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Review paper

Advanced colorectal cancer treatment in Europe: what have we achieved?

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The goal of the present paper is to review how treatment of advanced colorectal cancer has evolved during the last 10 years and to make some suggestions on how that disease could be managed today. 5-Fluorouracil (5-FU) combined with folinic acid (FA) remains the basis for advanced colorectal cancer treatment. In Europe, infusional 5-FU is considered to be more active and better tolerated than bolus 5-FU. New agents including oral 5-FU prodrugs UFT/FA, and capecitabine, tomudex, irinotecan and oxaliplatin have been shown active in advanced colorectal cancer. At presentation the combination of infusional 5-FU/FA with irinotecan or oxaliplatin is considered to be superior to any of these agents used alone, yielding a median survival of up to 16–19 months. Second-line therapy could further prolong survival in selected patient populations. Eventually chemotherapy could allow curative resection of previously unresectable hepatic and pulmonary metastases. [© 2002 Lippincott Williams & Wilkins.]

Key words: Cancer, chemotherapy, colon, colorectal, irinotecan, oxaliplatin.

Introduction

In industrialized countries, colorectal cancer is the second most common malignancy after lung cancer in men and breast cancer in women. In Europe in 1990, there were approximately 170 000 new cases and over 90 000 deaths due to the disease.[1]

Surgery is currently the first-line treatment for colorectal cancer. From the early 1960s to the late 1980s, the 5-year survival of surgically treated colon and rectal cancer soared from 43 to 61% and from 38 to 58%, respectively.[2] This happened before active adjuvant chemotherapy was available. Whether this was due to better surgery and peri-operative care or to earlier diagnosis remains unknown. At the beginning of the 1990s, adjuvant chemotherapy following curative surgery was shown to have a significant impact on survival in patients with Dukes' C colon cancer. The impact of this therapeutic approach on the survival of colon cancer patients in the general population has not yet been evaluated. The place of adjuvant chemotherapy in Duke's B2 patients remains controversial[3,4] and today, treatment of all B2 patients should not be recommended.[5]

The goal of the present paper is to review how treatment of advanced colorectal cancer has evolved during the last 10 years and to make some suggestions on how the disease could be managed today.

5-Fluorouracil (5-FU) was synthesized in 1957[6] and various schedules of bolus 5-FU were designed. Initial reports indicated response rates around 20%, based on an average of available clinical trials with response rates ranging from 0 to 87%.[7] This wide variability of response rates was probably due to patient heterogeneity and inadequate, non-standardized, response measurement. Further, well-conducted studies showed that the true response rate of 5-FU does not exceed 10–15%. The first investigation with bolus 5-FU and folinic acid (FA) started in the early 1980s.[8] Many studies were initiated, the majority of which demonstrated superior response rates for 5-FU/FA compared to 5-FU alone. A meta-analysis of all available data, in 1992, revealed a response rate of 23% with the 5-FU/FA combination as compared with 11% for 5-FU alone. No difference in survival was found, although one should keep in mind that most of these trials were designed and powered to identify a difference in response rate only.[9] Other ways of administering 5-FU were also investigated. Progress in portable pump technology allowed the administration of 5-FU as an i.v. infusion over prolonged periods of time (24, 48, 72 h or

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indefinitely). This approach became universally accessible in the early 1990s.

A number of new agents, including CPT-11, oxaliplatin and tomudex, investigated in the early 1990s became available on the market. Tomudex was approved in 1995. CPT-11 was approved for second-line treatment in 1997 and for first-line treatment in 1999. Oxaliplatin became available in 1999. The last two agents are not yet available in all European countries (in 2001). Oral 5-FU prodrugs including UFT/FA (Orzel) and capecitabine (Xeloda) have been recently registered.

