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Level of evidence of irinotecan clinical trials and recent data in colorectal cancer

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Abstract

Combination chemotherapy based on bolus or infusional 5-fluorouracil (5-FU), folinic acid (FA), together with either irinotecan or oxaliplatin has become the standard of care for the first-line treatment of metastatic colorectal cancer. The practice of combining 5-FU/FA with irinotecan or oxaliplatin is based on data from randomised clinical trials, and these are complicated by the variety of endpoints used, including overall survival, progression-free survival and response rate. An evidence-based system has been developed by the United States National Cancer Institute, whereby oncology clinical trials are ranked according to the trial design and the endpoints assessed. According to this system, the highest levels of evidence for the benefit of first-line combination therapy on overall survival are achieved with the combination of irinotecan and bolus and/or infusional 5-FU/FA. Thus, if evidence-based medicine is to be our aim, the combination of 5-FU/FA plus irinotecan should be the standard of care for the first-line treatment of metastatic colorectal cancer.

Keywords: Colorectal cancer; Irinotecan; Levels of evidence; Metastatic

1. Introduction

For many years, clinicians have relied on 5-fluorouracil (5-FU) to treat their colorectal cancer patients [1]. Combining the drug with folinic acid (FA) enhanced its cytotoxicity [2], and the combination of 5-FU/FA has been the standard of treatment for advanced and metastatic colorectal cancer.

Over the years, a variety of regimens of 5-FU alone or in combination with FA have been developed in an attempt to optimise treatment. Commonly used regimens include the bolus Mayo Clinic regimen [3], the bolus and infusional de Gramont regimen [4], and the infusional AIO (Arbeitzgemeinschaft Internische Onkologie) regimen (developed and popular in Germany) [5]. Although infusional regimens of 5-FU/FA have improved response rates and median progression-free survival compared with bolus [2,4–6], and generally have improved tolerability [6], overall survival benefits have not been reliably demonstrated. Because of the lack of a reproducible survival advantage of infusional regimens and the convenience of bolus administration, bolus regimens are still widely used in many centres and countries, particularly in the United States.

In the late 1990s and early 2000s, data from a number of key phase III randomised clinical trials conclusively demonstrated that irinotecan improved survival as both second- and first-line therapy in patients with advanced colorectal cancer compared with 5-FU/FA alone [7–9] or (in the case of one trial in the second-line setting) best supportive care [10]. In the last few years, another drug, oxaliplatin, has also emerged as an effective component of 5-FU/FA-based regimens, with randomised studies showing a significant improvement in progression-free survival compared with 5-FU/FA alone [11–13]. The currently approved first-line treatment for metastatic colorectal cancer in Europe is infusional 5-FU/FA combined with either irinotecan or oxaliplatin. In the United States (US), irinotecan with bolus or infusional 5-FU/FA and oxaliplatin with infusional 5-FU/FA are approved for use first line.

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2. United States National Cancer Institute levels of evidence in oncology clinical trials

The data available in the literature have been obtained from clinical trials of varying design, such as randomised and non-randomised, and using a variety of end points, such as overall survival, progression-free survival and response rate. The applicability of information from clinical studies to clinical practice will depend on a number of factors, including how robust the study design is and how relevant the endpoints are to the desired treatment goal.

An invaluable tool in the interpretation of clinical trial data has been provided by the US National Cancer Institute (NCI), which has developed a formal ranking system of levels of evidence designed to assist physicians' understanding and application of data from oncology clinical trials [14]. Each trial has a two-tier ranking according to both its design and its study endpoints (Table 1). In terms of trial design, the gold standard is the double-blinded, randomised trial: this is assigned a ranking of 1(i). However, in the field of oncology, it is frequently not possible to blind the physician to the therapy delivered as there are often marked differences in the therapeutic procedure or the side effects of the treatment: nonblinded trials are assigned a ranking of 1(ii), and this represents the highest level of evidence for most oncology trials. For endpoints, the most important one to patients is probably all-cause mortality (ranked A): this is also the easiest to define and the least subject to investigator bias. Quality of life is also an important endpoint for the patient (ranked C). Indirect surrogate endpoints, such as progression-free survival, disease-free survival and response rate may be useful in the absence of other endpoints, but are all subject to investigator interpretation and do not necessarily translate into a direct patient benefit, such as survival: these are given a D ranking. Examples of recorded levels of evidence are shown in Fig. 1.

