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REVIEW ARTICLE

Chemotherapy for Advanced Colorectal Carcinoma: Fact and Fable

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ABSTRACT

For more than 40 years, 5-florouracil has been the mainstay of treatment for advanced colorectal carcinoma. Despite its many modulations by other agents or changes in scheduling of its delivery with resultant improvement in response rates, the increase in absolute survival has been modest at best. A generally nihilistic approach has been widely adopted due to this lack of significant improvement and single-agent 5-florouracil remained the cornerstone of therapy for this disease whilst exciting developments with combination chemotherapy have been observed in other tumours, for instance, for breast cancer. The recent introduction of irinotecan and oxaliplatin into the field of colorectal oncology has revolutionised our armamentarium and, at long last, combination chemotherapy becomes a reality for this group of patients. Higher response rates (35 to 55% versus 20%) over regimens with modulated 5-florouracil are now accompanied by a definite increase in overall survival, together with clear documentation of the absence of deterioration in quality of life. Such a development, athough modest, represents a step forward. In this review, the many myths and fables related to the use of chemotherapy for advanced colorectal carcinoma will be appraised and lessons from key international trials will be presented. These facts form the basis for the paradigm shift that is beginning to be locally observed, in the field of colorectal carcinoma.

Key Words: *Antineoplastic combined chemotherapy regimens, Colorectal cancer, Palliative chemotherapy*

INTRODUCTION

Colorectal carcinoma (CRC) is one of the leading malignancies in Hong Kong. In the year 1995 to 1996, cancer of the colon accounted for 9.3% of all newly diagnosed cases and 7.8% of all cancer deaths, while the corresponding figures for cancer of the rectum were 5.4% and 4.2%, respectively. The incidence and mortality from CRC is increasing for both men and women, and CRC is ranked second in the list of leading cancer sites and fatal cancers, representing 14.7% of the former and 12.1% of the latter.[1]

At the time of diagnosis, for every hundred patients, 5 have locally advanced, inoperable disease, 25 have metastases, and 25 of the remaining 70 patients presenting with resectable tumours will experience later recurrence. Hence, more than 50% of patients may require palliative chemotherapy at some stage. With nearly 2900 new cases of CRC diagnosed in 1996,[1] for example, it can be estimated that approximately 1500 patients may have required palliative chemotherapy at some stage in disease management.

In contrast to advances seen in other areas of oncology, progress in palliative chemotherapy for advanced colorectal carcinoma (ACRC) has been slow and plagued by myths and misconceptions which reflect, in part, the vested interests of the pharmaceutical industry (Table 1).

Table 1. Misconceptions concerning chemotherapy for advanced colorectal carcinoma (ACRC).

Palliative chemotherapy for ACRC is futile — survival benefit is an illusory endpoint
Early treatment is no better than delayed treatment
Surgery for the primary tumour is mandatory
Continuous treatment in responders is imperative
Response rates have no bearing on survival
One novel agent is superior to the others

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Table 2. Issues to be considered regarding chemotherapy for advanced colorectal carcinoma.

Rationale for treatment
Arguments for early rather than late treatment
Controversy over the need for surgery to the primary lesion
Controversy over the length of treatment
Relationship between response and survival
Novel agents: new oral agents, oxaliplatin, irinotecan
Controversy over the relative merits of novel agents
Economic aspects of novel therapy

To facilitate a realistic approach to the management of ACRC, this review will consider recent literature and discuss therapeutic options and the theoretical basis upon which decisions regarding treatment can be made (Table 2). Less evidence-based aspects of chemotherapy, for instance, use of neoadjuvant therapy before surgical resection of metastatic disease, and adjuvant chemotherapy for high risk patients with stage III colorectal cancer, are beyond the scope of this review and will not be discussed.

ISSUES IN THE MANAGEMENT OF ADVANCED COLORECTAL CARCINOMA

Should Palliative Chemotherapy Be Given for Advanced Colorectal Carcinoma?

The current status of palliative chemotherapy with conventional regimens based on 5-fluorouracil (5-FU) is best summarised by a systematic overview of 5 randomised controlled studies comparing chemotherapy with best supportive care in ACRC.[2] This analysis was incorporated into a policy document on the commissioning of cancer services prepared by the Department of Health in the UK. The analysis found a consistent benefit of between 3 and 6 months in survival when palliative chemotherapy was used. Moreover, quality of life (QOL) was noted to be equal or better with early active treatment before symptoms occurred.[2]

A more recent meta-analysis by the Colorectal Cancer Collaborative Group reviewed the data from 13 trials, 10 of which were randomised controlled studies. One study utilised a regimen based on irinotecan (CPT-11). A total of 1365 patients were included in the analysis and individual patient data was available for 7 of the 13 trials. When individual patient data was analysed, a 35% reduction in the risk of death (95% confidence interval [CI], 24 to 44%) corresponding to a hazard ratio of 0.65 was observed. This represented an absolute improvement in survival of 16% at both 6 and 12 months, and an increase in median survival of 3.7 months (8 versus 11.7 months).[3] There was significant heterogeneity in the chemotherapy regimens used, but most were based on 5-FU. When the study using CPT-11 was excluded, analysis showed persistence of statistical significance, with a hazard ratio of 0.69. The difference in overall survival (OS) remained significant when all the published data were included in the analysis. As trials with a crossover design were included, the observed difference may have underestimated benefits because when the control group received treatment, prognosis would be improved, thereby reducing the difference observed. In essence, such survival benefits are likely to be real and probably of a larger magnitude than that reported.