The most commonly used bolus 5-FU/FA regimen include:

(i) The Mayo Clinic schedule which is given monthly for 5 days with low-dose FA (5-FU 425 mg/m^2; FA 20 mg/m^2).[10]
(ii) The Machover schedule which is given monthly for 5 days with high-dose FA (5-FU 400 mg/m^2; FA 200 mg/m^2 over 2 h by infusion).[11]
(iii) The Roswell Park schedule which is given weekly (5-FU 500 mg/m^2; FA 500 mg/m^2 over 2 h by infusion).[12]

The most commonly used infusional 5-FU schedules include:

(i) The Lokich regimen which is given as a protracted infusion (5-FU 300 mg/m^2).[13]
(ii) The de Gramont schedule given as a 48-h both bolus and continuous infusion bimonthly (5-FU 400 mg/m^2 bolus, 600 mg/m^2 c.i. over 48 h, FA 200 mg/m^2 over a 2-h infusion day 1 and 2 before 5-FU).[14]
(iii) The Grupo Espanol para el Tratamiento de Tumores Digestivos (TTD) regimen given as a 48-h infusion weekly (5-FU; 3000 mg/m^2).[15]
(iv) The Arbeitsgemeinschaft Internistische Onkologie (AIO) regimen given as a 24-h infusion weekly (5-FU 2600 mg/m^2; FA 500 mg/m^2).[16]
(v) A chronomodulated delivery schedule (5-FU 700 mg/m^2; FA 300 mg/m^2/day, peak delivery rate at 04:00 a.m. for 5 days).[17]

Many controversies still remain regarding which of these regimens is the most active and should be seen as a reference. Although there is no direct comparison of the various bolus or infusional 5-FU regimens, one would generally assume that all bolus 5-FU regimens are essentially alike, as are all infusional ones. Only three trials attempted to compare the activity of an infusional 5-FU regimens to a bolus one.

Protracted 5-FU infusion

Protracted 5-FU infusion was compared to bolus 5-FU alone. Although the response rates are 30 and 7%, respectively ($p<0.001$), the corresponding median survival times were 10.3 and 11.2 months ($p=0.379$).[13] The de Gramont schedule was compared to the Mayo Clinic program. The response rate was 32.6 versus 14.4% ($p=0.0004$), the progression-free survival (PFS) was 27.6 versus 22.0 weeks and the median survival time was 14.3 versus 13.1 months ($p=0.067$).[14] A recent comparison of the AIO regimen to the Mayo Clinic program designed to identify a difference in PFS showed a 2-month difference in PFS in favor of the AIO regimen.[18] Supporting these single trial data, a meta-analysis of studies comparing infusional versus bolus 5-FU suggested an advantage in terms of response rate and survival in favor of the infusional treatment.[19]

Toxicity profile

The toxicity profile of infusional 5-FU appears more favorable with less leukopenia (1 versus 20%, Lokich), granulocytopenia (1.9. versus 7.3%), thrombocytopenia (1 versus 3%, Lokich; 1.9 versus 7.3%, de Gramont), stomatitis (3 versus 11%, Lokich; 1.9 versus 7.3%, de Gramont) and diarrhea (2.9 versus 7.3%, de Gramont). Hand–foot syndrome was observed mainly with infusional 5-FU (23%, Lokich). Due to the lack of undisputable scientific evidence of the superiority of a regimen over another in terms of overall survival, all these regimens are utilized worldwide, with bolus 5-FU (Mayo and Roswell Park regimens) mainly given in the USA and infusional 5-FU (de Gramont, AIO and TTD regimens) mainly given in Europe.

During the last 10 years it became also apparent that treating patients with chemotherapy would significantly improve survival as compared to treating them with best supportive care only (median survival 12 versus 6 months)[20] and that administering chemotherapy at an early stage, before symptoms are present, may also significantly improve survival as compared to giving it when the patients are symptomatic (median survival 7 versus 12 months).[21]

Response rates and median survival

If we try to have a better understanding of the level of activity of the various available treatments in

advanced colorectal cancer we could try to map out the response rates and median survival into figures. Although it may be questionable to compare the results of clinical trials with different patient populations, such an analysis represents a natural, intuitive way of visualizing data.

Figure 1 represents the distribution of response rates derived from phase III studies of the bolus 5-FU/FA regimens as compared to the infusional 5-FU and the 5-FU prodrugs. Responses may vary from less than 10[22,23] to more than 40%[10] for the bolus 5-FU[10,14,15,22–35] and from 16[38] to 44%[16] for the infusional 5-FU.[13–16,36–38] Median survival times show even more overlap (Figure 2). Using the median survival time with best supportive care study of 5 months as a benchmark, it is clear that the survival with both bolus 5-FU (range 8.5–14 months)[26,30] and infusional 5-FU (range 10–19.9[36–38] months) appear to be longer. This great variability for a given schedule is probably mainly due to patient selection criteria. However, the three randomized studies comparing bolus to infusional 5-FU suggest an advantage of the infusional 5-FU over the bolus one in terms of response rate[13] and PFS.[14,16] None of these trials were designed to identify an overall survival advantage. With respect to oral 5-FU-based drugs, the results of the phase III trials comparing Orzel and Xeloda to the Mayo Clinic regimen show comparable levels of activity in terms of response rate (Figure 1) and survival times (Figure 2).[22,31,33,34]

