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Optimising outcomes in colorectal cancer March 2010

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This publication is a summary of a recent presentation by Professor Aimery de Gramont, Head of the Medical Oncology Service, Hôpital Saint-Antoine, Paris, France. He spoke to colorectal oncologists, oncology registrars, nurses, and colorectal and hepatobiliary surgeons in Auckland, Wellington and Christchurch in March 2010 about optimising outcomes for metastatic colorectal cancer.

Colorectal cancer (CRC) is a major health problem worldwide, with an estimated one million people diagnosed with CRC each year and it is the third most common cancer in men (after prostate and lung) and women (after breast and lung), as well as the fourth leading cause of cancer death.[1] These statistics are mirrored by CRC prevalence rates in New Zealand, France, the UK and the US.[1-5] Its prognosis has dramatically improved over the last 20 years due to screening and early detection strategies, as well as advances in surgical techniques and adjuvant therapy.[1,3,4] However, there has been only a modest improvement in survival for patients who present with advanced neoplasms.[6]

What is the optimal combination for systemic chemotherapy?

The role of chemotherapy in the treatment of CRC has grown considerably over the last 20 years. Traditionally, first-line metastatic CRC (mCRC) was treated with bolus 5-fluorouracil (5-FU), then with various bolus or infusional 5-fluorouracil (5-FU) regimens that most commonly consisted of the AIO regimen (infusional 5-FU and folinic acid [FA]), which demonstrated superior response rates (RRs) to 5-FU alone, as did the MAYO Clinic schedule (a bolus 5-FU/FA regimen). A comparison designed to identify a difference in progression-free survival (PFS) between these regimens showed a 2-month difference in PFS in favor of the AIO regimen; toxicity of both regimens was improved by addition of the oral fluoropyrimidines such as capecitabine, which conveniently and effectively delivers 5-FU in a protracted fashion.[7,8]

The addition of the newer drugs irinotecan and oxaliplatin to 5-FU/LV resulted in improved RRs and PFS in large, randomised trials, as well as improving median overall survival (OS) length beyond 21 months.[9,10] The N9741 trial led to both FDA approval of the FOLFOX regimen for the treatment of mCRC and to a widespread adoption of this regimen as the preferred first-line treatment for patients with mCRC in the US.[11]

More recently, the FOLRIRI regimen (infusional 5-FU/LV and irinotecan) was developed with the aim of improving efficacy without increasing toxicity. FOLFIRI significantly improves the palliative treatment of mCRC patients compared with LV5FU alone, with median survival times in excess of 20 months reported.[12] A comparison between first-line FOLFIRI and FOLFOX6 revealed comparable OS (20.6 months for FOLFOX6 and 21.5 months for FOLFIRI), PFS, and time to progression.[10] Only toxicity profiles differed between the treatment arms (neurotoxicity being the predominant dose-limiting toxicity with FOLFOX and a greater risk of alopecia and diarrhoea with FOLFIRI). This was followed by a comparison of FOLFOX4 with XELOX (capecitabine plus oxaliplatin), in which the two regimens were found to be equivalent.[13]

Angiogenesis inhibition in CRC

In an effort to further improve therapeutic effects of chemotherapy alone, researchers have integrated targeted therapies into treatment strategies for CRC, including the use of anti-vascular endothelial growth factor (VEGF) antibodies (bevacizumab) with conventional chemotherapy regimens. In a US-based trial (Hurwitz et al.) investigating the clinical activity of bevacizumab in patients with previously untreated mCRC, its addition to IFL was compared with IFL alone (the standard regimen in the US at that time). The IFL/bevacizumab combination improved the overall RR by 10%, PFS, and OS, significantly and by more than 4 months; a much more active regimen than IFL alone, and not adding to the toxity profile.[14] Notably, the difference in OS and PFS between the two treatment arms was relatively constant at 4.7 and 4.4 months.

