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Review

Colorectal Cancer—Is There an Alternative to 5-FU?

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INTRODUCTION

COLORECTAL CANCER (CRC) is a major cause of morbidity and mortality in industrialised countries. Each year, in the U.S. and Europe, more than 300 000 new cases are diagnosed and over 150 000 patients die of the disease [1, 2]. The prognosis associated with this malignancy is, therefore, poor with over half of all diagnosed patients dying following metastatic spread.

Surgery is generally the first-line treatment option for CRC. For patients with early-stage disease (Dukes' stage A or B_1), this approach affords a relatively good prognosis, although it is less effective in patients with more advanced disease (Dukes' stage B_2, B_3 or C). For example, patients with lymph node involvement (Dukes' stage C) carry a 50% risk of relapse following resection [3]. For this reason, adjuvant chemotherapy is often prescribed for patients with Dukes' stage C disease in an effort to reduce the high risk of recurrence. Use of adjuvant chemotherapy in patients with Dukes' stage B disease has been questioned, but a recent meta-analysis demonstrated equal benefits for this approach in Dukes' stage B and C [4]. For patients with advanced disease, chemotherapy or best supportive care are currently the mainstay of treatment. However, the extent to which these two approaches are used varies markedly between Europe and the U.S. In the U.S., most patients are offered palliative chemotherapy whereas in Europe such treatment is less frequently used and a symptomatic approach involving best supportive care is often adopted.

CHEMOTHERAPY FOR ADVANCED DISEASE

Since its introduction over 35 years ago, 5-fluorouracil (5-FU) has remained the only effective chemotherapeutic option available for the treatment of CRC. However, response rates achieved with bolus 5-FU monotherapy are typically less than 10%. Efforts have, therefore, focused on the use of various 5-FU-based regimens and administration schedules to enhance the therapeutic efficacy of this agent.

5-FU modulation

The use of folinic acid to modulate the activity of 5-FU has been the most widely investigated strategy to date, and the first to elicit promising results in terms of both response rate and survival. In a meta-analysis of nine randomised studies, a response rate of 23% was reported for 5-FU plus folinic acid compared to 11% for 5-FU monotherapy (odds ratio 0.45; 95% CI 0.34–0.60; $P < 10^{-7}$) [5]. Individual studies have also demonstrated a significant survival benefit [6] and prolongation of time to disease progression [6] with 5-FU plus folinic acid. These results have ultimately led to the adoption of this combination as the standard regimen for the treatment of advanced CRC.

Both high ($\geq$200 mg/m^2) and low (20 mg/m^2) doses of folinic acid have been employed in clinical practice because of a lack of conclusive data in the past to demonstrate a clear advantage for either dose. However, more recently, three studies have clearly demonstrated that low-dose is as active as high-dose folinic acid in terms of both response rate and survival using a monthly schedule of 5-FU (425 mg/m^2) plus folinic acid (20 mg/m^2) (Mayo Clinic regimen) [7–9]. In view of these results, the Mayo Clinic regimen is now widely adopted in clinical practice as the standard low-dose regimen.

Other biochemical modulation strategies have been less successful. For example, the impressive response rates reported with 5-FU plus α-interferon in early phase II investigations were not confirmed in subsequent phase III studies. Furthermore, the incidence of severe toxicity (e.g. gastro-intestinal and neurotoxicity) associated with this regimen is high.

Combination therapy

A promising response rate (19 versus 10%; $P < 0.0001$) and a small survival benefit (10.7 versus 9.1 months) have been reported with 5-FU plus methotrexate compared to 5-FU alone in a recent meta-analysis [10]. However, as this regimen has not consistently shown survival benefits in individual studies it is not considered to be a first-line alternative to 5-FU monotherapy.

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Continuous infusion

Another approach, aimed at increasing the therapeutic efficacy of 5-FU, has involved the administration of this agent by continuous intravenous infusion in order to prolong the exposure of CRC cells to the cytotoxic action of 5-FU. Continuous infusion versus bolus administration elicited a marked improvement in response rate in early studies (23 to 25%) [11, 12]. In a more recent investigation, patients treated with bimonthly bolus then continuous infusion of 5-FU (22 h) plus high-dose folinic acid showed a significant improvement in progression-free survival time (29.5 versus 22.8 weeks; $P = 0.008$) and response rate (34 versus 17%; $P = 0.002$) when compared with those patients who received one-monthly bolus 5-FU (days 1–5) plus low-dose folinic acid [13]. However, in this study, probably as a result of patient crossover to continuous infusion 5-FU, no statistically significant difference in overall survival was reported between the two regimens. Similarly, a randomised investigation evaluating the efficacy of seven 5-FU regimens showed a positive survival trend in favour of the unmodulated infusion regimens [9]. Continuous or 24-h infusion of 5-FU alone elicited a 2 month greater survival duration than 5-FU bolus.