New agents

The last 5 years have witnessed the development of three new agents active in colorectal cancer: tomudex (Raltitrexed) is an inhibitor of thymidylate synthase, oxaliplatin (Eloxatine) is a diamino cyclohexane platinum complex and an alkylating agent, and CPT-11 (Irinotecan) is a topoisomerase 1 inhibitor. As single agents in previously untreated patients their response rates of around 20% and their median survival times of 10–15 months are in the range of what can be obtained with most of the 5-FU regimens (Figures 3 and 4).[23,32,36,39–41]

More recently, attempts have been made to treat colon cancer in second-line after failure of a 5-FU-based regimen with CPT-11 and oxaliplatin. CPT-11 has been compared, in a randomized fashion, to best supportive care and best infusional 5-FU (investigators had the choice between three infusional regimens). In both trials the patients had to be resistant to a first-line 5-FU regimen, to have a WHO

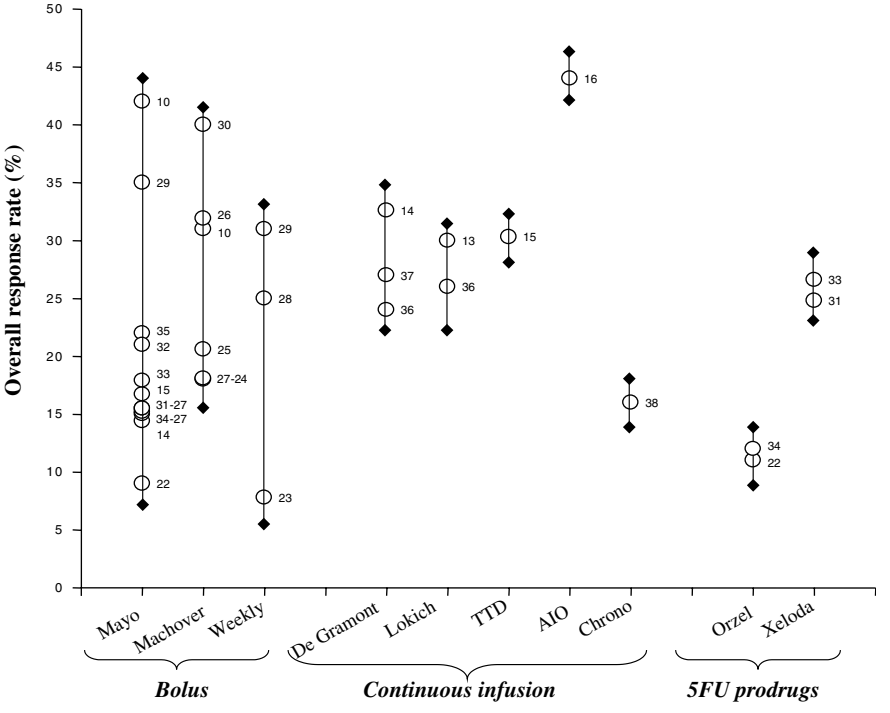

Figure 1. Single-agent therapy, distribution of objective response rates of bolus, infusional 5-FU/FA and oral 5-FU prodrugs (phase III data).

