QoL were different, we constructed a combined outcome as follows: (+) and (=) as (+), (=) and (−) as (−), (+) and (−) as (=). The weight of the QoL/toxicity combination versus PoL outcomes was considered in the conclusions and recommendations of the authors.

Fig. 1 shows the 'rational' conclusions, based on possible combinations of QoL/toxicity and PoL outcomes. 'E' means that it would be rational to advise the experimental arm and 'S' refers to the standard arm. We expected that in situations in which outcomes were equal or opposite, the authors' conclusions would depend on the setting and subject of the trial as formulated in the two hypotheses. All conclusions

QoL/toxicity / Survival	+	=	-
+	E	E	?
=	E	?	S
-	?	S	S

Fig. 1 – Rational advice based on the PoL versus QoL/toxicity outcomes of the experimental arm.

that were different from the 'rationale' in this model or that were based on equal or opposite outcomes were highlighted. In this way, we could indicate whether the authors' conclusion was expected or unexpected according to our preset hypotheses.

The reviewed trials were analyzed by two researchers separately (SdK, JH). Any discrepancies between the two researchers concerning the analysis (about 6/28 trials outcomes were analyzed differently) were resolved in a face-to-face discussion until consensus was reached. Most discrepancies had their origin in uncertainties about the study design, i.e. about which arm was experimental and which was control. The second author (PW) was in all cases (3/28 trials) able to clarify these uncertainties.

3. Results

In total, 28 trial papers were selected and categorized in accordance with our two hypotheses. According to the first hypothesis, as shown in the first column of Tables 1 and 2, 23 trials were placed in the 'first-line treatment' category, four trials in the 'second-line treatment' category, and one trial included patients with both first- and second-line treatment. According to the second hypothesis, as shown in the second column of Tables 1 and 2, nine trials were placed in the 'ways of drug administration' category, 12 trials in the 'added drug' category, and seven trials in the 'single drug' rest category.

Table 1 shows an overview of all different results of QoL-, toxicity- and PoL-related outcomes as reported in each paper. In 11 out of 28 trials, QoL outcomes were significantly different between the experimental and control arm; in one trial there was no clear difference. In 6 out of 11 trials, the QoL outcomes were better in the experimental arm; in three trials they were worse. As for toxicity, in 23 out of 28 trials toxicity outcomes were significantly different between the two arms; in three trials the difference was unclear. In 17 out of 23 trials, the experimental arm was more toxic and in six trials less toxic than the control arm. With regard to PoL, in 14 out of 28 trials the outcomes were significantly different between the two arms; in one trial the result was unclear. In 12 of these 14 trials the experimental arm showed an increase in PoL; the other two showed an increase in PoL for the control arm.

In Table 2, the results regarding QoL, toxicity, the QoL/toxicity combination and PoL are presented, reflecting whether the experimental arm was better (+), equal (=) or worse (−) than the standard arm. Based on these results the 'rational' conclusions (see Section 2) were compared to the authors' conclusions. We found that according to our 'rationale' nine trials should have concluded that the experimental arm was better (E) and six trials that the standard arm was better (S). In the other 13 trials, we found no direct clear conclusion because the QoL/toxicity and PoL outcomes were either equal or opposite. In just one (Maughan) out of the 15 (E and S) conclusive trials the authors' conclusions were not in agreement with this 'rationale'.

Authors' conclusions in the 13 trials with equal or opposite QoL/toxicity and PoL outcomes were evaluated with respect to the first and second hypothesis (not mentioned in Table 2). Regarding our first hypothesis, the authors' conclusions were mainly based on PoL-related outcomes in both first-line treatment (9 out of 11) and second-line treatment (1 out of 2), whereas we would have expected that for second-line treatments QoL-related outcomes would play a more important role. However, the low number of second-line trials limits the value of this observation. Regarding our second hypothesis, the authors' conclusions were also mainly based on PoL-related outcomes in the 'administration' category (2 out of 4) and in the 'added drug' category (3 out of 5), whereas we expected that for trials in the 'administration' category QoL-related outcomes would be of overriding importance.