Interestingly, these positive findings were not clearly replicated in the following phase III XELOX-1/NO16966 trial comparing FOLFOX4 and XELOX with or without bevacizumab in 1400 patients with CRC.[15] XELOX proved noninferior to FOLFOX, with the addition of bevacizumab to both regimens significantly improving PFS by 20% versus chemotherapy without bevacizumab, although this was a less substantial improvement in PFS (by a median of 1.4 months) than what was observed in the Hurwitz trial. In addition, the NO16966 trial documented a non-statistically significant, modest improvement in OS, and no benefit in RR.

The best treatment should use the best chemotherapy regimen according to tumour sites and patient's condition and prognosis, in combination with the best targeted therapies when feasible, according to biomarkers. In addition, the best treatment should use the best strategy, which combines salvage surgery at the optimal time when feasible after tumour shrinkage and the sequential or combined use of all available drugs. Chemotherapy holidays should be offered whenever possible to maintain a good quality of life, not forgetting that the second- and third-line possibilities are driven by the choice of the first-line therapy.

Prof. de Gramont explained these findings: in NO16966, patients in the placebo as well as the bevacizumab arm received treatment for only 6 months, whereas in the Hurwitz trial, median treatment durations were 27.6 weeks in the IFL/placebo group and 40.4 weeks in the bevacizumab/IFL group. In NO16966, all patients stopped treatment before progression, due to oxaliplatin-specific cumulative neurotoxicity; 71% of bevacizumab recipients and 53% of placebo recipients were not treated until disease progression. He pointed out that they should have been treated as per the study protocol, which specified that patients discontinuing oxaliplatin could continue with a fluoropyrimidine plus placebo or bevacizumab.

An exploratory analysis of the PFS while on therapy was done, comparing progressive disease or death from any cause (the usual PFS definition) to that analysis adjusted so that patients in whom progressive disease or death ocurred longer than 28 days from the last dose of study treatment were censored from the time of the last scan showing no progressive disease. This was intended to assess the true effect of the study drug by censoring patients who went off treatment without progression.

As shown in Figure 1, the new curves for the on-treatment PFS definition resemble much more closely those seen in the Hurwitz trial. On-treatment PFS was statistically better than for the usual PFS group, suggesting that continuation of bevacizumab may further improve PFS.

The complication rate with bevacizumab was low: gastrointestinal perforation grade 3/4 affecting only 0.6% of patients in this trial, versus 0.3% of placebo recipients. Likewise, bevacizumab was associated with increases in bleeding, arterial thromboembolic events, hypertension, and proteinuria. Nevertheless, all of these side effects occurred in less than 2% of patients.

Inhibition of the EGFR pathway

The second targeted therapy to become available was cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor (EGFR) pathway.

The addition of cetuximab to FOLFIRI in the first-line treatment of patients with EGFR-expressing mCRC in the CRYSTAL study significantly improved the RR by 10%, extended PFS by 0.9 months and OS by one month.[16] However, a retrospective analysis on a subset of 540 patients with the *KRAS* mutation revealed that the greater activity obtained by adding cetuximab to FOLFIRI was limited to patients with *KRAS* wild-type (WT) tumours (RR 59% vs 43%; median PFS 9.9 months vs 8.7 months; median OS 24.9 vs 21 months); no benefit was obtained in patients with *KRAS*-mutated tumours (RR 36% vs 40%; median PFS 7.6 vs 8.1 months; median OS 17.5 vs 17.7 months).

However, an unknown value that may affect the *KRAS* WT population OS survival curve is the proportion of patients who crossed over to cetuximab and received further chemotherapy lines, although this has never been reported. While the median duration of PFS is 10 months, this benefit is seen *after* progression in many of the patients. Thus, another explanation is needed for the difference in survival.

The major adverse effects of cetuximab included skin reactions, infusion-related reactions and diarrhoea. Despite these events, the positive PFS results position FOLFIRI plus cetuximab as another option for treatment.