Data on QOL and toxicity were incomplete, however, and no firm conclusions could be drawn from this report in this regard. Ten trials included toxicity data, but only 4 used a validated scale. For QOL evaluation, 6 of the 13 trials reported data, with different instruments being employed. Of these 6 studies, 3 showed QOL benefits with treatment,[4-6] 2 showed no difference with treatment,[7,8] and the sixth reported poorer QOL ratings with chemotherapy treatment.[9] That, nonetheless, does not imply a lack of palliative value as it was only a result of the trial designs and lack of validated instruments being utilised in many of the studies. In fact, 3 of the studies that employed modern validated instruments of QOL showed consistent benefits despite the presence of side effects.[4,5,10]

In summary, there is now compelling evidence supporting the use of chemotherapy for ACRC, with clear documentation of survival benefits. Such benefits are modest. Nevertheless, as therapy is palliative, the impact on QOL becomes an important endpoint. Although the favourable QOL outcome observed in several studies in the advanced setting is promising, optimal timing of treatment commencement is still an open question to many experts.

Should Early Treatment Be Recommended?

In a study conducted by the Nordic Gastrointestinal Tumour Adjuvant Therapy Group,[10] 183 asymptomatic patients with ACRC were randomly assigned to receive early or delayed chemotherapy, with the latter being given when symptoms occurred. The median symptom-free period for the delayed group was only 2 months and 57% of patients in this group eventually commenced chemotherapy. QOL evaluation in a subset of patients

receiving early chemotherapy showed no deterioration in QOL and the median survival was 9 and 14 months for each study group, respectively, favouring immediate chemotherapy, although the trend did not reach statistical significance. This trial has been the subject of widespread discussion and criticism, especially as 43% of patients in the delayed treatment group did not receive chemotherapy. However, this has been described as a realistic consequence of the decision to defer palliative chemotherapy.[11]

Another study showing favourable results for early treatment randomly assigned patients with ACRC for whom first-line 5-FU had failed to second-line CPT-11 plus supportive care, or supportive care alone.[5] A statistically significant improvement in 1-year survival rates with second-line chemotherapy (14% versus 36%) and an increase in median survival of 2 months were observed.

A contrary observation was made following a combined analysis of an Australian study and a Canadian trial with similar designs, involving 168 patients in total. Both trials were plagued by poor accrual and approximately 32% of patients in the delayed group did not receive chemotherapy. The median delay before commencement of chemotherapy in the expectant group was 5 months. There was no difference in survival observed.[12]

Overall, there seems to be more evidence supporting the early use of palliative chemotherapy in asymptomatic patients with ACRC. This is the consensus view expressed at different levels throughout the medical community, ranging from undergraduate medical textbooks on colorectal cancer,[13] to specialist colleges' recommendations,[14] and also at the national policy level such as that outlined by the National Health Service Executive in the UK.[2]

Is Surgery for the Primary Lesion Always Required?

It has been conventional practice for patients with ACRC to undergo resection of the primary lesion prior to palliative therapy. This stems from the expectation that complications such as bleeding or bowel obstruction related to the primary tumour may thus be avoided, even in cases where the primary lesion has been asymptomatic. The survival of such patients is often limited by metastases, with surgery delaying palliative chemotherapy. Addressing this issue, Scroggins et al reported the findings of the management of 89 asymptomatic patients.[15] Sixty six patients were treated with surgery, while 23 received initial chemotherapy with surgery being delayed until the appearance of clinical symptoms. There was no statistically significant difference in median survival and 2-year survival between the 2 groups of patients, although the operative morbidity and mortality were 30.3% and 4.6%, respectively. The surgery-free survival rate at 2 years for the no-surgery group was 91.3%, and only 2 of the 23 patients (8.7%) required surgery for intestinal obstruction during their remaining years. Moreover, no haemorrhage or perforation was observed in the no-surgery group.

