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Adjuvant chemotherapy of colon cancer current strategies

Carlo Barone

Oncologia Medica, Università Cattolica del S. Cuore, Roma, Italy

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ABSTRACT

Adjuvant chemotherapy has become a standard of care in patients with early stage colon cancer. 5-Fluorouracil modulated by leucovorin is the mainstay of treatment, but it has evolved from the bolus administration to continuous infusion and combination therapy. Oral fluoropyrimidines may be an alternative to bolus 5-fluorouracil plus folinic acid. The benefit of adjuvant therapy is established in stage III colon cancer, whereas in stage II the evidence supporting the adjuvant therapy is still poor. Current issues concern the duration of treatment, the development of new schedules and strategies including biological agents and the identification of prognostic and predictive biological markers.

1. Introduction

Since the early 1990s, adjuvant chemotherapy was recommended as a treatment for stage III colon cancer, following the pioneer studies of Wolmark et al. and of Moertel et al.[1,2] However, amongst the drugs used in those trials, only 5-fluouracil (FU) is still the mainstay of colon cancer adjuvant therapy. Levamisole is no longer recommended as its role is unclear, whereas the subsequent studies in the United States (US) and Europe have established the role of the biomodulation of FU with folinic acid (leucovorin, LV). A statistically significant improvement in disease-free (DFS) and overall survival (OS) was confirmed in all patients receiving adjuvant therapy.[3] None of the two more used schedule of bolus FU in combination with LV (Mayo Clinic or Roswell Park schedules) resulted superior nor high dose compared to low dose LV.[4–7] Furthermore, other potential modulators of FU, such as methotrexate (MTX) or interferon (IFN) added some toxic effect but no clinical benefit, compared to the combination of bolus FU and LV. Therefore, this combination, whatever the schedule (Mayo Clinic or Roswell Park), became the standard adjuvant chemotherapy for colon cancer up to the first 2000s.

2. Refinement of fluoropyrimidine monotherapy

Following the improved survival with reduction of some toxic effect observed in advanced colorectal cancer (CRC) through the administration of FU by continuous infusion, these regimens were also evaluated in the adjuvant setting.[8,9] None of the trials found a significant benefit in favour of the infusional schedule, but the patients treated with continuous infusion FU had less toxicity compared with the patients treated with bolus FU. As a result, in Europe the hybrid semimonthly LV5FU2 schedule became the comparator arm in trials evaluating the combination therapy in the adjuvant setting.

The continuous FU infusion carries the need of indwelling intravenous catheters and infusion pump as well as raises the risk of catheter contamination and thrombosis. For this reason, oral fluoropyrimidines were developed with the aim of avoiding these risks meanwhile preserving the improved tolerability of continuous infusion. The X-ACT trial randomised patients with stage III colon cancer to capecitabine (XEL) or bolus FU/LV (Mayo Clinic) and showed that XEL was at least equivalent to bolus FU as far as DFS (the primary end-point) and OS were concerned.[10] Hand–foot syndrome and hyperbilirubinemia aside, the safety profile was more favourable with XEL. An equivalence in DFS and OS with similar toxicity was

E-mail address: carlobarone@rm.unicatt.it
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also shown by the other oral fluoropyrimidine, UFT, plus leucovorin in comparison to the Roswell Park regimen.[11]

3. Combination therapy

A major change in survival of patients with advanced colorectal cancer came at the end of 1990s with the addition of l-Oxaliplatin (OXA) and Irinotecan (IRI) to FU/LV, in particular to the hybrid regimen LV5FU2. The same combination regimens were therefore translated into the adjuvant treatment.

The addition of OXA to FU/LV was first shown to be beneficial by the European MOSAIC trial, which included 2246 stages II and III patients with the primary end-point of improving DFS. The 3-year DFS was significantly higher with FOLFOX than with LV5FU2 (78.2% versus 70.2%; $p = 0.002$); this translates as a 23% reduction in the risk of recurrence.[12] A recent update confirmed the significant difference (5-year DFS 73.3% versus 67.4%; $p = 0.003$) and the reduction in the risk of recurrence.[13] The analysis by stage showed a statistically significant improvement in DFS only for stage III patients. After 6 years of follow-up a statistically significant OS benefit (73% versus 68.6%; $p = 0.029$) was confirmed in stage III subgroup, but not in stage II subgroup nor for the overall patient population. The results obtained in the MOSAIC study have been confirmed by another large trial, the US NSABP C-07, which randomised 2407 stages II and III patients to bolus FU/LV or to the same regimen with OXA.[14] The 3-year DFS was significantly improved with combination treatment (76.1% versus 71.8%). In both studies the OXA-related peripheral neuropathy was a not irrelevant concern, not only for its incidence or severity, but especially for the persistence; in the MOSAIC study grades 1–2 neuropathy was still present in 15% of patients after 4 years of follow-up and in NSABP C-07 it persisted in more than 10% of patients for over 2 years.