The addition of cetuximab to the FOLFOX4 regimen was then investigated in a phase II comparison with FOLFOX4 alone in 337 patients with EGFR-expressing tumours (OPUS trial).[17] In the whole population, the combination regimen increased the RR (45.6% vs 35.7%), but the difference was of borderline significance (p=0.064), and the median PFS was the same for each arm (7.2 months). However, a retrospective analysis on 233 patients, for whom the *KRAS* status was known, demonstrated that in patients with *KRAS* WT, the combination regimen obtained a significantly greater RR (61% vs 37%), but was less beneficial for PFS (median 7.7 vs 7.2 months); the addition of cetuximab did not benefit patients with mutated *KRAS*.

Importantly, the same concerns surround the results from the OPUS trial as for those from the CRYSTAL trial, in that the population could not be retrospectively tested for crossover treatment status. Again, no information has been published as to the numbers of patients who crossed-over to cetuximab after progression. Nevertheless, OPUS can be considered to be a positive trial.

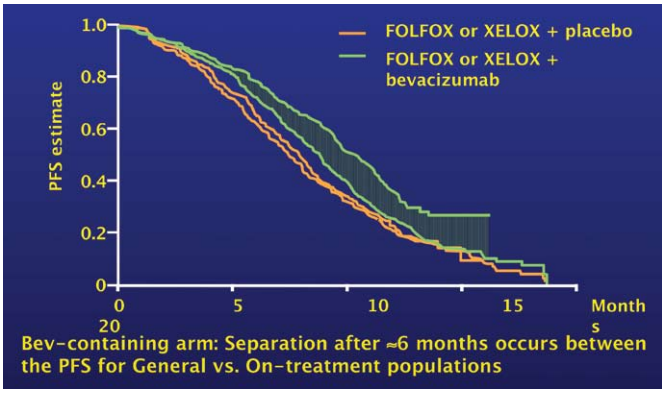

Figure 1: PFS in NO16966: General and on-treatment populations

Unfortunately, these results have not been confirmed by the large (n=2400) UK-based MRC COIN trial investigating the efficacy of FOLFOX or XELOX with and without cetuximab in the first-line treatment of mCRC.[18] A second goal of this trial was to evaluate a stop-and-go treatment strategy versus continuation of the drug. In the prospective analysis of the *KRAS* WT population, there was no evidence of a difference in either PFS or OS between patients given cetuximab and those who were not (median 8.6 months for PFS in both arms; median 17.0 vs 17.9 months for OS). As a result, the combination of oxaliplatin plus cetuximab cannot be recommended in the first-line setting, based on outcomes from a negative large trial (COIN) and positive small phase II trial (OPUS).

The PRIME trial

Positive results have also been reported from the PRIME trial, but the data are less mature. This trial investigated first-line FOLFOX4 with or without panitumumab in 1183 mCRC patients; of 1096 with identified *KRAS* status, 656 were wild-type.[19] Panitumumab is another monoclonal antibody directed against the EGFR. The addition of panitumumab to FOLFOX4 significantly increased PFS by 1.6 months in *KRAS* WT patients, and increased their RR by 7% (55% vs 48% on FOLFOX4 alone). However, OS values merely showed a trend towards increased survival for panitumumab. Prof. de Gramont noted that once again, treatment crossover must be analysed for this trial.

Combining EGFR and VEGF inhibition

In view of preliminary clinical data seeming to support a treatment approach that combines the EGFR and VEGF inhibition, the phase III US-based Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) trial explored the addition of an EGFR antibody to combination chemotherapy and bevacizumab.[20] Patients with mCRC received a standard FOLFOX or FOLFIRI regimen plus either bevacizumab alone or bevacizumab plus panitumumab. After a planned interim analysis, the trial was discontinued, with a worse efficacy seen in the panitumumab arm. Furthermore, *KRAS* analyses showed adverse outcomes for the panitumumab arm in both WT and mutant groups.