In view of the choice of first-line treatment approaches available for metastatic colorectal cancer in Europe, it is appropriate to examine the clinical data for the use of irinotecan- and oxaliplatin-based combinations in terms of NCI levels of evidence.

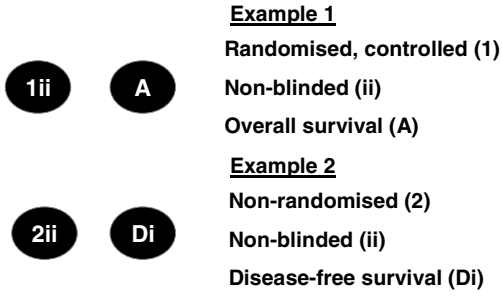

Fig. 1. Recording levels of evidence.

Table 1
US National Cancer Institute levels of evidence for adult cancer treatment studies

Strength of study design		Strength of endpoints	
1(i) Double-blinded randomised controlled clinical trial	Gold-standard study design. Physician is blinded to treatment allocation before and after randomisation.	A. Total mortality	The most important endpoint for patients, the most easily defined endpoint and the least subject to investigator bias
1(ii) Non-blinded randomised controlled clinical trial (allocation schema or treatment delivery)	Assigned if blinding of the therapy delivered cannot be accomplished. This is often the case with oncology trials, due to the often marked difference in procedures or adverse events of treatments.	B. Cause-specific mortality	
		C. Carefully assessed quality of life	Very important to patients
2. Non-randomised controlled clinical trial	Trials in which treatment allocation is known to the investigator prior to obtaining informed consent from the patient.	D. Indirect surrogates D(i) Disease-free survival D(ii) Progression-free survival D(iii) Tumour response rate	All are subject to investigator interpretation. Also, they do not directly translate into patient benefit, such as survival or quality of life
3. Case series 3(i) Population-based 3(ii) Consecutive series 3(iii) Non-consecutive cases	These have the weakest form of study design but may be the only available or practical information regarding a therapeutic strategy. These studies do not have internal controls		

Adapted from [14].

3. Levels of evidence for irinotecan in metastatic colorectal cancer trials

3.1. Irinotecan as second-line therapy

Two independent randomised phase III trials showed that the use of irinotecan second-line following disease progression on 5-FU-based therapy significantly improved survival compared with bolus 5-FU/FA alone [7] or best supportive care [10]. Survival was prolonged by 2.3 ($P = 0.035$) and 2.7 ($P = 0.001$) months, respectively. Furthermore, the quality of life of the patients was either significantly improved [10] or unchanged [7]. For both studies, the levels of evidence reached 1(ii) A for overall survival and 1(ii) C for quality of life. These trials represent extremely high levels of evidence for the efficacy of an agent following failure on 5-FU-based therapy.

3.2. Irinotecan in first-line therapy

Shortly after the second-line data were published, two randomised phase III trials investigating combinations of irinotecan and 5-FU/FA as first-line treatment both achieved the highest level of evidence (1(ii) A) for the benefit of irinotecan [8,9] (Table 2). In one trial, reported by Saltz and colleagues, 683 patients were randomly assigned to receive either irinotecan (125 mg/m^2) in combination with 5-FU (500 mg/m^2) and FA (20 mg/m^2) weekly for four weeks every six weeks (IFL, $n = 231$); the Mayo Clinic regimen of bolus 5-FU (500 mg/m^2) and FA (20 mg/m^2), for five days every four weeks; or irinotecan alone 125 mg/m^2 weekly for four weeks every six weeks [8]. An intention-to-treat analysis showed that the addition of irinotecan to bolus 5-FU/FA led to a significantly prolonged overall survival compared with bolus 5-FU/FA alone (median 14.8 versus 12.6 months, $P = 0.04$).

In the other trial, reported by Douillard *et al.* [9] 387 patients were randomised to receive either bolus and/or infusional 5-FU/FA alone, according to the de Gramont regimen (bi-weekly, LV5FU2) or the AIO regimen (once weekly), or in combination with irinotecan. Treatment regimens were as follows: irinotecan (80 mg/m^2) plus 5-FU (2300 mg/m^2 by 24-h infusion) and FA (500 mg/m^2), once weekly ($n = 54$); irinotecan (180 mg/m^2) on day 1 plus 5-FU (400 mg/m^2 bolus and 600 mg/m^2 by 22-h infusion) and FA (200 mg/m^2) on days 1 and 2, bi-weekly ($n = 145$). For patients not receiving irinotecan, the regimens were: 5-FU (2600 mg/m^2 by 24-h infusion) and FA (500 mg/m^2), once weekly ($n = 43$); or the de Gramont regimen as described above ($n = 143$). Overall survival was significantly longer in patients receiving irinotecan compared with those receiving bolus and/or infusional 5-FU/FA (median 17.4 versus 14.1 months, $P = 0.031$) (Table 2).