4. Discussion

In this study, we analyzed the importance of QoL- versus PoL-related outcomes as study objective in RCTs comparing chemotherapeutic regimens in patients with advanced colorectal cancer. RCTs represent the standard by which health-care professionals make evidence-based decisions about treatments. The interpretations authors made in these RCTs, largely influence final clinical decision-making by physicians. The question whether palliative chemotherapy is mainly meant to prolong life or to palliate symptoms has, as far as we know, never been studied in this way.

If PoL-related and QoL-related outcomes were opposite, the authors based their conclusions mainly on PoL-related outcomes. Two other observations confirmed our finding that in the authors' evaluation of trial outcomes PoL was a more important outcome measure than QoL. Firstly, the evaluation of QoL outcomes was generally less elaborate and, if mentioned at all, always came after the description of the PoL and toxicity outcomes. Space restrictions or interests of the journals in which the papers were published might have played a role in this. Secondly, the primary endpoints almost always considered PoL-related outcomes; QoL- and toxicity-related outcomes were often secondary endpoints.

By summarizing the outcome data as we did in Table 2, the magnitude of the different outcomes disappeared. This is a shortcoming of our study in the weighing of the different outcomes. However, QoL- and PoL-related outcomes are hard to compare objectively anyway, so we could not have done this differently. Furthermore, one could say that the unequal numbers of trials per category complicated the interpretation of our findings. Even though second- and third-line chemotherapy is widely used in clinical practice, just 5 out of 28 trials involved second-line treatment and we could not find any trial involving third-line treatment. Most trials were in the 'first-line' and 'added drug' categories. This unequal distribution of trials in the different categories made it harder to make a good comparison as formulated in the two hypotheses. However, in this critical review we had no intention to quantify our data, and we think we succeeded in showing the trends.

Through our selection criteria we limited our study to trials that included a QoL assessment. This may have introduced a bias, because trials without a QoL assessment of course place even more emphasis on prolongation-related outcomes than we found.

Table 1 – Review trials, in alphabetic order by first author, study design, results on QoL, toxicity- and survival-related outcomes, as reported in trial articles

First hypothesis	Second hypothesis	Trial (first author, year of publication, reference)	Study design (experimental versus control)	QoL (experimental versus control)	Toxicity (experimental versus control)	Prolongation-related (experimental versus control)
First-line chemotherapy	Ways of administration	Caudry, 1995[11]	FUMIC or FUcont versus bolus FU-FA	n.s., only at 4 months FUcont 53% is better than FU-FA 27% ($P = 0.04$)	FUMIC arm stopped because of tox. Tox. FUcont 62% versus FU-FA 69% ($P = ?$), diarrhea FUcont 18% versus FU-FA 45% ($P = 0.01$), HFS FUcont 46% versus FU-FA 8% ($P < 0.0001$)	RR FUcont 45.8% versus FU-FA 25% ($P = 0.048$), PFS FUcont 8 versus FU-FA 4.4 months ($P = 0.0026$), OS FUcont 12.9 versus FU-FA 9.6 months ($P = 0.028$)
		Earlam, 1997[12]	Hepatic artery chemotherapy (HAC) versus systemic chemotherapy or symptom control	HAD sign. increased in control arm, syst. chemo lived sign. longer with abnormal HAD and RSC compared to HAC	More grade 3/4 stomatitis ($P = 0.01$) in syst. chemo compared to HAC	OS n.s.
		Sobrero, 2000[13]	MTX with 3 weekly or continuous 5-FU/LV versus MTX followed by bolus 5-FU/LV	n.s.	Grade 3/4 toxicity 13% versus 8%/cycle, sign. more stomatitis, HFS, diarrhea in exp. arm ($P = ?$)	RR 32% versus 13% ($P = 0.001$), PFS 6.2 versus 4.3 months ($P = 0.003$), OS n.s.
		Carmichael, 2002[14]	UFT (tegafur/uracil) versus 5-FU/LV	n.s.	Safety benefits for UFT/LV: less stomatitis/mucositis ($P < 0.001$), and febrile neutropenia ($P < 0.001$)	TTP, OS, TR, DR, TTR n.s.
		Douillard, 2002[15]	UFT/LV versus IV 5-FU/LV	n.s.	UFT/LV is sign. safer in diarrhea, nausea, vomiting, stomatitis, myelosuppression	OS, RR no difference, TTP UFT/LV 3.5 versus 5-FU/LV 3.8 months ($P = 0.011$)
		Köhne, 2003[16]	Weekly 24 h 5-FU (with or without LV) versus weekly bolus 5-FU/LV	n.s.	Grade 3/4 diarrhea was higher in experimental arm with LV, stomatitis and hematologic tox. was lower	OS did not differ among three groups, PFS sign. longer for FU24h + LV (5.6 months) versus without LV (4.1) or bolus (4.0) ($P = 0.029$), RR n.s.
		Price, 2004[17]	Circadian-timed 5-FU (CTI) + Mitomycin–C versus 5-FU daily 300 mg/m^2 + Mitomycin-C	n.s.	Grade 3/4 diarrhea occurred sign. more in CTI 19.8% versus 6.5% ($P < 0.001$)	RR, FFS, OS n.s.
	Added drug	Hill, 1995[18]	Interferon-α + 5-FU/LV versus 5-FU/LV alone	n.s.	Experimental arm more toxicity in the form of leucopenia ($P = 0.001$), mucositis ($P = 0.008$) and alopecia ($P = 0.0002$)	RR, FFS, OS n.s.