Similarly, results from the Dutch CAIRO2 trial, investigating the addition of cetuximab to XELOX and bevacizumab, report a significantly worse outcome for the combination of the two biological agents.[21] The results from these two large studies indicate that combining two targeted therapies is worse than using only one, even in *KRAS* WT cases.

Multimodality approach in MCRC

Besides selecting the best treatment, *the best strategy* should be chosen – other options such as salvage surgery ought to be considered besides RRs of different agents. Prof. de Gramont emphasised that even in some patients with metastases, cure is possible through surgery. Can resectability become a new endpoint? For instance, in the experience of the Paul Brousse Hospital concerning chemotherapeutic regimens used there between 1988 and 1996 in 701 patients who presented as nonresectable, 95 (14%) were eventually resected as a result of treatment.[22] At five years, 34% remained alive; chemotherapy thus

played a critical role in transforming one-third of nonresectable patients into patients in whom surgery was possible, for an eventual cure.

In another example, the GERCOR C97 study (a comparison of FOLFIRI with FOLFOX6), in which patients crossed-over after progression, achieved R0 resection in 13% of patients; a good outcome for a study that was not designed to show that patients can be resected after chemotherapy.[10] A preferable regimen to FOLFOX6 is FOLFOXIRI, a regimen associated with superior rates of RR, PFS, and OS, over FOLFOX6.[23] In addition, the R0 resection rate of 15% with FOLFOXIRI is highly consistent with the C97 study.

Using targeted therapies (bevacizumab, cetuximab, panitumumab) the RR can be increased by 10%, which translates to a 2% increase in R0 resection rates – thereby achieving cure in almost one-third of these patients.

Patients with a good response to chemotherapy can undergo resection and it is important to define the group of patients classified as resectable or unresectable. Without a multidisciplinary approach, too many patients can be considered as resectable, when in fact they are not. The best strategy for the majority of patients is to avoid giving all the available drugs at the beginning of the teatment. This means there will be therapeutic options available in the treatment arsenal for later in the disease process.

Sequence or Combination?

In their recent analysis of survival according to lines of availability of chemotherapeutic agents, Grothey and colleagues demonstrated that there is a strong correlation between survival and percentage of patients who received all available agents (5-FU, irinotecan, oxalipatin).[9] In this analysis, when 50% of patients receive all three, more than 18 months median survival can be expected. When 70% of patients receive all of the active drugs, this survival duration can be expected to reach 20 months. Importantly, a treatment sequence of 5-FU followed by FOLFOX then by irinotecan does not equate to FOLFOX followed by irinotecan, as the RR is not as great, therefore the benefits of surgery may not be so marked. Prof. de Gramont states that patients should receive doublet regimens, not triplet combinations.

Second-line metastatic therapy

It is important to consider the possibility of second-line therapy as a reserve. For example, the addition of bevacizumab to FOLFOX4 improved survival duration in patients with previously treated mCRC; RR, PFS, OS were all improved with second-line bevacizumab.[24] If oxaliplatin-based treatment is given first, outcomes can be expected to resemble those seen with the EPIC trial, in which patients with EGFR-expressing mCRC who had failed first-line oxaliplatin-based therapy received irinotecan alone or in combination with cetuximab.[25] The addition of cetuximab to second-line irinotecan prolonged PFS, but did not increase OS.