Similar findings were reported by investigators at the Royal Marsden Hospital in the UK.[16] In this retrospective study, 193 patients who underwent surgery for the primary lesion, and 70 patients who received palliative chemotherapy, were identified. The principal aim was to evaluate rates of complications due to the primary lesion in these 2 groups. Preserved performance status (PS; 0-1) was observed for 79% of the surgery group and 67% of the no-surgery group. Low rates of complications, including intestinal obstruction, gastrointestinal bleeding, peritonitis, fistula development, and the need for gastrointestinal surgery were recorded, with no significant difference between the groups observed. Statistically significant differences were noted in higher rates of blood transfusion and need for radiotherapy in the no-surgery group (20.6% and 23.2% versus 10% and 12.4%, respectively).

Although the data are limited, it is highly probable that with careful selection, asymptomatic patients can be managed without surgery to the primary lesion. The importance of an asymptomatic clinical state in this selection process cannot be over-emphasised and, for those patients who have potentially resectable metastases, this expectant approach is not a suitable option. Nonetheless, in the presence of alternative treatment modalities which may control the primary lesion or its complications, for instance, chemo-irradiation for a rectal primary tumour, local excision, electrocoagulation, laser recanalisation and, last but not least, expandable metal wire stents, the no-surgery expectant approach certainly represents a viable option to be considered.

Is Continuous Treatment Essential?

Unlike adjuvant chemotherapy where the number of cycles or length of chemotherapy is relatively well defined, the optimal duration of palliative treatment in ACRC is unknown. This is illustrated by a recent

survey in the UK, which showed that 50% of oncologists would treat for up to 6 months, 30% for up to 3 months, and 20% would continue treatment until progressive disease was observed.[17] Data on this aspect of ACRC is, in many ways, at least as important as efforts to improve treatment regimens. Take, for instance, the recently reported French study using CPT-11 based chemotherapy as first-line treatment in ACRC, in which Douillard et al noted a median survival of approximately 17 months for patients in the experimental arm.[18] If treatment is continued for 6 months, patients are receiving chemotherapy for up to one third of their remaining lifespan. Apart from cost considerations, this also raises ethical issues that need to be addressed.

Maughan et al recently presented a paper on this topic at the American Society of Clinical Oncology Meeting on the results of the Medical Research Council study MRC CR-06B.[19] Patients with ACRC were treated with 1 of 3 palliative regimens for 12 weeks. 354 patients who were either responders or with stable disease were randomly assigned to either continue therapy until progression (CTP) or to discontinue treatment and then recommence the same therapy at disease progression (DTR group). For those in the CTP group, treatment was continued for a median of 91 days and was stopped due to disease progression in 44%, toxicity in 15%, and decision of the physician or patient in 35% of patients. For the DTR group, the median time to therapy recommencement was 134 days; the median time with treatment was then 83 days. Serious side effects and toxicity in association with poorer QOL scores were more frequently seen in the CTP group. There was no statistically significant difference observed between the groups in terms of overall progression-free survival (PFS), OS, and median survival, yielding hazard ratios of 1.16 and 0.87 for the former 2, and 11.2 months and 11.8 months for the latter in the CTP and DTR groups, respectively. Hence, there is currently no clear evidence supporting continuous therapy. Preliminary results of this study suggest possible gains in QOL in association with lessened toxicity when the 'stop and restart' policy is adopted for patients who are positive responders or have stable disease. It is imperative that this aspect of treatment of ACRC be clarified by future studies.

Can Improved Response Be Translated into Better Survival for Advanced Colorectal Carcinoma?

One of the most controversial aspects of palliative chemotherapy for ACRC is the uncertain relationship between response rates and survival, a problem also found with respect to many other tumours in the advanced setting. The gain in response rates observed in many novel therapeutic manoeuvres is often not translated into a meaningful advance in other endpoints, especially in terms of survival.

The relationship between response rate and survival was explored in a recent study reported by Buyse et al.[20] Individual patient data for 3791 patients with ACRC who had received 5-FU-based chemotherapy were analysed. This analysis confirmed that an increase in tumour response rate was translated into an increase in OS but only small benefits were seen. For instance, when the response rate increased from 20 to 40% (with an initial median survival of 14 months), the new median survival rose to approximately 15.7 months. The cause of such dilution of benefits is multi-factorial and is possibly due to the presence of effective second-line therapy, the low overall response rate, the very low complete response rate, and the observation that the latter 2 are often short-lived.[20]

Similar findings were reported by a much larger French study in which data from 13,500 patients were analysed.[21] Despite the heterogeneity of regimens used, an almost identical relationship between response rate and survival endpoints emerged, with every 11.4% improvement in response rate increasing the OS by 1 month. All these correlations were statistically significant. Thus, an impressive doubling of response rate from 20 to 40% would see an OS benefit of 14.5% (eg from 12.20 months to 13.97 months). The predictions derived from these 2 studies are borne out by 2 recently reported phase III studies employing novel agents in the first-line setting in ACRC — an increase in response rate from 20% to approximately 40% was accompanied by a corresponding improvement in median survival from 12.6 months to 14.8 months in 1 study,[22] and from 14.1 months to 17.4 months in another.[18]

The possible influence of second-line therapy on first-line therapy benefits was the subject of a recently reported German study.[23] With the aid of mathematical modelling, the investigators evaluated the data of 3825 patients treated with first-line palliative chemotherapy. Survival was explored as a function of response to first- and second-line therapy. When OS from first- and second-line treatment were considered together, long-term survival became almost identical between the group (Figure 1).