Following the development of capecitabine as an alternative to bolus FU/LV in the adjuvant therapy and its established efficacy in combination with OXA in advanced CRC, a trial has been conducted comparing XEL plus OXA with bolus FU/LV as adjuvant therapy in stage III colon cancer. The planned safety analysis has been recently reported, that demonstrates that XELOX has a manageable tolerability profile; however, the features of the comparator arm should not be overlooked. Efficacy data will be available in the next year.

Taking into account its efficacy in advanced CRC, the not favourable results of the addition of IRI to FU/LV are surprising. The CALGB 89803 study comparing bolus FU/LV plus IRI (IFL) with the same combination without IRI was prematurely closed due to an excess of 60-day all-cause mortality in the IFL arm (2.5% versus 0.8%).[15] The combination of IRI with LV5FU2 (FOLFIRI), which has an established efficacy in advanced disease, was compared to LV5FU2 in the European PETACC-3 study with DFS as primary end-point. The 3-year DFS resulted higher in the experimental arm, but not significant (63.3% versus 60.3%; $p = 0.09$).[16] The reasons for the failure of these trials and for their poorer survivals are unknown, but could be attributable – at least in part – to the trial design or the IRI regimen used by some of these trials. In the PETACC-3 study, in fact, the definition of DFS is different from that used in the MOSAIC trial. Provided that the relapse free survival (RFS) in the PETACC-3 study matches with DFS in the MOSAIC study, the RFS difference between FOLFIRI and LV5FU2 in the PETACC-3 study becomes borderline statistically significant in favour of the experimental arm.

4. End-points

Although the improvement in OS seems the most appropriate end-point in order to demonstrate a benefit from adjuvant therapy, it might be heavily influenced by progress in the treatment of metastatic CRC. Furthermore, the evaluation of OS requires a long time compared to the development of knowledge in this field. For this reason in the last decade there has been a move toward using surrogate end-points such as DFS, that combines the advantage of being evaluable more rapidly and of being unaffected by post-relapse treatment. Its predictive potential for OS is accepted by most authors.

The Adjuvant Colon Cancer End Points (ACCENT) group has analysed the pooled individual data of 20,898 patients from 18 randomised controlled trials of adjuvant colon cancer therapy consisting of FU with either LV or levamisole, demonstrating that 3-year DFS correlates with 5-year survival.[17] The correlation is stronger in stage III than in stage II disease. In this analysis, DFS was defined as the time from randomisation to the first event of either recurrent disease or death from any cause, excluding the occurrence of second primary tumours as events. However, in some studies, such as the PETACC-3, this definition corresponds to RFS, whereas DFS included second primary cancer, colonic or not. Actually, the definition of DFS was a critical point. In fact, the study did not meet the primary end-point of improving DFS, but there was a significant improvement of RFS, which was a secondary end-point.

The ACCENT Group study has validated the use of DFS as primary end-point in the place of OS; however, it should be remembered that the definition of events used might prevent the capture of the possibility of treatment-related second malignancies.

5. Stage II colon cancer

Stage II patients have a lower risk of relapse compared with stage III patients. Therefore, any incremental benefit from adjuvant treatment is likely to be proportionally smaller in magnitude and this means that a larger number of patients would be required for adequate statistical power in comparison with stage III. Actually, many studies powered for showing a benefit in stage III have also included stage II patients. For example, in the MOSAIC study separate analyses were planned for the stage II subgroup, but they failed to reach the statistical significance. Similarly, a trial which randomised 500 stage II patients between FU/LV and observation has not found any significant difference in OS and DFS between the two arms.[18]

The largest randomised study of patients with stage II disease is the Quick And Simple And Reliable (QUASAR) 'uncertain indication' trial.[19] In this trial, 3239 patients were enrolled in whom the role of adjuvant chemotherapy was

considered uncertain by the treating physician. The patients were randomised between observation and different schedules of FU/LV ± levamisole. The study demonstrated a significantly reduced recurrence (risk ratio 0.78; $p = 0.001$) and improved survival (risk ratio 0.82; $p = 0.008$) in favour of the treatment arm. The results should be interpreted prudently because of the heterogeneity of study population, treatment and follow-up.