In an attempt to provide a definitive answer to the controversy of continued use of bevacizumab in mCRC after progression on first-line chemotherapy, the first-line Bevacizumab Regimens: Investigation of Treatment Effects (BRiTE) registry was initiated in 2004.[26] Data concerning 1445 patients who had primary progressive disease revealed markedly longer survival after primary progression among bevacizumab recipients, compared with those who received therapy without bevacizumab or no further treatment (31.8, 19.9, and 12.6 months, respectively). In a multivariate analysis accounting for pre- and post-treatment variables, post-progression bevacizumab was associated with a significantly longer survival time. However, this analysis has substantial potential for selection bias, so the question of just how beneficial bevacizumab remains beyond progression is expected to be answered by the Irinotecan Bevacizumab Continuation Trial (iBET) trial (SWOG 0600), in which patients who progressed after treatment with an oxaliplatin plus bevacizumab regimen were randomised to either FOLFIRI and cetuximab or FOLFIRI and bevacizumab. The trial was specifically designed to directly compare bevacizumab with cetuximab after progression, and the analysis will also account for *KRAS* WT patients. Results will be reported shortly.

In Europe, an ongoing TML trial is similarly investigating the efficacy of bevacizumab on progression in patients who received combination oxaliplatin plus bevacizumab as first-line therapy and are then randomised to receive irinotecan-based chemotherapy only or in combination with bevacizumab. The primary objective of this trial is OS.

Third-line therapy

Prof. de Gramont highlighted the fact that third-line therapy options with a biological are limited to cetuximab, when bevacizumab is used in earlier lines. In third-line regimens, cetuximab may remain active in heavily pretreated patients as seen in those on the NCIC CTG CO.17 trial, published in 2007.[27] In this trial, the positive results attributed to cetuximab (higher RR, prolonged OS and PFS) were limited to patients with *KRAS* WT tumours.

Similarly, response to panitumumab was confined to *KRAS* WT patients in a randomised phase III study involving 463 patients.[28] Panitumumab almost halved the risk of disease progression/death versus patients receiving only best supportive care (BSC) (HR 0.54), significantly prolonged PFS and favoured objective response rates, but had no effect on OS.

'Stop-and-Go' strategies

The benefits of irinotecan and oxaliplatin in OS for patients with mCRC are accompanied by added toxicity, notably dose-limiting neurotoxicity, in the case of oxaliplatin. The concept of treatment breaks has therefore been explored in the OPTIMOX1 study, by comparing continuous FOLFOX4 until progression with a regimen of higher-dose oxaliplatin (FOLFOX7) for 6 cycles, followed by 5-FU/LV for 12 cycles, followed by FOLFOX7 for 6 cycles.[29] Both regimens produced a similar duration of disease control (9 vs 10.6 months), as well as overall survival (19.3 vs 21.2 months) and PFS. However, safety was much improved with the stop-and-go strategy, especially with regard to neurotoxicity.

The benefit of the stop-and-go strategy was confirmed in the first-line treatment of mCRC in the CONcePT (Combined Oxaliplatin Neurotoxicity Prevention) Trial.[30] The strategy significantly prolonged the time to treatment failure (median 5.6 vs 4.2 months) and PFS (median 12.0 7.5 months), and improved RR (44% vs 29%). Moreover, the occurrence of grade 3+ neuropathy was significantly reduced (10% vs 24%).

Chemotherapy holidays

The Italian GISCAD trial compared a continuous with an intermittent first-line treatment in 331 patients with mCRC.[31] They received FOLFIRI either until progression, or every 4 months (2 months of treatment, alternated with 2 months of rest). At a median follow-up of 30 months, the intermittent approach proved to be as equally effective as the continuous one: RR, 33% vs 36%; median PFS, 6.2 vs 6.5 months; and median OS, 16.9 vs 17.6 months, respectively.

However, disappointing outcomes have been reported with the concept of chemotherapy-free intervals evaluated by the OPTIMOX2 phase II study.[32] Patients received the OPTIMOX1 regimen (mFOLFOX7 until progression, with adjusted oxaliplatin and 5-FU doses) or mFOLFOX7 for 6 cycles and then no maintenance until progression, at which time FOLFOX7 was reintroduced. Response rates were similar between the treatment groups, while OS favoured the maintenance therapy arm (median OS, 26 vs 19 months). This negative impact suggests that the OPTIMOX1 strategy is preferable to a chemotherapy-free interval. Prof. de Gramont reasons that chemotherapy cannot be stopped before progression; patients have immediate progression and the opportunity to achieve a cure through surgery is lost.