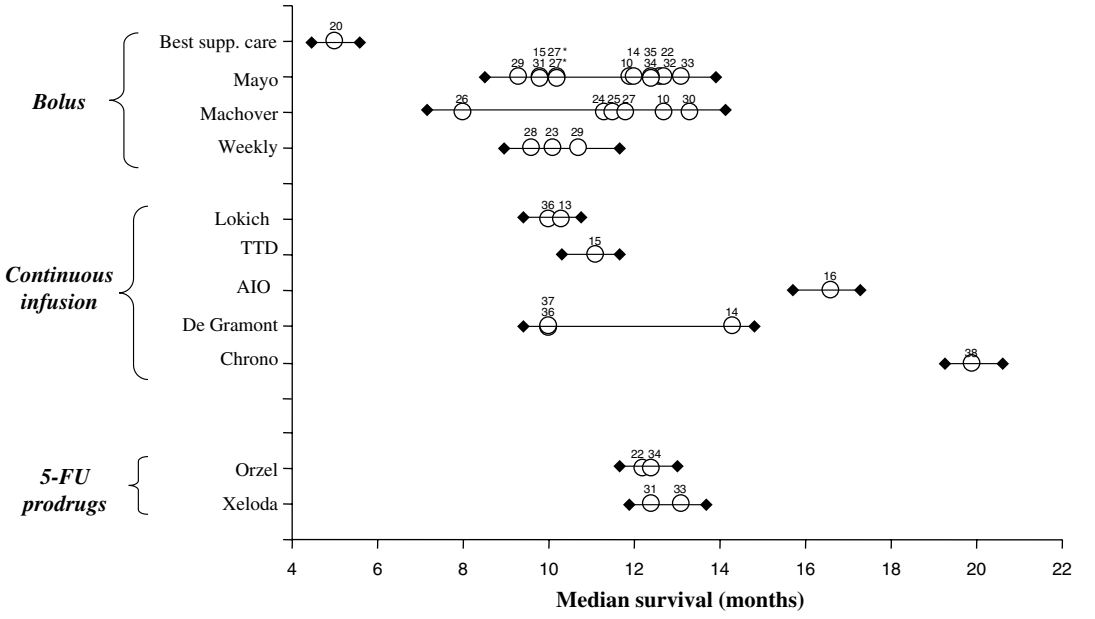

Figure 2. Single-agent therapy, distribution of median survival times for bolus, infusional 5-FU/FA and oral 5FU prodrugs (phase III data).

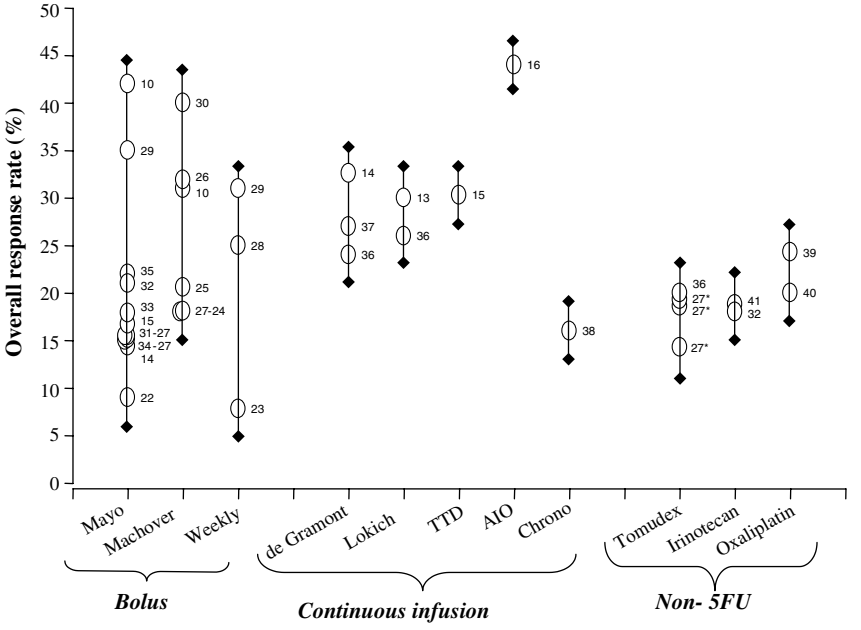

Figure 3. Single-agent therapy, distribution of objective response rates of bolus, infusional 5-FU/FA versus tomudex, irinotecan (phase III data) and oxaliplatin (phase II data).

performance status $\leqslant 2$, and adequate liver and renal function. CPT-11 was given as a 30-min infusion at the dose of 350 mg/m^2 every 3 weeks. The main end points were survival and quality of life (QoL). The response rate has not been reported. In both studies there was a significant survival benefit in favor of CPT-11 with a median survival time of 9.2 versus 6.5 months ($p=0.0001$) for the best supportive care study and 10.8 versus 8.5 months ($p=0.04$) for the best infusional 5-FU.[42,43] Although direct comparison between the two studies is questionable, the survival difference looks greater in the treatment arm versus