In another randomised trial (EORTC 40986), further investigating the benefit of adding irinotecan to the infusional AIO regimen of 5-FU/FA, while the trial design was robust, the level of evidence achieved was 1(ii) D(ii) [15]. The trial was designed to administer irinotecan, 5-FU and FA according to the schedules used in the Douillard study [9]. The addition of irinotecan significantly improved the response rate (54.2% versus 31.5%, $P < 0.0001$) and the duration of progression-free survival (8.8 versus 6.3 months, $P < 0.0001$). While overall survival in the irinotecan was in excess of 20 months, the difference between the treatment arms did not attain statistical significance (20.1 versus 16.9 months) (Table 2). The lack of a significant difference in overall survival may be due to the fact that nearly two-thirds (62%) of patients randomised to first-line 5-FU/FA received second-line therapy with irinotecan.

4. Levels of evidence for oxaliplatin in metastatic colorectal cancer trials

4.1. Oxaliplatin/5-FU/FA versus 5-FU/FA

The addition of oxaliplatin to various regimens of 5-FU/FA was assessed in three randomised trials [11–13].

Table 2
Levels of evidence for the efficacy of adding irinotecan to bolus and/or infusional 5-FU/FA regimens as first-line therapy for metastatic colorectal cancer

Regimen	*N*	Response rate (%)	Median PFS (months)	Median OS months	*P* value for OS	Level of evidence
Bolus and infusional 5-FU/FA (de Gramont) and infusional 5-FU/FA (AIO)	385	22	4.4	14.1	0.031	1(ii) A
+ irinotecan [9]		35	6.7	17.4		
Bolus 5-FU/FA	457	21	4.4	12.6	0.04	1(ii) A
+ irinotecan [8]		39	7.0	14.8		
Infusional 5-FU/FA (AIO)	430	32[a]	6.3	16.9	NS	1(ii) D(ii)
+ irinotecan [15]		54[a]	8.8	20.1		

5-FU, 5-fluorouracil; FA, folinic acid; AIO, Arbeitzgemeinschaft Internische Onkologie; N, number of patients; PFS, progression-free survival; OS, overall survival; NS, not significant.

[a] Unpublished information. See text for details of doses.

Table 3
Levels of evidence for the efficacy of adding oxaliplatin to bolus and/or infusional 5-FU/FA regimens as first-line therapy for metastatic colorectal cancer

Regimen	*N*	Response rate (%)	Median PFS (months)	Median OS months	*P* value for OS	Level of evidence
Bolus and infusional 5-FU/FA + oxaliplatin [11]	400	22 51	6.2 9.0	14.7 16.2	NS	1(ii) D(ii)
Chronomodulated 5-FU/FA + oxaliplatin [13]	200	16 53	6.1 8.7	19.9 19.4	NS	1(ii) D(ii)
Bolus 5-FU/FA + oxaliplatin [12]	252	23 48	5.3 7.9	16.1 20.4	NS	1(ii) D(ii)

5-FU, 5-fluorouracil; FA, folinic acid; N, number of patients; PFS, progression-free survival; OS, overall survival; NS, not significant. See text for details of doses.

In all three trials, there was no statistically significant increase in survival and the level of evidence for the efficacy of oxaliplatin was only 1(ii) D(ii) for each trial (Table 3).

In one of these trials, oxaliplatin (125 mg/m^2 day 1) was added to a 5-day course of chronomodulated 5-FU (700 mg/m^2 day) and FA (300 mg/m^2/day) [13]. In another, oxaliplatin (85 mg/m^2 day 1) was combined with LV5FU2 regimen of 2-h infusion of LV (200 mg/m^2/day) followed by a 5-FU (bolus 400 mg/m^2/day and 22-h infusion 600 mg/m^2/day) for two consecutive days biweekly [11]. In the third trial, oxaliplatin (50 mg/m^2) plus infusional 5-FU (2000 mg/m^2 24-h infusion) and FA (500 mg/m^2), once a week for four weeks every five weeks, was compared with the bolus Mayo Clinic regimen of 5-FU (425 mg/m^2) and FA (20 mg/m^2), days 1–5 every four weeks [12]. In all three trials, the addition of oxaliplatin significantly improved the response rate and the progression-free survival. However, any differences in overall survival did not reach statistical significance.