Seymour, 1996[19]	Interferon-α + 5-FU/LV versus 5-FU/LV alone	QoL was adversely affected in experimental arm (less improvement of symptoms and more new symptoms)	Experimental arm more tired at 6 and 12 weeks ($P = 0.01$ and $P = 0.04$ resp), more dry mouth at 6 weeks ($P = 0.01$) and more hair loss ($P = 0.006$ and $P = 0.02$)	OR, PFS, OS n.s.
Ross, 1997[20]	Mitomycin-C + 5-FU versus 5-FU alone	Global QoL scores were better at 24 weeks ($P = 0.012$)	Grade 3/4 thrombocytopenia 11% versus 0% ($P = 0.0006$)	OR 54% versus 38% ($P = .024$), FFS 7.9 versus 5.4 months ($P = 0.033$), OS n.s.
Comella, 2000[21]	Two experimental arms! 5-FU/LV + Irinotecan (A) or 5-FU/LV + Raltitrexed (B) versus 5-FU/ LV + Methotrexate (C)	Median value of QoL score after 3 months 78 versus 70 versus 60 ($P = ?$), so A is better than C	Tox. grade 4 neutropenia 22% versus 8% versus 6% ($P = ?$), diarrhea grade 3/4 16% versus 16% versus 4% ($P = ?$)	RR 34% versus 24% versus 24% ($P = ?$), TTP 38 versus 25 versus 27 weeks ($P = ?$)
De Gramont, 2000[22]	Oxaliplatin + 5-FU/LV versus 5-FU/LV alone	Overall median QoL scores were comparable, time to deterioration of global health status of 20% and 40% was sign. prolonged in experimental arm ($P = 0.0039$ and $P = 0.0004$)	Grade 3/4 neutropenia 41.7% versus 5.3% ($P < 0.001$), grade 3/4 diarrhea 11.9% versus 5.3% ($P = 0.015$), grade 3 neurosensory toxicity 18.2 versus 0% ($P < 0.001$)	PFS 9.0 versus 6.2 months ($P = 0.0003$), RR 50.7% versus 22.3% ($P = 0.0001$), OS n.s.
Douillard, 2000[23]	Irinotecan + 5-FU versus 5-FU alone	QoL did not differ between groups, after two imputation methods QoL was sign. better and PS deterioration occurred later in Irino group	Some grade 3/4 effects were more frequent in Irinotecan but were predictable, reversible, non-cumulative, and manageable. Neutropenia grade 3/4 28.8% versus 2.4% ($P = 0.001$), also diarrhea 13.1 versus 5.6% ($P = 0.028$) and asthenia 6.2% versus 0.7% ($P = 0.011$)	RR 49% versus 31% ($P < 0.001$), RR ITT 35% versus 22% ($P < 0.005$), TTP 6.7 versus 4.4 months ($P < 0.001$), OS 17.4 versus 14.1 months ($P = 0.031$)
Saltz, 2000[24]	Irinotecan + 5-FU/LV versus 5-FU/LV or Irinotecan alone	n.s.	Diarrhea grade 3/4 22.7% versus 13.2% versus 31% ($P = ?$), mucositis grade 3/4 2.2% versus 16.9% versus 2.2% ($P = ?$)	Results for 5-FU/LV and Irinotecan alone were similar. PFS 7 versus 4.3 months ($P = 0.004$), RR 39% versus 21% ($P < 0.001$), OS 14.8 versus 12.6 months ($P = 0.04$)
Unger, 2001[25]	5-FU + *E. coli* Extract versus 5-FU + placebo	n.s.	CTC: all 3 categories were reduced in *E. coli*-Extract group ($P = ?$)	OR ($P = ?$), OS n.s.
Blanke, 2002[26]	TMTX (Trimetrexate) + 5-FU/LV versus 5-FU/LV + placebo	n.s.	Diarrhea 3/4 41% versus 28% ($P = 0.008$), grade 3/4 nausea 14% versus 7% ($P = 0.041$), hypersensitivity reaction 15% versus 7% ($P = 0.029$)	PFS, OS, RR n.s.