5-FU infusion regimens also possess a favourable toxicity profile. Of note, myelosuppression occurs less frequently with these regimens than with 5-FU bolus regimens [9, 11–13]. The lower frequency of grade 3/4 leucopenia is particularly noteworthy [9, 11–13], and has been shown to translate into a lower incidence of sepsis [11] and sepsis-related death [12]. Continuous intravenous infusion of 5-FU may also facilitate reduced inpatient and outpatient hospital attendance because of its ambulatory nature. However, 5-FU infusion regimens are associated with hand and foot syndrome, potential Hickman line complications, and the continued presence of an infusion pump may interfere with the patient's daily activities [12].

Chronomodulation

The efficacy and tolerability of 5-FU–platinum complex combination regimens are both enhanced when administered in circadian (chronomodulated) rather than constant infusion regimens [14–16]. The lower toxicity of the chronomodulated regimen has been shown to allow greater dose intensification leading to an improvement in response rate [16]. Indeed, chronomodulation more than doubled the activity of 5-FU–platinum complex chemotherapy against CRC and this permitted surgery for previously unresectable metastases in a significant proportion (25%) of patients [16].

BENEFITS OF CHEMOTHERAPY

Patient quality of life is particularly important when assessing the benefits of chemotherapy for advanced CRC. In this setting, many clinicians have previously perceived that any treatment-related gains were more than offset by the negative effects on the patient's well-being due to toxicity and the use of complex administration schedules. However, recently, a number of studies have demonstrated that chemotherapy could provide considerable benefit in terms of improved quality of life and survival compared to supportive care alone in advanced disease.

In a small randomised study, the administration of chemotherapy (5-FU, folinic acid and cisplatin) to patients with advanced disease was associated with a doubling of the survival time (11 versus 5 months; $P = 0.006$) and an improvement in quality of life compared to supportive care alone [17]. The benefit of administering chemotherapy to asymptomatic patients with advanced CRC was also highlighted in a Nordic study; overall survival was 5 months longer for patients randomised to receive chemotherapy when asymptomatic compared to those patients who received treatment only after having developed symptoms. In addition, symptom-free survival and time to disease progression were 8 and 5 months longer, respectively, in the early treatment group ($P < 0.001$) [18]. A study conducted by the North Central Cancer Treatment Group also supports the benefit of chemotherapy in terms of improvement in time to disease progression, performance status, weight gain and survival [6].

LIMITATIONS OF EXISTING CHEMOTHERAPY

Although extensive clinical investigations have been conducted, no new effective anticancer agents have become available for the first-line treatment of advanced CRC since the introduction of 5-FU over 35 years ago and any clinical benefit achieved with current 5-FU-based regimens is relatively modest. Furthermore, although a profusion of regimens and administration schedules are used in the treatment of advanced disease, clinical studies have failed to demonstrate a clear advantage of any single regimen.

Existing chemotherapy regimens are also inconvenient to both patients and medical staff; invariably the patient must attend hospital on a number of consecutive days during each treatment cycle or, alternatively, must receive chemotherapy on an inpatient basis. The level of inconvenience is, therefore, largely schedule-dependent. For example, the Mayo Clinic regimen involves the daily administration of 5-FU plus folinic acid for 5 consecutive days every 4 to 5 weeks. Although administration of this regimen may not necessitate hospitalisation, it may, at least, require frequent hospital attendance on an outpatient basis.

Another limitation of existing therapies is the frequent development of significant toxicity including leucopenia, mucositis, diarrhoea, dermal toxicity (including palmar–plantar erythrodysesthaesia associated with continuous infusion), alopecia and nausea/vomiting [7, 8, 12]. Importantly, the development of concomitant severe leucopenia and mucositis is potentially life-threatening and can be complicated by local infection, bleeding and an increased risk of septicaemia.