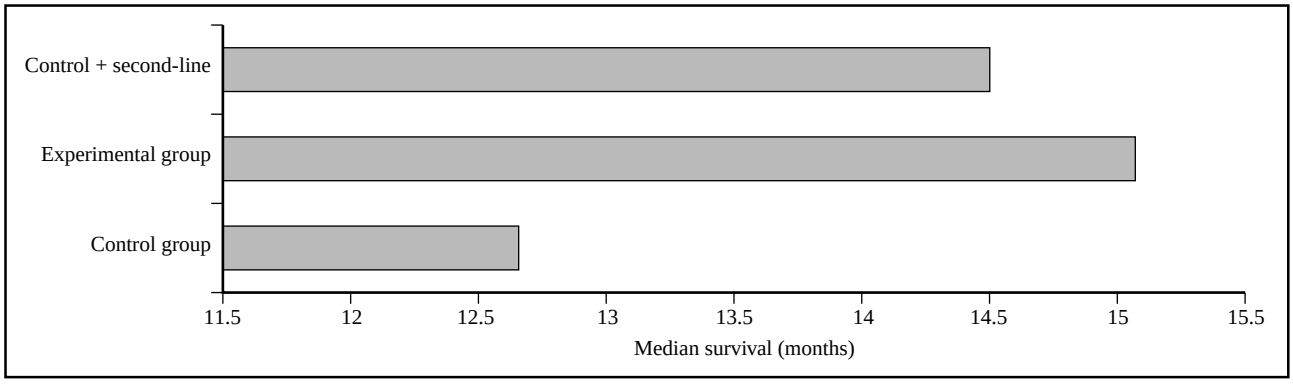

Figure 1. The impact of an effective second-line therapy on survival. If the control arm has a response rate of 20% and a median overall survival of 12.7 months and the experimental first-line therapy is associated with a superior response rate of 50% and a median overall survival of 15.1 months, the use of an effective second-line treatment will prolong the median overall survival of the control group to 14.5 months, hence diluting the impact of the experimental first-line therapy.

Nonetheless, there are other factors that might influence the optimal regimen to be used, including the declining number of patients suitable for second-line therapy, potential changes in physical condition and PS of the patient, the palliative value of the regimen, the impact on QOL and toxicity, and the lack of effective further lines of therapy. All these variables need to be considered separately and then factored together for an individual patient to decide the best regimen to be used as first-line treatment.

Novel Chemotherapeutic Agents

For more than 40 years, 5-FU has been the mainstay of treatment for advanced colorectal carcinoma. Despite its many modulations by other agents,[24-32] and changes in scheduling of delivery with resultant improvement in response rates,[33] the increase in absolute survival has been modest at best. The recent introduction of irinotecan and oxaliplatin now allows effective combination chemotherapy for this disease (Table 3). Other emerging treatments include the new oral chemotherapeutic agents that have impressive efficacy, low toxicity, and offer the additional advantage of better QOL for patients undergoing palliative chemotherapy. For the sake of brevity, only tegafur uracil (UFT), capecitabine, CPT-11, and oxaliplatin will be discussed in this review, as these are the most commonly employed novel agents in Hong Kong.

Tegafur Uracil

UFT is a compound agent consisting of uracil, a dihydropyrimidine dehydrogenase (DPD) inhibitor, and tegafur, a 5-FU prodrug, in a fixed ratio of 4:1. In 2 randomised controlled trials, UFT in combination with leucovorin was compared to 5-FU plus leucovorin in patients with ACRC.[34,35] There were no statistically significant differences in response rates, time-to-progression and OS, although the UFT-leucovorin regimen was better tolerated with fewer side effects. UFT is now incorporated into regimens containing CPT-11 or oxaliplatin and is also the subject of an adjuvant chemotherapy study of the National Surgical Adjuvant Breast and Bowel Project (NSABP C-06). Until further results are available, given its equivalence to the conventional regimen, UFT use is considered limited at present.

Capecitabine

Capecitabine is an inactive 5-FU prodrug that is well-absorbed orally and subsequently metabolised in the liver to 5-deoxy-5-fluorocytidine (DFCR). This is then

Table 3. Commonly employed novel regimens for advanced colorectal carcinoma.