(*continued on next page*)

Table 1 – *continued*

First hypothesis	Second hypothesis	Trial (first author, year of publication, reference)	Study design (experimental versus control)	QoL (experimental versus control)	Toxicity (experimental versus control)	Prolongation-related (experimental versus control)
		Punt, 2002[27]	TMTX (Trimetrexate) + 5-FU/LV versus 5-FU/LV alone	n.s.	Most prominent tox. was diarrhea, less in TMTX (P = ?)	PFS 5.4 versus 4.1 months (P = 0.003), OS and TR n.s.
		Hurwitz, 2004[28]	IFL + Bevacizumab versus IFL + placebo	nm	Grade 3 hypertension 11% versus 2.3%, but easily managed	OS 20.3 versus 15.6 months (P < 0.001), PFS 10.6 versus 6.2 months (P < 0.001), RR 44.8% versus 34.8 (P = 0.004), DR 10.4 versus 7.1 (P = 0.001)
	Single drug	Allen-Mersh, 1994[29]	Continuous hepatic-artery floxuridine infusion versus symptom palliation	n.s.	Pump- and catheter-related morbidity, no treatment-related hepatotoxicity	OS 405 versus 226 days (P = 0.03)
		Loprinzi, 1994[30]	Hydrazine Sulfate versus placebo	n.s., PS more rapid worsening (P = 0.003)	Less dysgeusia (P = 0.04) in experimental arm	OS worse (P = 0.034)
		Cunningham, 1995[31]	Raltitrexed versus MAYO regimen (5-FU/LV)	n.s.	Tomudex patients stay shorter in hospital, mucositis 2% versus 22%, leucopenia 10% versus 26%, transaminases 10% versus 0% (for all P < 0.001)	RR, TTP and OS n.s.
		Coccini, 1998[32]	Raltitrexed versus fluorouracil + high-dose LV	In favor of Raltitrexed at week 2 in dimensions related to mobility, usual activities, general health (P = 0.019, 0.002, 0.003 resp)	Less grade 3/4 stomatitis 2% versus 16% (P < 0.001), more clinically insignificant elevated transaminase levels in Raltitrexed 13% versus 0% (P < 0.001)	RR and OS ns, TTP sign. shorter in Raltitrexed 3.1 versus 5-FU/LV 5.1 months (P < 0.005)
		Maughan, 2002[33]	Raltitrexed versus Gramont regimen or Lokich (continuous infusion) regimen	Raltitrexed worse for emotional functioning (P = 0.022), HADS reduction in anxiety in Lokich (P = 0.003) and Raltitrexed (P < 0.0001)	Treatment-related deaths: 18, 1, 2 (P = 0.0002), due to combined gastrointestinal and hematological tox, more toxic effects in Raltitrexed (nausea, anorexia, diarrhea, neutropenia) (P < 0.01), more stomatitis in Lokich (P < 0.01)	OS, PFS ns, SP no diff between Gramont and Lokich regimen
Second-line chemotherapy	Ways of administration	Fuchs, 2003[34]	Once every 3 weeks versus weekly Irinotecan dosing regimen	n.s.	Grade 3/4 diarrhea less in experimental arm 19% versus 36% (P = 0.002)	1-OS, OS, TTP n.s.
		Lal, 2004[35]	Defined duration versus continuous Irinotecan	n.s.	No grade 3 diarrhea No febrile neutropenia	FFS and OS n.s.