In view of the limitations of existing therapies, there is a need for the development and introduction of new anticancer agents with greater or equivalent efficacy, improved tolerability and more convenient administration schedules.

NEW CHEMOTHERAPEUTIC OPTIONS

Some new chemotherapeutic agents are currently in development for the treatment of CRC. These include the monoclonal antibody 17-1A, the topoisomerase I inhibitor irinotecan (Campto®), a new platinum derivative, oxaliplatin (L-OHP®), and the thymidylate synthase inhibitor raltitrexed (ZD1694, Tomudex®).

Monoclonal antibody 17-1A

17-1A is a murine monoclonal antibody designed to target the CO17-1A antigen located on CRC cells. In compari-

son to observation alone, 17-1A has demonstrated utility in the adjuvant setting in patients with Dukes' stage C disease who have undergone potentially curative surgery; after a median follow-up of 5 years, the investigators reported a reduction in death rate of 30% ($P = 0.05$; log-rank) and a decrease in recurrence rate of 27% ($P = 0.05$; log-rank) with postoperative 17-1A therapy [19]. Despite these promising results, 17-1A has failed to demonstrate significant utility in the treatment of advanced CRC to date. However, the evaluation of the clinical activity of a number of other monoclonal antibodies, currently in various stages of development (e.g. MN-14, 105AD7 and A7), is awaited with interest.

Irinotecan (Campto®)

Topoisomerase I facilitates the transcription and translation of genetic material through the relaxation and recombination of supercoiled DNA. Inhibition of this enzyme induces DNA damage resulting in cell death. While the preclinical and clinical activity of a number of topoisomerase I inhibitors (e.g. topotecan, GG211 and 9-aminocamptothecin) is still being investigated, irinotecan has already demonstrated promising activity in the treatment of CRC.

Irinotecan is a semisynthetic water soluble derivative of camptothecin (an alkaloid extract of the plant *Camptotheca accuminata*). It is converted *in vivo* to the active metabolite SN-38 by a carboxylesterase. The activity of irinotecan has been investigated both as first- and second-line treatment of advanced CRC in phase II studies in the U.S., Japan and Europe.

Studies conducted in Japan and the U.S., which employed weekly or intermittent regimens and irinotecan doses of 100 to 150 mg/m^2, reported response rates of 15–32% in chemotherapy-naive patients and 22–25% in pretreated patients [20–23]. In a subsequent European phase II study, 213 patients with metastatic CRC and a WHO performance status of $\leqslant 2$ were treated with irinotecan 350 mg/m^2 once every 3 weeks [24]. Among the 178 patients who had not received more than one prior 5-FU-based chemotherapy regimen and who were considered eligible for efficacy analysis, response rates were comparable in those who were chemotherapy-naive (18.8%; 95% CI 8.9–32.6%) and those who had received prior chemotherapy (17.7%; 95% CI 11.5–25.5%) [24]. Among the 62 evaluated patients who had experienced disease progression while previously receiving 5-FU, 16.1% responded to irinotecan indicating a lack of cross-resistance between these two drugs. The response rate among patients who had progressed following 5-FU therapy was 19.1%. The median duration of the objective response (9.1 months) and time to achieve an objective response (9.3 weeks) did not differ between the two groups. Although these results are noteworthy, the incidence of severe toxicity in this study was high; 39% of patients experienced grade 3/4 delayed diarrhoea and 47% experienced grade 3/4 neutropenia [25]. Preventive treatment with high-dose loperamide and the encephalinase inhibitor, acetorphan, has demonstrated utility in the management of delayed diarrhoea. Results of ongoing trials will clarify the place of irinotecan in clinical practice.

Oxaliplatin (L-OHP®)

A response rate of 10% was reported in patients refractory to 5-FU treated with oxaliplatin [26]. No data are available on the use of single-agent oxaliplatin as first-line treatment. In combination with 5-FU and folinic acid, response rates of between 28 and 58% were reported following first- and second-line treatment with oxaliplatin [14–16, 27].

Oxaliplatin administration is typically associated with minimal haematological toxicity; moderate nausea and vomiting; mild, infrequent diarrhoea and neither nephrotoxicity nor audiotoxicity. The dose-limiting toxicity is a peripheral and/or pharyngo-laryngeal dyesthaesia caused and aggravated by the cold. This effect is dose-dependent in terms of duration and intensity and, in some cases, may cause functional impairment which is generally reversible upon discontinuation of treatment [28].