4.2. Oxaliplatin/5-FU/FA versus irinotecan/5-FU/FA

Results from a randomised Intergroup trial (N9741) directly comparing a number of different treatment regimens, including combinations of oxaliplatin/5-FU/FA and irinotecan/5-FU/FA, were recently reported by Goldberg *et al.* [16]. The trial demonstrated a statistically significant prolongation of survival with the addition of oxaliplatin to infusional 5-FU/FA (FOLFOX4; oxaliplatin 85 mg/m^2, day 1, 5-FU 400 mg/m^2 bolus and 600 mg/m^2 22-h infusion, days 1 and 2, every two weeks) compared with bolus IFL (irinotecan 125 mg/m^2, bolus 5-FU 500 mg/m^2 and FA 20 mg/m^2, weekly for four weeks every six weeks). In this study, FOLFOX4 was associated with a significantly higher response rate (45% versus 31%, $P = 0.002$), longer time to progression (median 8.7 versus 6.9 months, $P = 0.0014$) and a longer overall survival (median 19.5 versus 15 months, $P = 0.0001$) compared with IFL. Accordingly, therefore, this study achieved a level of evidence of 1(ii) A.

However, there are a number of issues which may have had a significant impact on the survival outcome seen in this trial. The first is the use of two different 5-FU/FA regimens in the comparator arms. Infusional 5-FU/FA regimens are associated with improved response rates and median progression-free survival and better tolerability than bolus regimens [2,4–6]. However, in Goldberg's study, only the oxaliplatin arm used an infusional 5-FU/FA regimen; irinotecan was added to a bolus 5-FU/FA regimen. A more valid comparison of oxaliplatin- and irinotecan-based regimens requires the use of the same 5-FU/FA schedule in each arm. Another issue concerns salvage therapy at the time of disease progression: 67% of IFL patients received salvage therapy, with only 24% receiving oxaliplatin, whereas 75% of FOLFOX4 patients received therapy, with 60% receiving irinotecan. Thus, more patients in the FOLFOX4 arm were exposed to salvage therapy with an active agent to which advanced disease had not previously been exposed. Finally, it should be remembered that N9741 was not designed to compare the effects of the different treatment arms on survival. We need to turn to a phase III crossover trial, reported by Tournigand *et al.* [17], to better understand the impact of adding irinotecan or oxaliplatin to the same 5-FU/FA regimen. This trial investigated the sequential use of irinotecan (180 mg/m^2) plus the simplified bolus and infusional LV5FU2 regimen (FOLFIRI) followed on disease progression by oxaliplatin (100 mg/m^2) in combination with the same 5-FU/FA regimen (FOLFOX6) compared with the reverse schedule (FOLFOX6/FOLFIRI) [17]. After two lines of chemotherapy, the median second progression-free survival (the primary endpoint of the study) was 14.2 months with FOLFIRI first-line and 10.9 months with FOLFOX6 first-line. First-line response rates were 56% for FOLFIRI and 54% for FOLFOX6. More patients with FOLFIRI (74%) were exposed to second-line treatment with the other active agent than with FOLFOX6 (62%) (oxaliplatin and irinotecan, respectively). Although there was no significant difference in the median overall survival times between FOLFIRI/FOLFOX6 and FOLFOX6/FOLFIRI (21.5 versus 20.6

months, respectively), the schedule using FOLFIRI/FOLFOX6 achieved the longest recorded survival in a phase III trial.

5. Conclusions

It is now generally accepted that patients with metastatic colorectal cancer should be offered first-line chemotherapy with a 5-FU/FA regimen in combination with another active agent, such as irinotecan or oxaliplatin. However, the data from clinical trials are confusing, basing treatment benefit on a variety of endpoints, such as response rate, progression-free survival and overall survival. While tumour response rate and progression-free survival may be useful surrogate endpoints, overall survival is the most reliable, unbiased indicator of outcome and arguably the most important endpoint for patients. Evidence-based analysis of the various trials of 5-FU/FA in combination with irinotecan or oxaliplatin shows that to date, only irinotecan/5-FU/FA has shown survival benefits compared with 5-FU/FA alone in trials designed to assess this endpoint. Thus, if we agree that evidence-based medicine is the desired approach, then 5-FU/FA plus irinotecan should be the standard of care in the first-line chemotherapy of metastatic colorectal cancer.

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