	Added drug	No studies				
	Single drug	Cunningham, 1998[36]	Irinotecan + supportive care versus supportive care alone	QoL sign. better for Irinotecan	More patients in exp arm experienced severe events, especially neutropenia, nausea, vomiting and diarrhea ($P = ?$)	Overall survival was better in experimental arm ($P = 0.0001$) with 1-OS 36.2% versus 13.8%
		Rougier, 1998[37]	Irinotecan once every 3 weeks versus fluorouracil by continuous infusion	n.s.	69% versus 54% experienced at least one grade 3/4 adverse event ($P = 0.013$), Toxicity Table 3, which is referred to, is published elsewhere[38]	1-OS 45% versus 32% ($P = 0.035$), OS 10.8 versus 8.5 months ($P = ?$), PFS 4.2 versus 2.9 months ($P = 0.03$), disease progression 36.4% versus 56.2% ($P = 0.002$)
First- and second-line chemotherapy	Ways of administration	No studies				
	Added drug	Gray, 2001[39]	First or second line: radioactive Yttrium (SIR) + regional hepatic artery chemotherapy (HAC) versus HAC alone	n.s.	No increase in grade 3/4 tox.	PR + CR 44% versus 17.6% ($P = 0.01$), TTP 15.9 versus 9.7 months ($P = 0.001$), OS n.s.
	Single drug	No studies				

Abbreviations. ATP, acute toxic profile; CR, complete response; DR, duration of response; DT, (drug) tolerability; eq, equivalent; FFS, failure-free survival; FU-FA, bolus fluorouracil plus leucovorin; FU-cont, continuous fluorouracil infusion; FUMIC, Fucont plus cyclophosphamide and mitomycin C; GHS, Global Health Status; HAD, hospital anxiety and depression scale; HAC, Hepatic artery chemotherapy; HFS, hand-foot syndrome; ITT, intention to treat; kg, body weight; nm, not mentioned; n.s., not significant; OR, overall response; OS, overall survival; 1-OS, survival in one year; PainFS, pain-free survival; PB, palliative benefits; PFS, progression-free survival; PR, partial response; PS, (impact of treatment on) performance status; QoL, quality of life score; RR, (objective) response rate; RSC, Rotterdam symptom checklist; saf, safety; SIP, sick impact profile; SIR, radioactive Yttrium; SP, symptom palliation; TE, toxic effects/adverse events; TMTX, Trimetrexate; TRS, tumour-related symptoms; TTF, time to treatment failure; TTP, time to (disease) progression; UFT, tegafur/uracil.

Table 2 – Authors' results, conclusions from this study, and authors' own conclusions