Of interest, several clinical studies have assessed the potential benefits of chronomodulated combination regimens of oxaliplatin plus 5-FU/folinic acid [14–16]. In a phase III multicentre randomised trial of previously untreated CRC patients, oxaliplatin (20 mg/m^2/day) and 5-FU/folinic acid (600/300 mg/m^2/day) were administered by continuous infusion over 5 days every 3 weeks using a flat-rate ($n = 47$) or chronomodulated rate ($n = 45$) [16]. In the chronomodulated group, peak delivery occurred at 4.00 a.m. for 5-FU/folinic acid and at 4.00 p.m. for oxaliplatin. Of the 92 recruited patients, 18% had received previous adjuvant chemotherapy and/or radiotherapy, 47% had more than two metastatic sites and 87% had liver involvement. Chronomodulation was associated with a greater 5-FU dose intensity (+22%) and a lower incidence of grade 3/4 toxicity (89 versus 19%). Stomatitis, the major dose-limiting toxicity, occurred almost nine times more frequently with flat-rate infusion. Chronomodulation elicited a higher objective response rate (53 versus 32%), a longer median duration of survival (19 versus 14.9 months) and a tendency towards greater progression-free survival (8 versus 11 months). This trial was terminated prematurely due to chemical inactivation of oxaliplatin with the basic pH of 5-FU and a second study, designed to avoid this problem, was initiated. The results and conclusions of this second investigation are in accordance with those of the first [16]. Furthermore, chronomodulation permitted surgery for metastases in 25% of 252 patients in a retrospective analysis, with a suggestion that survival might also be prolonged by around 6 months compared with standard strategies [16].

Raltitrexed (ZD1694, Tomudex®)

The development of raltitrexed is the result of extensive research efforts to produce a direct, specific thymidylate synthase (TS) inhibitor without secondary effects on RNA or protein synthesis.

TS is unique to the formation of DNA and essential for the production of the DNA precursor thymidylate (TMP) (Figure 1). Inhibition of this enzyme prevents cell division, resulting in cell death. The commonly used TS inhibitor, 5-FU, inhibits TS indirectly requiring prior conversion to active metabolites (most importantly FdUMP). 5-FU also has non-specific effects on RNA and protein synthesis which is believed to contribute markedly to the toxicity profile of the drug. Research efforts have, therefore, focused on the development of direct, specific TS inhibitors with an improved toxicity profile. A number of TS inhibitors are currently in development (e.g. AG331, AG337 and LY231514), but the quinazoline folate analogue raltitrexed

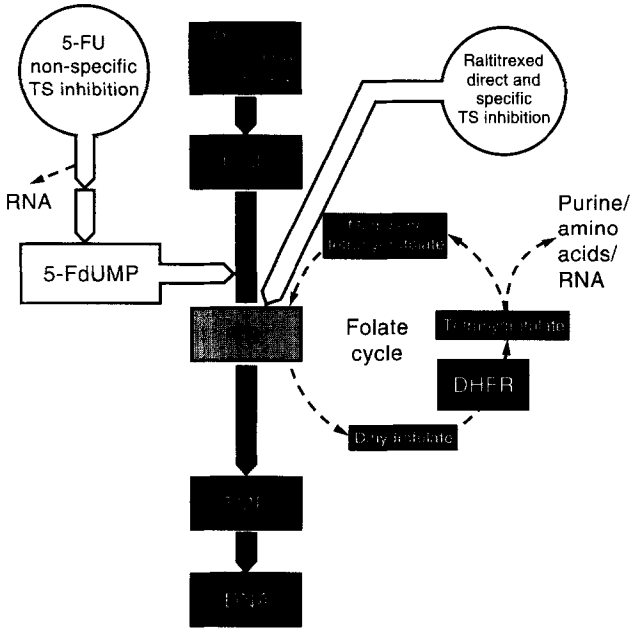

Figure 1. Inhibition of thymidylate synthase (TS) by raltitrexed (ZD1694, Tomudex®) and 5-fluorouracil (5-FU). DHFR, dihydrofolate reductase; dUMP, deoxyuridine monophosphate; 5-FdUMP, 5-fluorodeoxyuridine monophosphate; TMP, thymidylate.