Regimen	Schedule	Frequency	Reported response rates	Median survival
Irinotecan + 5-FU + leucovorin[18]	Irinotecan 180 mg/m^2 over 90 minutes, day 1 Leucovorin 200 mg/m^2, days 1 and 2 5-FU bolus 400 mg/m^2 over 10 minutes, days 1 and 2 5-FU infusion 600 mg/m^2 over 22 hours, days 1 and 2	2-week cycles	35-39%	14.8-17.4 months
Oxaliplatin + 5-FU + leucovorin[55]	Oxaliplatin 85 mg/m^2 over 2 hours, day 1 Leucovorin 200 mg/m^2 over 2 hours, days 1 and 2 5-FU bolus 400 mg/m^2 over 10 minutes, days 1 and 2 5-FU infusion 600 mg/m^2 over 22 hours, days 1 and 2	2-week cycles	50.7-53%	16.2-19.4 months

Abbreviation: 5-FU = 5-fluorouracil.

converted to 5-deoxy-5-fluorouridine (DFUR) by cytidine deaminase in the tumour and the liver. The final step involves the conversion of DFUR to 5-FU by thymidine phosphorylase (TP), the concentration of which is higher in the tumour than in normal tissues. This preferential activation pathway therefore forms the basis of capecitabine's tumour-selective activity, and such targeted action has been confirmed in a recent clinical study.[36] In 2 randomised controlled trials, capecitabine alone has been shown to have equivalent activity to bolus 5-FU plus leucovorin.[37,38] One study showed a significantly higher response rate while all other endpoints, including those for survival, were essentially equivalent between both arms in both trials. With respect to toxicity, capecitabine was generally less toxic than 5-FU plus leucovorin, the only exception being hand-foot syndrome which occurred more frequently with capecitabine. Again, since the time-to-progression and OS were noted to be equivalent, the conclusion that capecitabine is equivalent to 5-FU plus leucovorin remains current. Given their equivalence, capecitabine is now being used to replace 5-FU plus leucovorin in many ongoing studies, some with incorporation into CPT-11- or oxaliplatin-based regimens,[42] while a further study involves its use alone as an adjuvant therapy in stage III disease.

Irinotecan

CPT-11, a potent topoisomerase I inhibitor, is derived from *Camptotheca acuminata* or Xi Shu. It is converted into SN-38 which binds to the topo-I-DNA cleavable complex, stabilises it, and prevents religation. This then leads to double strand breaks when the replication fork collides with the cleavable complex.[43]

The clinical use of CPT-11 in colorectal carcinoma started in the 1990s with promising phase II and III results being reported in patients with ACRC in both first- and second-line treatment settings.[5,44-46] Studies reported by Cunningham et al[5] and Rougier et al,[46] confirmed the efficacy of single agent CPT-11 when compared to best supportive care alone, or to infusional 5-FU after first-line 5-FU failure, respectively, demonstrating statistically significant improvement in survival as well as benefits in other surrogate endpoints.[5]

In the first-line treatment setting, Saltz et al reported a multicentre study undertaken in the USA, Canada, Australia, and New Zealand.[22] 683 chemotherapy-naive patients with ACRC were randomly assigned to receive bolus 5-FU plus leucovorin alone, CPT-11 alone, or a combination of CPT-11 plus bolus 5-FU and leucovorin. The single agent CPT-11 was analysed by descriptive statistics only. Response rate, time-to-progression, and OS were all noted to be significantly superior in the combination group (response rates, 39% in the combination group versus 21% in the Mayo Clinic control group; PFS, 7 months versus 4.3 months; OS, 14.8 months versus 12.6 months). Regarding toxicity, the combination group showed a lower incidence of diarrhoea compared with patients receiving single agent CPT-11, and a lower rate of neutropenia when compared with the Mayo Clinic control group.

This trial has been the subject of numerous criticisms, especially with respect to its design. The trial design was somewhat unusual in that the only planned statistical testing was between the combination group and the Mayo Clinic group although the randomisation process involved all 3 groups. The design of the study has already been critiqued by other experts, the view being that to take into account the multiple testing performed might have rendered the survival difference non-significant.[47]

Douillard et al randomly assigned a total of 338 patients to receive 1 of 2 infusional 5-FU plus leucovorin regimens, with or without CPT-11.[18] As in the study by Saltz et al,[22] statistically significant superiority in terms of response rate, time-to-progression and median survival were all in favour of the CPT-11-containing group (response rate, 34.8% versus 21.9%; time-to-progression, 6.7 months versus 4.4 months; median survival, 17.4 months versus 14.1 months). Diarrhoea, neutropenia, and infection were more frequent in the experimental arm, in contrast to the Saltz study.[22] However, QOL assessment showed no difference between the 2 groups.[18]