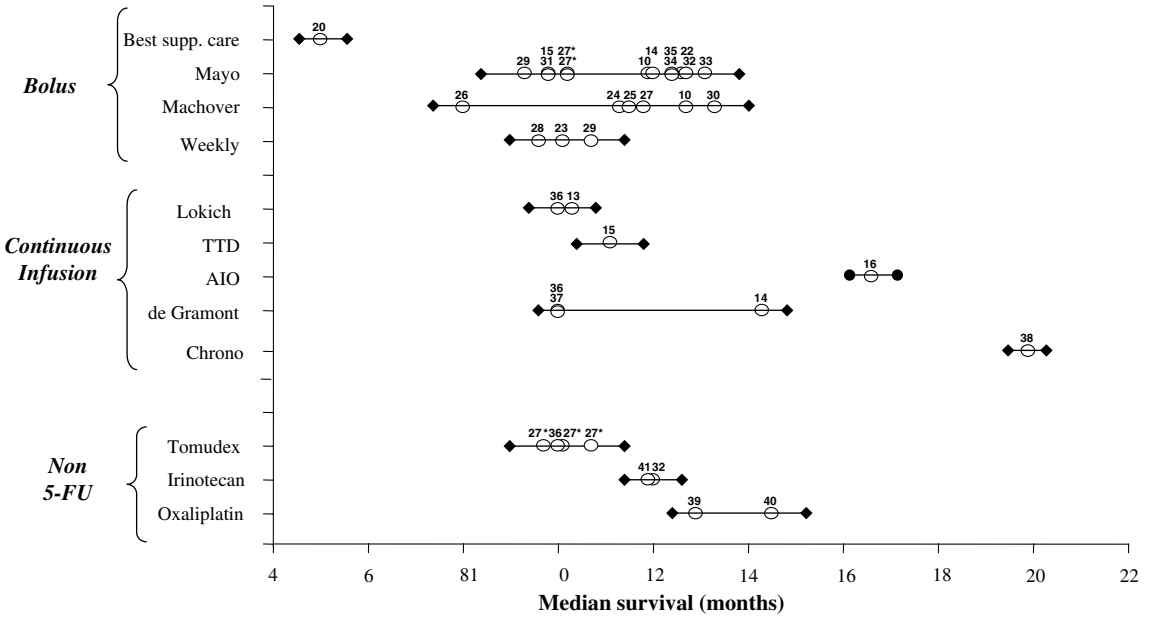

Figure 4. Single-agent therapy, distribution of median survival time with bolus, infusional 5-FU/FA and tomudex, irinotecan (phase III data) and oxaliplatin (phase II data).

best supportive care, suggesting that infusional 5-FU might have some activity as second-line treatment after failure of a 5-FU bolus-based regimen.

Oxaliplatin

Oxaliplatin, as single agent, has been used in second-line therapy at the dose of 130 mg/m^2 in two studies. The response rates were 10 and 11%. The median survival times were 8.2 and 10 months, comparable to the median survival times observed in the randomized CPT-11 studies.[44]

For more than 40 years, 5-FU alone and later in combination with FA or other modulators was the only possible treatment for advanced colorectal cancer. Today, many agents and many options are available. Preclinical studies suggested that the combination of 5-FU, oxaliplatin and irinotecan could be synergistic.[45] An additive or synergistic effect has also been demonstrated in randomized studies of 5-FU/FA alone versus its administration in combination with oxaliplatin[38,46] and irinotecan.[32,47] Such an effect is also strongly suggested by the non-randomized comparison of 5-FU/FA,[32,38,46,47] oxaliplatin,[39,40] and irinotecan[32,41] alone and in combination,[32,47] as well as of Raltitrexed alone[22] and in combination with oxaliplatin[48] (Figure 5).

The combinations of 5-FU/FA with either oxaliplatin or CPT-11 are currently the most active treatments available in advanced colorectal cancer.