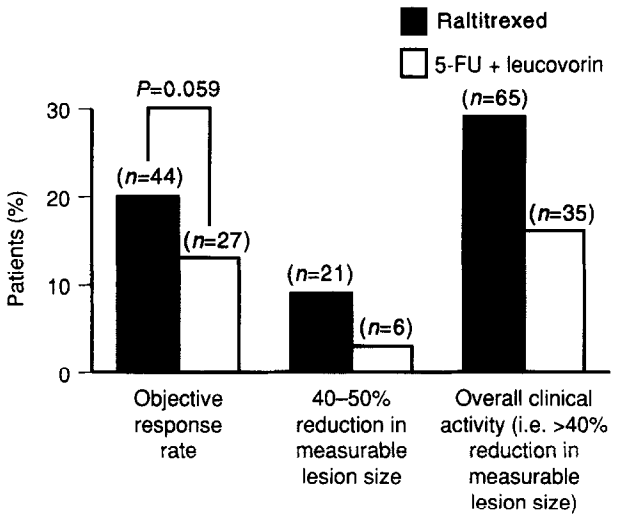

Figure 2. Efficacy results from the phase III comparative trial of raltitrexed versus 5-fluorouracil (5-FU) plus folinic acid (Mayo regimen) in the treatment of advanced colorectal cancer [30].

(ZD1694, Tomudex®) is the most advanced, having demonstrated promising activity as a single-agent, in the first-line treatment of advanced CRC in phase II and III investigations [29, 30].

A raltitrexed dosage schedule of 3 mg/m^2 administered as a short 15-min infusion once every 3 weeks has been evaluated. The use of a simple dosage schedule is possible as a result of extensive polyglutamation; raltitrexed is taken up into cells via the reduced folate membrane carrier system and polyglutamated to more potent forms. This prolongs the intracellular retention of raltitrexed, extending TS inhibition and thus permitting the use of a single-dose schedule once every 3 weeks.

177 patients with advanced or metastatic CRC and at least one measurable lesion were enrolled in the pivotal phase II study [29]; prior treatment with palliative chemotherapy was not permitted. Using the WHO/UICC criteria recommended by the U.S. National Cancer Institute ($\geqslant$ 50% reduction in tumour size) to assess an objective response, 4 complete and 41 partial responses were reported (response rate 26%; 95% CI 19–33%) with a median duration of response of 5.7 months. Median time to disease progression was 4.2 months and median survival time 9.6 months.

These promising results were subsequently confirmed in the large phase III study comparing the efficacy and tolerability of raltitrexed with the Mayo Clinic regimen of 5-FU plus low-dose folinic acid [30]. Using the same entry and evaluation criteria as during the phase II study, 439 patients were randomised to receive raltitrexed or daily 5-FU (425 mg/m^2) and low-dose folinic acid (20 mg/m^2) for 5 consecutive days every 4 to 5 weeks. Response rates comparable to those reported in the phase II study were achieved; 20% of patients treated with raltitrexed and 13% of patients treated with the Mayo regimen experienced a complete or partial response (odds ratio 1.7, 95% CI 0.98–2.81; $P = 0.059$). Furthermore, 9% of patients in the raltitrexed cohort and 3% in the Mayo regimen cohort experienced a 40–50% reduction in measurable lesion size (Figure 2). There was no statistically significant difference in time to disease progression between the two treatment groups; the median time to disease progression for raltitrexed-treated patients was 144 days.

In the phase III investigation, treatment with raltitrexed was associated with a significantly lower incidence of severe (grade 3/4) leucopenia and mucositis compared to treatment with the Mayo regimen (Table 1). This probably accounted for the higher percentage of raltitrexed-treated patients receiving their treatment on time without a significant dosage reduction (74% versus 52%). The administration of raltitrexed was associated with a significantly higher increase in liver transaminases in comparison to the Mayo regimen

Table 1. Incidence of severe adverse events (WHO grade 3 or 4) for patients in the phase III comparative trial of raltitrexed versus 5-FU plus low-dose folinic acid (Mayo regimen) in the treatment of advanced colorectal cancer [30]

Adverse event	Raltitrexed (n = 222)	5-FU plus folinic acid (n = 212)
Diarrhoea	29 (13%)	25 (11%)
Nausea and vomiting	27 (12%)	18 (9%)
Leucopenia*	22 (10%)	56 (26%)
Increased transaminases*	22 (10%)	0 (0%)
Anaemia	11 (5%)	3 (1%)
Infection	11 (5%)	11 (5%)
Asthenia	10 (5%)	4 (2%)
Pain	9 (4%)	14 (7%)
Constipation	6 (3%)	6 (3%)
Fever	6 (3%)	4 (2%)
Thrombocytopenia	7 (3%)	1 (1%)
Mucositis*	5 (2%)	46 (22%)

*$P < 0.001$.