First hypothesis	Second hypothesis	First author, publication date	QoL	Tox	QoL/Tox	PoL	'Rational' conclusion	Authors' conclusion from abstract
First-line chemotherapy	Administration	Caudry, 1995	=	–	–	+	?	E, FUcont schedule (. . .) offers sign. advantages, in terms of response and survival, over weekly FU-FA
		Earlam, 1997	+	+	+	=	E	E, Randomization to symptom control only was associated with increased anxiety. QoL with systematic chemotherapy was impaired by side effects. HAI was associated with similar survival to systemic chemotherapy but with better sustained QoL during additional survival
		Sobrero, 2000	=	–	–	+	?	E, Alternating, schedule-specific biochemical modulation of FU is more active than MTXT (. . .)
		Carmicheal, 2002	=	+	+	=	E	E, The study failed to demonstrate improved TTP; however, the study confirms significant safety improvements (. . .)
		Douillard, 2002	=	+	+	=	E	E, UFT/LV provided a safer, more convenient oral alternative to a standard bolus IV 5-FU/LV regimen (. . .) while producing equivalent survival
		Köhne, 2003	=	–	–	+	?	S, Neither FU24h + LV nor FU24h prolong survival, relative to bolus FU + LV. LV increases PFS if added to FU24h, but increases toxicity
		Price, 2004	=	–	–	=	S	S, This study confirms the high RR and OS figures for the combination of 5-FU in Mitomycin-C. However, dose intensification of 5-FU using a circadian-timed, flat-rate infusion did not lead to improved response or survival
	Added drug	Hill, 1995	=	–	–	=	S	S, This study confirms that 5-FU is effective in treating the symptoms associated with metastatic colorectal carcinoma, with only mild to moderate toxicity and maintenance of QoL. Interferon three times weekly does not enhance these palliative benefits
		Seymour, 1996	–	–	–	=	S	S, Interferon-α, at a dose that impaired QoL. Did not improve the efficacy of 5-FU/LV. The power of this trial is sufficient to exclude with 95% confidence a benefit of 15% in OR of 10 weeks in median survival. Accordingly, we cannot recommend the use of Interferon as a clinical modulator of 5-FU/LV (. . .)
		Ross, 1997	+	–	=	=	?	E, Exp arm results in FFS and response advantage, tolerable tox. and better QoL when compared to 5-FU alone but no OS advantage
		Comella, 2000	+	?	?	?	?	E, CPT-11 + 5-FU/LV compares favorably, in terms of activity and toxicity, with other combination regimens (. . .)
		De Gramont, 2000	+	–	=	+	E	E, The combination seems beneficial as first-line therapy (. . .), demonstrating a prolonged PFS with acceptable tolerability and maintenance of QoL
		Douillard, 2000	+	–	=	+	E	E, Irino plus 5-FU was well-tolerated and increased RR, TTP, and OS, with a later deterioration in QoL. This combination should be considered as a reference treatment (. . .)
		Saltz, 2000	=	–	–	+	?	E, Weekly treatment with Irinotecan + 5-FU/LV is superior to a widely used regimen of 5-FU/LV (. . .) in terms of PFS an OS

		Unger, 2001	=	?	=	=	?	E, These results suggest a positive benefit-risk ratio of the additional application of LC-Extract to 5-FU (...) especially for administration of high dose of 5-FU
		Blanke, 2002	=	–	–	=	S	S, The inclusion of TMTX did not yield any sign. improvements in RR, PFS, OS
		Punt, 2002	=	?	=	+	E	E, The addition of MTXT to 5-FU/LV results in a small but sign. improvement in PFS without adding toxicity or worsening QoL (...)
		Hurwitz, 2004	?	–	–	+	?	E, The addition of Bevacizumab (...) results in statistically significant and clinically meaningful improvement in survival
	Single drug	Allen-Mersh, 1994	=	–	–	+	?	E, This was the first demonstration that survival can be prolonged with normal QoL in patients with colorectal liver metastases. We conclude that hepatic-artery floxuridine infusion can be recommended for suitable patients
		Loprinzi, 1994	–	+	=	–	S	S, This study failed to demonstrate any benefit for hydrazine sulphate. Thus, hydrate sulphate is currently not recommended for use in routine clinical practice
		Cunningham, 1995	+	–	=	=	?	E, Raltitrexed has benefits in terms of higher response rates, reduced toxicity and more frequent palliative benefits when compared with 5-FU/LV in the management of advanced colorectal cancer, and has a more convenient administration schedule
		Coccini, 1998	+	+	+	–	?	E, Raltitrexed is confirmed as an effective option in the first-line palliative management of ACC, with comparable efficacy to 5-FU/LV and tolerability advantages (in terms of reduced incidence of stomatitis, diarrhea and leucopenia) over 5-FU/LV
		Maughan, 2002	–	–	–	=	S	E, Raltitrexed showed similar RR and OS (...) and was easier to administer, but resulted in greater toxicity and inferior QoL
Second-line chemotherapy	Administration	Fuchs, 2003	=	+	+	=	E	E, Similar efficacy and quality of life. The regimen of once every three weeks was associated with a significant lower incidence of severe diarrhea
		Lal, 2004	=	=	=	=	?	S, There seems to be little benefit for the control arm, though the drug was well tolerated without any deterioration in QoL
	Added drug	No studies						
	Single drug	Cunningham, 1998	+	–	=	+	E	E, Despite the side effects of treatment, patients (...) have longer survival, fewer tumour-related symptoms, and better QoL when treated with Irinotecan
		Rougier, 1998	=	–	–	+	?	E, (...) second-line Irinotecan significantly improved survival in patients with advanced colorectal cancer
First- and second-line chemotherapy	Administration	No studies						
	Added drug	Gray, 2001	=	=	=	+	E	E, The combination of single injection of SIR plus HAC is substantially more effective in increasing tumour responses and PFS (...)
	Single drug	No studies						