On the basis of these studies, the CPT-11-based regimen was approved by the USA Food and Drug Administration (FDA) in March 2000 as the regimen of choice in the first-line treatment of patients with ACRC. A combined analysis of the previous 2 studies incorporating further data was reported at the American Society of Clinical Oncology meeting in 2000.[48] The p value for survival reported (0.046) indicated a statistically significant effect, although the clinical relevance of the finding was weakened by the multiple analyses performed. Recently, safety data from 2 USA trials employing the Saltz CPT-11 regimen were released and caution was recommended regarding its use.[49] The North

Central Cancer Treatment Group (NCCTG) conducted a study (N9741) in patients with metastatic ACRC. The Saltz regimen was used for the control group and was compared to an oxaliplatin plus 5-FU and leucovorin regimen and a regimen of CPT-11 plus oxaliplatin.[50] Another trial was conducted by the Cancer And Leukaemia Group B (CALGB trial C89803) comparing the Saltz regimen to the regimen with 5-FU plus leucovorin as adjuvant chemotherapy in patients with stage III colorectal carcinoma. Excessive rates of death within the first 60 days of therapy associated with the use of the Saltz regimen compared with 5-FU plus leucovorin were noted in both trials (N9741, 4.8% vs 1.8%; C89803, 2.2% vs 0.8%), which culminated in a halt of accrual into the N9741 and a permanent closure of the C89803.

An expert panel reviewed the safety data of the N9741 and C89803 and issued a special report in September 2001.[51] The panel recommended a number of measures for ensuring future safety (Table 4) and added that, given the more impressive safety profile of the Douillard et al study,[18] this design should be considered for future adjuvant and metastatic trials. This view is echoed by UK investigators who were testing an infusional regimen for metastatic colorectal cancer (MRC CR08-FOCUS).[52] There are also provocative new data available showing that body surface area (BSA) is not a reliable predictor of CPT-11 clearance or the pharmacokinetics of its metabolite SN-38, with the latter being implicated in complications such as diarrhoea and myelosuppression.[53] Hence, more studies are needed to define an optimal method of administration of CPT-11.[54]

Table 4. Recommendations by the independent panel on the safety and use of irinotecan (adapted from Rothenberg et al[51]).

General
1. Improved criteria should be developed for attribution of cause of death
2. Real-time monitoring of life-threatening or fatal adverse events or hospitalisations to hasten identification of unexpectedly frequent or severe clinical toxicities is desirable
Specific
1. Increased awareness regarding various syndromes associated with irinotecan
2. Weekly assessment by an experienced clinician, especially during weeks 3 and 4
3. More aggressive treatment of diarrhoea using the European approach with frequent monitoring and appropriate use of prophylactic antibiotics
4. Appropriate prophylactic antibiotic use in any patient with prolonged diarrhoea
5. Careful consideration of grade and duration of toxicity and its impact on patient's status before administration of any subsequent cycle
6. Discontinuation of irinotecan in patients suffering significant treatment-related diarrhoea
7. Abdominal cramping should be considered as and treated as for diarrhoea
8. Blood tests should be obtained no more than 48 hours prior to scheduled treatment
9. Changes in electrolytes, including hyponatraemia, hypernatraemia, hypokalaemia and/or metabolic acidosis may reflect early physiologic consequences of irinotecan toxicity and close monitoring and aggressive treatment is warranted
10. Older individuals should be followed especially closely

In summary, trials of CPT-11 regimens for ACRC have shown superior efficacy, albeit modest, with respect to survival, compared with that seen with 5-FU plus leucovorin treatment. However, CPT-11 has been associated with toxicity and constant vigilance and aggressive treatment of any complications are of paramount importance. Similar to capecitabine, there are now ongoing trials, apart from the defunct C89803, that study the role of CPT-11 in the adjuvant setting but results from these trials will not be available for several years.

Oxaliplatin

Oxaliplatin is a novel organoplatinum which forms DNA adducts and is not recognised by the DNA mismatch repair (MMR) complex. The dose-limiting side effects of oxaliplatin include paraesthesia and, to a lesser extent, haematological and gastrointestinal toxicities. Three European phase III trials studying the role of oxaliplatin plus 5-FU and leucovorin as first-line treatment in patients with metastatic colorectal carcinoma have been reported. A French group compared the FOLFOX4 regimen (oxaliplatin plus 5-FU and leucovorin) with LV5FU2 (5-FU plus leucovorin) in 420 patients.[55] Despite the higher, statistically significant response rate (50.7% vs 22.3%; $p = 0.0001$) and longer PFS (9 vs 6.2 months; $p = 0.0003$) observed in the experimental group, there was no significant improvement in OS (16.2 months vs 14.7 months). Giacchetti et al investigated use of a chronomodulated regimen of 5-FU plus leucovorin with or without oxaliplatin.[56] Significantly higher response rates and PFS were noted but again no significant OS benefit was observed.