(Table 1), but these changes were generally self-limiting and asymptomatic.

There was a difference in the resources required to manage the toxicity in both treatment groups. Raltitrexed-treated patients required fewer days for treatment in the intensive care unit (9 versus 29 days) and fewer community visits (69 versus 230 days). The frequency of outpatient visits was similar in both treatment groups, but more raltitrexed-treated patients required days on the ward for the management of toxicity (1048 versus 789 days); however, these findings were considered to be due to protocol-driven requirements.

Quality of life was evaluated in the phase III study using the validated standard quality-of-life questionnaire developed by the European Organisation for the Research and Treatment of Cancer (EORTC). Although no overall difference in patient well-being was demonstrated between patients treated with raltitrexed or the Mayo regimen in this study, both patient groups experienced an improvement in terms of emotional function, sleep disturbance, pain and global quality of life. Furthermore, palliative benefit was reported at least as frequently for raltitrexed as for the Mayo regimen with 34% and 15% of patients in the raltitrexed treatment group compared to 25% and 12% of patients in the Mayo treatment group experiencing improvement in performance status and weight gain, respectively. The absence of a significant advantage in terms of quality of life for the raltitrexed compared to the Mayo regimen may have been related to the scheduling of the quality of life questionnaire. Because patients completed the questionnaire before their first treatment cycle and thereafter every 12 weeks until disease progression, scheduling of the questionnaire coincided more frequently with patients who received raltitrexed (3-weekly cycling) compared to those who received the Mayo regimen (4 to 5 weekly cycling). This meant that raltitrexed-treated patients were more likely to have completed the questionnaire within a few days after having received their treatment.

There was a reduction in the amount of time required for drug administration in the raltitrexed cohort; the mean length of hospital stay per cycle for drug administration was 0.7 days for raltitrexed-treated patients compared to 3.1 days for patients receiving the Mayo regimen. This is likely to reduce the amount of travel time for the patient and time spent away from work and their carers. It is also anticipated that the single-dose, 3-weekly outpatient administration of raltitrexed will also save nursing, pharmacy and medical time allowing an efficient re-allocation of these resources.

Additional phase III studies are currently in progress to gain further understanding of the role of raltitrexed in the first-line management of advanced CRC. A prospective randomised European phase III study is being conducted to compare the efficacy and tolerability of raltitrexed versus bolus 5-FU plus high-dose folinic acid (Machover regimen). It will also encompass a number of specific health economic issues including assessment of patient quality of life and duration of hospital stay for chemotherapy.

FOR THE FUTURE

The impact of advanced CRC on healthcare institutions, patients and their families cannot be underestimated and the need for new anticancer agents to supersede or to be used in combination with standard 5-FU therapy has never been greater. In the mid-1990s, we are finally entering a promising new era for the management of this malignancy with the clinical development of several novel anticancer agents. One such agent is raltitrexed (ZD1694, Tomudex®) which offers similar advantages in terms of objective response, time to disease progression, palliative effects and survival as conventional regimens of 5-FU plus folinic acid. Raltitrexed has demonstrated an advantage in terms of improved tolerability vis-à-vis the conventional Mayo regimen. The less intensive raltitrexed dosing schedule may also confer further advantages in terms of cost savings and quality of life benefits compared to conventional chemotherapy regimens in the future. Furthermore, in view of the benefits of adjuvant chemotherapy demonstrated in the treatment of Dukes' stage B and C colorectal cancers in several clinical studies [31, 32], evaluation of the role of raltitrexed in this setting is worth continuing. Current data would also suggest that, in the second-line treatment of CRC, irinotecan and oxaliplatin in combination with 5-FU may ultimately improve the prognosis of patients unresponsive to, or relapsing, after conventional 5-FU-based chemotherapy regimens. Chronomodulation of 5-FU/folinic acid plus oxaliplatin appears particularly promising in this respect.

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