Explanation. The outcomes of QoL, toxicity, and PoL as the authors reported them were summarized: the experimental arm was better (+), equal (=), or worse (–) than the control arm. Regarding toxicity the (+) sign meant that the experimental arm was less toxic and the other way around. If the results on a specific outcome were not mentioned or not clear regarding the statistical significance, a question mark was used. Conclusions were summarized as follows: the experimental arm was better than the standard (E), the authors were not clear (?), or they said it was better not to use the experimental arm but to use the standard arm (S).

This review considered trials in advanced colorectal cancer. Recently, this tumour has been shown to be relatively chemo-sensitive: the mean life expectancy has increased from 8 to 21 months, expanding treatment possibilities from none to several sequential lines of treatment.[8] Our findings could have been different if other tumour types had been incorporated in the review, but we expect that, also in relatively chemo-non-sensitive tumours, PCT mainly focuses on life prolongation. This opinion is based on the fact that our review showed that most trials concerning second-line treatment, where life expectancy was decreased, seemed to focus even more on PoL-related outcomes than those concerning first-line treatment. However, it would be interesting to further study the main purposes of PCT within other tumour types.

A remarkable additional finding in this study was that in most cases toxicity does not affect QoL outcomes. This was demonstrated by the fact that in 17 trials, toxicity was significantly higher in the experimental arm, whereas QoL was negatively affected in only two of these trials. This finding has at least two implications. Firstly, that toxicity scores compared to QoL scores may discriminate better between the experimental and control arm and are therefore more informative. And secondly, it seems that toxicity and QoL are two different aspects that cannot be exchanged with or neutralized by each other. For the purpose of our study we combined these two outcomes; this should however not be a reason to also do this in a different context. We found that the authors often concluded by saying that the survival gain in their trial was significantly better, and that the toxicity of the experimental arm was worse but apparently tolerable, as it did not affect the QoL scores. However, since we found that toxicity and QoL assessment measures seem to be different phenomena and QoL assessments are less discriminating between the experimental and control arm, we think that one should be very careful to advise highly toxic treatments because of equal or high QoL outcomes.

From this review, it can be deduced that a lack of clarity exists regarding the main purposes of palliative chemotherapy, which is encountered in most phase III trials. Apparently, the discussion about what should be the main purpose of PCT has not been settled yet.[9] The lack of clarity regarding the main aim of PCT in general seems to be related to conceptual confusion. Although in palliative care the word 'palliative' refers to QoL improvement, this review shows that the authors' conclusions focused primarily on PoL-related outcomes. Within palliative care the possible treatment effects on life expectancy, whether extending or reducing, are at most of secondary importance (and are often regarded as indifferent and sometimes even undesirable).[10] On the other hand, we found that within palliative chemotherapy the treatment effects on QoL, whether positive or negative, were of secondary significance. This is why toxicity, for example, appears to be acceptable in the context of palliative treatments. To prevent misunderstandings, it probably would be better to use the concept of palliative chemotherapy only in the few cases where the main emphasis of chemotherapy lies on QoL improvement. In all other cases we suggest the use of the term 'life-prolonging chemotherapy'. The preset hypotheses about different emphases in the weighing of QoL-related versus PoL-related outcomes, depending on the setting and subject of the study, may be a good guide to determine the main focus of trials on chemotherapy in patients with advanced cancer. The hypotheses may also help to make practitioners aware of the beforehand-given structure within RCTs.

Conflict of interest statement

None declared.

Acknowledgements

Supported by Grant No: CJA 04006/UVA 2003-2785 from the Dutch Cancer Foundation, Amsterdam, The Netherlands. The funding agreement ensured the authors' independence in designing the study, interpreting the data, and writing and publishing articles. We thank Nelleke Koedoot, Mirjam Sprangers, and Bert Schadé for comments on a draft of this manuscript.

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