In a critical appraisal of 4 trials involving incorporation of CPT-11 or oxaliplatin into a 5-FU plus leucovorin regimen,[18,22,55,56] Grothey and Schmoll suggested the following explanations for the apparently discordant results:[57]

- An imbalance in prognostic factors between the groups in the study by de Gramont et al, favouring the control group.[55]

- The presence of effective second-line treatment, including aggressive surgical resection of metastases, which may have reduced the impact of first-line treatment. This was particularly evident in the study by Giacchetti et al, where the duration of OS was exceptionally long in both groups compared to other studies.[56]
- The controversial statistical design of Saltz et al's study, in which 3 groups were randomised but analysis was confined to the 2 groups with the largest observed difference (as previously discussed).[22]
- The presence of more potent control groups in both oxaliplatin studies, as evidenced by the consistently longer PFS and OS than in the control groups of the CPT-11 studies, which may have reduced the likelihood of detecting statistical significance. By the same token, the presence of less potent control groups in the Saltz et al study may have resulted in a greater likelihood of detecting a difference.[22]
- The statistical design of the oxaliplatin studies, with crossover from the control group to the experimental group, may have diluted the initial survival benefits. Moreover, in some study designs, OS was not the primary endpoint, and thus, patient numbers may not have been sufficient to detect subtle differences in OS.

To clarify the impact of crossover, an ongoing phase III study of oxaliplatin treatment (coordinated by the National Institute for Clinical Excellence [NICE], UK) that prohibits crossover has just completed the accrual phase, and results are eagerly awaited.

A third trial comparing an oxaliplatin-containing weekly infusional 5-FU plus leucovorin regimen with the Mayo Clinic bolus 5-FU plus leucovorin regimen was recently reported by a German group.[58] Of 219 patients eligible for evaluation of efficacy, response rate and PFS were significantly different, favouring the experimental group (response rate, 51.4% vs 21.5%; PFS, 8 months vs 5.6 months). Survival was 16.7 months and 20.4 months for the Mayo regimen and experimental group, respectively. Such data were not considered mature at the time of reporting as 69.3% of the control group and 80.2% of the experimental group were still alive.

The toxicity profile was comparable for both groups and not significantly different from other reported studies. On the basis of the first 2 studies where mature data failed to show survival benefit, the USA FDA decided against approval of first-line use of oxaliplatin-based chemotherapy in ACRC. Given the many problems in trial design and the impressive efficacy of this agent in terms of response rates and PFS — which is in the same range as CPT-11 — it remains highly likely that oxaliplatin has the same degree of activity as CPT-11; only with further studies can this hypothesis be proven or disproven. In addition — similar to other novel agents — notwithstanding the absence of proven survival benefit in stage IV patients, the role of oxaliplatin in the adjuvant setting is now being tested in 2 large phase III studies (Mosaic and NSABP C-07 study).

In short, novel oral agents are now available with very similar activity to the conventional 5-FU plus leucovorin regimen. Given the ease of oral administration — and hence better QOL — and the presence of satisfactory toxicity profiles, these oral agents will form an integral part of future chemotherapy. However, their lack of superiority over conventional therapy in terms of survival endpoints will determine their further development, at least in the metastatic setting, only as part of a combination regimen that incorporates other more efficacious novel agents. However, they may well have a role in the adjuvant setting, and data from ongoing studies are eagerly awaited. The combination of CPT-11 or oxaliplatin with 5-FU and leucovorin has now been shown to improve the response rate and PFS in patients with ACRC. In the case of CPT-11, a statistically significant difference in OS was observed, while the opposite finding was noted for the oxaliplatin regimen. Based on present clinical evidence, and design flaws in trials involving the latter agent, however, the oxaliplatin regimen cannot be discounted completely as a first-line option in the treatment of ACRC. Again, ongoing studies should clarify this issue in the near future.

Is One Novel Agent Better Than the Other?

As mentioned above, there are as yet no mature data suggesting any significant difference in efficacy between regimens based on either CPT-11 or oxaliplatin in the first-line setting. The much-awaited FOLFOX-FOLFIRI trial, in which CPT-11 was compared head-to-head with oxaliplatin in a sequential manner, reported similar toxicities (except sensory neuropathy), response rates, and PFS for first-line therapy.[59,60] The only significant difference was between the response rates for second-line therapy (FOLFIRI 4% and FOLFOX 15%), although this did not translate into a significant difference in OS.[60]

To date, there are no data confirming the superiority of any one regimen, at least in the first-line setting. Although differences in response rates exist for second-line therapy, the absence of a difference in OS — the most relevant endpoint for first- and second-line therapy — suggests that "the jury is still out", and the optimal sequence in which these agents should be employed is yet to be defined. Thus, the selection of an agent for first- or second-line use should be based upon the individual's tumour characteristics and prognosis, concurrent medical problems, current PS, and the anticipated toxicity profile — not only assessed as a simple function of the response rates reported by various studies.

How Cost-effective Are the Novel Agents?