Early chemotherapy holidays: negative impact on OS

In their investigation into who can potentially benefit from chemotherapy holidays after first-line therapy for mCRC, Perez-Staub and colleagues found that it is optimal to wait 6 months or more, before introducing chemotherapy-free intervals.[33] Median OS was 39.8 months in 94 patients who stopped chemotherapy after 6 months, versus 24.6 months when chemotherapy was stopped at or before 6 months (90 patients). These researchers then identified a subpopulation that clearly benefits from the stop-and-go strategy: patients who achieve

normal carcinoembryonic antigen (CEA) levels within 3 months of chemotherapy. In those 79 patients, median OS was 39.8 months, versus 27.4 months for 77 patients with persistently elevated CEA levels (p=0.015).[33]

In an analysis of 824 patients from the OPTIMOX1&2 database, after more than 3 months of combination therapy, 18% of the patients had a normal CEA which remained normal and 16% of the patients had an abnormal CEA which became normal. CEA levels normalised or decreased by more than 50% in 57 (34.5%) of 165 patients with elevated CEA level at baseline on FOLFOX4 versus 107 (62.6%) of 171 patients on LV5FU2 (p=0.0001).[33] Clearly, a complete break (without maintenance therapy) is possible, if CEA is normalised after 3 months. Conversely, a complete break is not feasible for those patients whose CEA remains elevated.

Concluding remarks: Best strategy in 2010

In today's treatment environment, Prof. de Gramont advises that one very simple question must be answered before any treatment decisions are made: What is the patient's general condition? The treatment algorithm depends on the answer: if the patient is very frail, in poor condition, then the only possible regimen consists of 5FU/capecitabine plus bevacizumab.

If FOLFOX has already been given in the adjuvant setting, de Gramont and colleagues consider the interval since treatment. If relapse occurs within 1 year of treatment, a good treatment option comprises FOLFIRI plus bevacizumab, followed by 6 cycles of FOLFOX7 or 6 XELOX plus bevacizumab.

If the interval to relapse exceeds 1 year, the patient can be treated as a patient with synchronous metastases. The next question to consider is if the metastases are operable or non-operable. If operable, the patient will receive the best combination, comprising 6 cycles of FOLFOX7 or XELOX. Cases that respond can proceed to surgery.

In cases of non-operable sites, prognostic factors must be considered. The two main prognostic factors for combination chemotherapy include serum lactate dehydrogenase (LDH) levels and performance status (PS). If LDH is elevated, or PS≥2 (poor prognosis), the patient should receive up to 6 FOLFOX7 or 6 XELOX. If LDH levels are normal, or PS<2 (good prognosis), the patient will receive more chemotherapy, with 6 FOLFOX7 or 6 XELOX plus bevacizumab. Then CEA levels are considered – whether elevated or normal: if normal, the patient is given 6 cycles of 5-FU or capecitabine and bevacizumab, after which chemotherapy is stopped.

If CEA levels are elevated or there is no response at operable sites treatment will continue with 5-FU or capecitabine and bevacizumab followed by surgery, then maintenance with erlotinib with or without bevacizumab. Then, if the disease progresses, the patient can receive another 6 cycles of FOLFOX7 or 6 XELOX plus bevacizumab, repeated if necessary.

Upon progression, third-line treatment comprises FOLFIRI3 (with or without bevacizumab). In cases of persistent disease progression, patients are given panitumumab or irinotecan plus cetuximab if *KRAS* WT.

Prof. de Gramont concludes that while this is a complex strategy, each step ends with a win. On the whole, at this point in 2010, median survival for patients with unresectable metastasis treated in an optimal way can exceed 30 months.

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