Adding oxaliplatin to 5-FU/FA (de Gramont schedule) led to a response rate of 50.5% and a PFS of 9.0 months for the combination as compared with 22% and 6.2 months for 5-FU/FA alone. Median survival times of 16.2 and 14.7 months were not statistically different in a trial powered for time to progression. The lack of a statistically significant survival advantage in favor of the combination could be due to the cross-over of 27.6% of the patients to the 5-FU/FA/oxaliplatin combination or to enrollment of too few patients.[46]

Europe

In Europe, a combination of CPT-11 180 mg/m^2 with bi-weekly 5-FU/FA (de Gramont schedule) every 2 weeks or 80 mg/m^2 with 5-FU/FA, AIO schedule weekly $\times$ 6 every 7 weeks, showed a response rate of 49%, a PFS of 6.7 months and a median survival time of 17.4 months as compared to 31%, 4.4 months and 14.1 months, respectively, for the corresponding 5-FU/FA alone regimen ($p<0.001$, $p<0.001$ and $p=0.031$).[47] The number of patients included in the AIO regimen is too small to allow any separate evaluation of this regimen which is being investigated further in a trial of the EORTC.

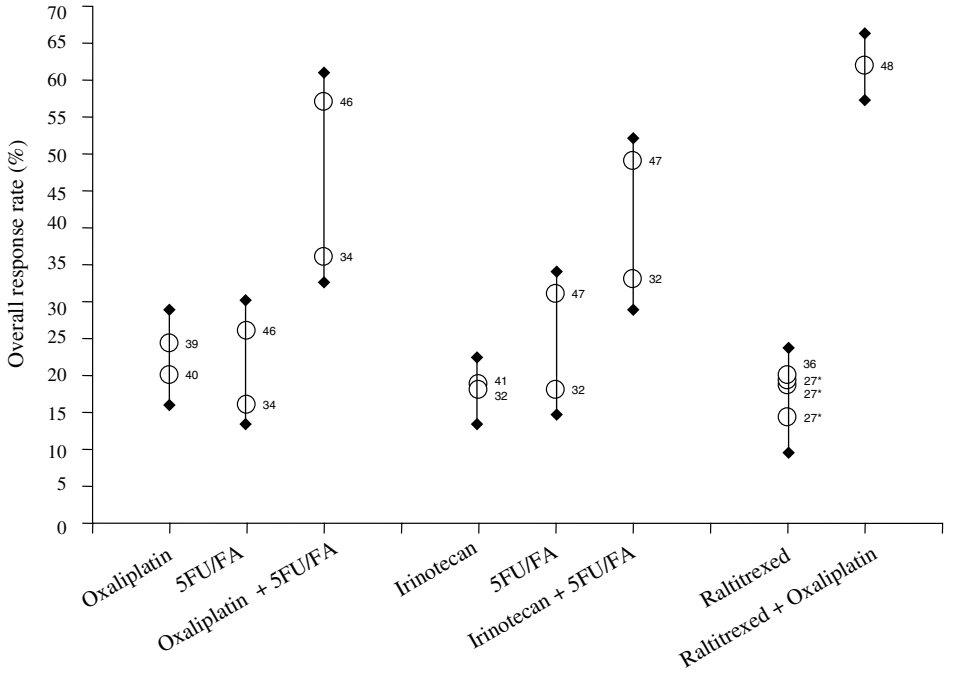

Figure 5. Distribution of objective response rates with single agents versus combination (phase II and phase III data).

USA

In the USA, a combination of CPT-11 125 mg/m^2 with 5-FU 500 mg/m^2 and FA 20 mg/m^2 bolus weekly $\times$ 4 every 6 weeks showed a response rate of 33%, a PFS of 5.0. months and a median survival time of 14.9 months as compared to 18%, 3.8 months and 12 months, respectively, for the 5-FU/FA alone arm.[32]

This additive/synergistic effect is also suggested in second-line therapy in patients failing after a 5-FU/FA regimen. The combination of infusional 5-FU/FA and oxaliplatin leads to a response rate of 20–46% as compared to 10% with oxaliplatin alone.[49–52] No relevant data exist for second-line CPT-11 combined with 5-FU/FA.

Goals

With all these treatments in hand, what are the goals that could be achieved by the year 2001. Which strategy could be offered to our patients in order to improve their outcome? Today, three objectives are achievable in advanced colorectal cancer: cure, prolongation of survival and QoL.