Novel agents are expensive when compared to conventional 5-FU-based regimens. Despite the advances in terms of OS and the absence of deterioration in QOL parameters reported in many studies, the use of such costly therapy is still limited — especially in the current climate of an economic downturn, cost containment, reduction in health and welfare budgets, and rationalisation of medical care provision. There have been attempts to quantify the economic aspects of these novel therapies.

Twelves et al evaluated data from one of the phase III studies on capecitabine, and observed that patients on oral chemotherapy had fewer hospital visits for drug administration and management of adverse events, and also required fewer supportive medications, including antimicrobials and 5-HT_3-antagonists.[61] On the other hand, home-based visits, day care, and office and telephone consultations were more frequent. While no specific financial data were reported in this medical resources use analysis, the investigators concluded that capecitabine treatment resulted in substantial savings in the use of resources relative to the Mayo Clinic regimen of 5-FU plus leucovorin.[61]

Vincent and Jonker reviewed the data summaries of phase III trials employing the Saltz-CPT-11 regimen and capecitabine, and compared the benefit-response and cost-effectiveness of the regimens.[62] They identified a subgroup of patients who might benefit in terms of a significant gain in survival when treated with the Saltz regimen (age <65 years; PS, 0; normal lactate dehydrogenase[LDH] levels, liver involvement, and no prior adjuvant 5-FU). Moreover, their analysis also suggested that the Saltz regimen represented a Canadian $32,215 per life-year gained overall. The cost-effectiveness ratio of the Saltz regimen was thought to be attractive for patients with a PS of zero and a normal LDH level, and unattractive for those patients older than 65 years who had previously received 5-FU adjuvant therapy and had an elevated LDH level. Capecitabine was con-sidered to have lesser toxicity and lower toxicity costs, and to provide cost savings — although no specific data were provided.[62]

Schmitt et al,[63] using the data reported by Douillard et al,[18] estimated the cost-effectiveness of the European regimen for CPT-11. Taking the French perspective of health insurance as the reference, they estimated that with CPT-11 as first-line therapy, a total of 35,850 Euros was required for each additional survival-year gained.[63] Such cost was considered to be within currently accepted limits for new chemotherapeutic agents.

A similar cost-effectiveness study on CPT-11was reported by Cunningham et al.[64] From a British perspective, £14,794 was required per life-year saved. An Italian group, however, reached the opposite conclusion in estimating the cost-effectiveness ratio of adding irinotecan to 5-FU plus leucovorin.[65] They noted a requirement of about 50,000 Euros per year of life gained, using the same clinical results of the Douillard study. In a subsequent analysis using the Saltz data and the pricing of the drug in Italy and the UK, together with a number of assumptions regarding consumption, the same Italian group concluded that the overall gain in survival was 2 months, and the cost per year of life gained was £32,706 — which was substantially higher than previous calculations by other groups, and was deemed unfavourable.[66]

Thus, there is no conclusive evidence as to whether or not the addition of novel agents to existing conventional therapy improves cost-effectiveness. The surprisingly conflicting conclusions drawn by various groups using the same set of data reflect differing assumptions underlying each evaluation. Such assumptions should ideally reflect local economic reality and health economics, the logistics of the local healthcare system, and potential costs incurred by second-line treatment and symptomatic management of untreated patients. There is as yet no reported cost-effectiveness study performed in Hong Kong for this aspect of colorectal cancer, and hence no conclusion can be drawn at present; any extrapolation from foreign studies is irrelevant at best.

CONCLUSION

In summary, during the past decade, similar to other areas of oncology, palliative chemotherapy in advanced colorectal carcinoma has undergone numerous advances that, in turn, culminated in a modest but sure step forward. There is now adequate evidence justifying its use with a reasonable probability of achieving clinical targets such as survival benefit with an equal or superior impact on QOL. There are now preliminary data suggesting that with careful selection, asymptomatic patients with advanced colorectal carcinoma may be managed without 'up-front' surgery. Moreover, the conventional dogma of continuous palliative chemotherapy until failure in responders is now being challenged by results of a recent study.[19] These areas require urgent research as they have direct bearing on patient welfare, and implications for healthcare economics. The relationship between response and survival in the setting of advanced disease has been uncertain in the past, and the subject of much debate. By the effort of various groups, a probable correlation has emerged, which appears to be consistent across studies. This finding will assist in placing the results of future research into perspective. The availability of apparently more efficacious agents appears to signal the beginning of combination chemotherapy for this disease. Response rates in the order of 35 to 55% and median survival of 14 to 17 months are to be expected with novel regimens. However, their true benefits are still modest, and certainly associated with significant costs at present. Nonetheless, when coupled with advances in other areas such as genetics, molecular oncology, and biological intervention employing predictive assay and tumour-adapted therapy, together with efforts in prevention and education, the prognosis for this group of patients will hopefully be improved in the future.

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