Cure in disseminated colorectal cancer has only been restricted to patients with limited metastatic disease to the liver or to the lung. If curative surgery was performed, 25–40% of resected patients were alive and free of disease at 5 years.[53] For patients with unresectable disease, cures remain unattainable. Phase II studies using chronomodulated 5-FU/FA and oxaliplatin suggested that some patients with non-resectable liver metastases exhibited a major tumor shrinking, allowing reconsideration of curative surgery. These patients enjoyed a prolonged survival.[54] More recently, 209 patients with non-resectable liver metastases received chronomodulated 5-FU/FA and oxaliplatin before surgery in an attempt to make the liver metastase(s) resectable. Fifty-eight patients had curative surgery. The median survival time was not reached at 4 years. Seventy-four patients were not candidates for surgery after therapy; their median survival time was around 15 months. Seventy-seven patients were operated upon but could not have curative surgery; their median survival was 4 years.[55] These data are appealing from various perspectives. Even if the patient population is highly selected, these data strongly suggest that a major survival benefit, and perhaps cure, could be obtained in patients previously thought to be candidates for palliative treatment only. Patients who were not operated had a survival time in the range of what is usually observed in advanced disease. However, for the patients with non-curative surgery a median survival time of 4 years is unexpectedly long. This could occur by chance in a

highly selected population of patients; however, it suggests the possibility that liver tumor debulking may play a major role in the control of disease in selected cases. Today we can only speculate on these observations. Therefore, there is an urgent need for properly designed trials investigating the place of combined chemotherapy and debulking surgery in the treatment of non-resectable liver metastases.

Despite the high variability of tumor response and survival reported in published trials, there is a trend in favor of prolonged survival in the most recently published randomized trials (Table 1) comparing the combination of 5-FU/FA and CPT-11 or oxaliplatin to the 5-FU/FA-alone arm. As compared to the 5–6 months survival observed in the best supportive care studies,[20] median survivals of up to 16 and 19 months have been observed with the combination of CPT-11 and oxaliplatin, respectively.[38,47]

Currently, our patient population is not homogenous in that it is composed of patients with rapidly and slowly progressing tumors. The former, generally, will not respond to treatment, will progress rapidly and will die very shortly despite treatment. Whether the new treatment combinations have the potential to change the outcome of these patients is suggested by the 2-month death rate observed in the 5-FU/FA with or without oxaliplatin study,[46] with 20 deaths occurring in the 5-FU/FA-alone arm versus two in the oxaliplatin-containing arm (database, Sanofi). The subset with slowly progressive disease will generally respond to either first- or second-line therapy or to both lines of treatment. Second-line randomized studies after failure of a 5-FU/FA bolus regimen using CPT-11 versus best supportive care[42] or best infusional 5-FU[43] definitely show a statistically significant survival benefit which may translate in to a prolonged survival estimated from the start of first-line treatment, of about 22–24 months with some patients surviving for more than 48 months.[56] Patients may even respond to a third-line oxaliplatin containing chemotherapy provided their performance status is maintained.[52]

QoL

QoL appears as a major outcome in drug development. Theoretically, based on adequate QoL data, new drugs could be approved both in the USA and in the European Community.

There are currently more than 20 different scales attempting to measure QoL changes during treatment.[57] This large diversity of instruments, by itself, underscores the difficulties in measuring what might well be beyond the realm of scientific testing: one's anxieties, fears and suffering are indescribable and inexpressible. Human misery and happiness cannot be reduced to a few observable countable facts.[58]

Moreover, attrition and missing data are major sources of bias, as, at each evaluation period, the comparisons will concern different sets of patients. Although it is generally admitted that missing data often reflects the poor general status of the patients and occurs mainly in those with progressive disease, it cannot be ruled out, considering the problems in expressing one's inner suffering, that some patients will simply refuse to answer any questionnaire even if they are in good general status.

Some QoL data available in advanced colorectal patients receiving chemotherapy suggest that QoL parallels the activity of chemotherapy. In a group of patients treated with 5-FU alone or 5-FU with a double modulation of methotrexate and leucovorin, the later had a partial response/stable disease rate of 54.5 and 55% had an improved QoL as compared to

Table 1. Evidence of treatment-related prolonged survival

	Treatment[a]	Median survival (months)
Scheithauer (1993)[20]	best supportive care	5
Poon (1991)[10]	5-FU/LDFA	12.6
de Gramont (1997)[14]	LV5/FU2	13.6
	5-FU/LDFA	12.7 (NS)
Giacchetti (2000)[38]	5-FU/FA chm	19.9
	5-FU/FA chm/oxaliplatin	19.4 (NS)
de Gramont (2000)[46]	LV5/FU2	14.7
	LV5/FU2+oxaliplatin	16.2 (NS)
Douillard (2000)[47]	5-FU inf/FA	14.1
	5-FU inf/FA	17.4 ($p=0.031$)
Saltz (2000)[32]	5-FU bolus/FA	12.6
	5-FU bolus/FA/CPT-11	14.8 ($p=0.04$)

[a]chm, chronomodulated; LV, leucovorin; LD, low dose.

13.6 and 9%, respectively, in the former.[59] In a study pooling the data of patients treated by 5-FU modulated by leucovorin and methotrexate or by leucovorin alone, among the 15 patients who responded, 13 had an improved QoL. Among the 18 patients with stable disease, seven had an improved QoL, while QoL worsened in all those with progressive disease.[60]

In the studies of CPT-11 versus best supportive care or infusional 5-FU given second-line after failure of bolus 5-FU, a survival advantage of CPT-11 over best supportive care and infusional 5-FU was demonstrated. Considering the toxicity profile of CPT-11, including frequent episodes of grade 3 and 4 neutropenia (47%) and late diarrhea (39%),[41] it is remarkable that a QoL advantage in favor of CPT-11 was observed in the best supportive care study.[42] In the infusional 5-FU study, no difference in QoL was observed, suggesting that, although CPT-11 is generally more toxic than infusional 5-FU, QoL was not worsened with CPT-11. These studies strongly suggest that in colon cancer, disease-related symptoms can be overcome and QoL improved with efficient chemotherapy even in the presence of chemotherapy-related toxicities.[42,43]

Other approaches to estimating QoL such as the median symptom-free survival also suggest that QoL may be improved by active chemotherapy. A study comparing immediate treatment at diagnosis to delayed treatment at the time of symptoms showed an 11-month median symptom-free survival in the immediate treatment group as compared to 2 months in the delayed treatment group ($p < 0.001$).[21] Comparable differences have been observed in a study comparing intrahepatic artery floxuridine versus no treatment.[61]

Recent trials

The most recent trials that compare combinations of 5-FU/FA with oxaliplatin[46] and CPT-11[32,47] did not show a QoL benefit in favor of the most active chemotherapy treatment, despite a significant survival advantage. The data on the CPT-11 studies are not yet published (except in abstract form) and it may be difficult to put forward any explanation for the lack of difference. As far as the 5-FU/FA/oxaliplatin study is concerned, most of the patients had a performance status of 0–1. Attrition occurred at each cycle as expected in that patient population. The reasons for missing data were not identified. However, it is surprising that about 15% of the patients had no baseline QoL data.[62] This could only be explained, as previously suggested, by the refusal of the patients who did not want to or were unable to express their physical and psychological problems. If this holds true, QoL data as measured today should be looked at very cautiously as, on one side, activity is judged only on an intent-to-treat analysis including all patients and the QoL data would be analyzed on those patients who are willing/able to fill in the emotionally demanding QoL questionnaires. More thoughts and research are needed in the field of QoL life measurements. Simplified instruments focusing more specifically on treatment related effects of anticancer treatment on QoL should be investigated.

Conclusion

At all stages of colorectal development, interventions are now underway to improve the outcome. Although effective prevention remains unproven it is clear that screening, early diagnosis and polyp resection are valuable methods to have an impact on the incidence of colorectal cancer and the identification of early potentially curable stages of the disease. Surgery by itself has dramatically improved the 5-year survival of colon and rectal cancer.[2] New surgical procedures could further improve survival. For example, in rectal cancer, total mesorectal excision appears to decrease the risk of local recurrence below 10%.[63] An aggressive surgical policy is a new approach with the potential to cure patients with liver and lung metastases. Major progress has been accomplished in the adjuvant setting, and there is the potential for further progress with new combinations including CPT-11 and oxaliplatin still being investigated. Eventually new agents and combinations including tomudex, CPT-11 and oxaliplatin are likely to be forthcoming. The data available strongly suggest that these new combination chemotherapy regimens will lengthen survival. Further research is needed for identifying the best combination and/or the best sequence. During the early years of this century we will witness major progress in the treatment of colorectal cancer.

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