Amongst the metanalyses that addressed this issue, that performed by the Cancer Care Ontario Programme (CCOP), included 4187 patients with stage II colon cancer showing a marginal not significant benefit for treated patients.[20] Based in part on these results, the ASCO issued guidelines recommending that adjuvant chemotherapy should be considered only in stage II patients having high-risk disease defined by the presence of at least one of the following features: T4 tumors, poorly differentiated histology, presentation with perforation or inadequate sampling (<13) of lymph nodes.[21] Noteworthy, the high-risk stage II patients in the MOSAIC trial were defined according to different criteria than that used in the ASCO guidelines.

6. Timing and duration of treatment

There are data to suggest that benefits from adjuvant treatment are reduced if treatment is delayed by more than 8 weeks after surgery. An analysis of patients with stage III colon cancer who received adjuvant chemotherapy and were recordered within the US 'Surveillance, Epidemiology, End Results' (SEER)-Medicare database found that a delay in commencement of treatment, defined as 3 or more months after surgery, was associated with an increase in colon cancer-specific mortality.[22] However, due to retrospective nature of the study, it is unknown if the reasons of the delay were related to the clinical conditions of patients.

As far the issue of treatment duration, there is no evidence that there is any additional benefit from treatment with FU/LV for longer than 6 months. On the other hand, the SAFFA randomised study demonstrated that 12 weeks of protracted venous infusion of FU is as effective as 6 months of bolus FU/LV.[23] Furthermore, no difference in DFS and OS was found in the 2×2 factorial GERCOR C96.1 study between 24 and 36 weeks of treatment as well as between LV5FU2 and monthly bolus FU/LV.[24]

The feasibility of shorter treatment is of particular interest with reference to the superior toxicity and efficacy of combination therapy.

7. Biological therapy and future development

The response rate achieved in metastatic disease is commonly regarded as the best surrogate marker for the efficacy of a given treatment as adjuvant treatment. The different outcome of MOSAIC and PETACC-3 studies, however, suggests that the activity of a regimen in advanced disease is not always a good predictor of its effect as adjuvant therapy. In addition, as far as the biological agents are concerned, the link between response rate in advanced disease and predicted activity in adjuvant therapy is not necessarily reliable. Rather, the identification of predictive markers for the activity of biological agents might be a more appropriate prerequisite of activity. In addition, if biological agents delay the manifestation of macrometastases rather than eliminate occult tumour cells, the concept that 3-year DFS is a valid surrogate for 5-year OS might not hold.

Despite the large diffusion of anti-EGFR and anti-VEGF therapy in CRC, the knowledge of precise predictive markers of their activity is limited. Recent reports supporting the link between the activity of anti-EGFR antibodies and the absence of K-RAS mutations or increased EGFR gene copies have induced the regulatory authorities to consider the absence of K-RAS mutations as a marker of susceptibility to anti-EGFR therapy.[25,26] On the other hand, the same widespread activity of anti-VEGF therapy, irrespective of any known biological marker, might raise some difficulty in classifying bevacizumab because it only indirectly targets the tumor. Given the mechanism of action of bevacizumab, it is possible that in adjuvant therapy an effect on DFS might be observed rather than on OS, unless a protracted VEGF inhibition leads to tumour cell apoptosis.

Bevacizumab is currently evaluated in two large international phase III trials in colon cancer adjuvant therapy (AVANT and NSABP C-08), addressing the effect of adding bevacizumab to FOLFOX as well to CAPOX, and in a phase III international adjuvant trial in rectal cancer (ECOG 5204). Other two studies, involving bevacizumab (ECOG 5202 and QUASAR-2), are restricted to high-risk stage II colon cancer. Finally, a Italian study of GISCAD plans to evaluate the duration of treatment with FOLFOX (3 versus 6 months) in high-risk stage II and in stage III patients as well as the addition of bevacizumab to high-risk stage III patients.

Anti-EGFR antibodies target a tumour cell-bound antigen; therefore, they may have some cytotoxic capability, but unfortunately the response rate as single agent therapy in advanced disease is low and the benefit of adding an anti-EGFR antibody to FOLFIRI o FOLFOX in the whole population of almost two large phase III trials in advanced CTC is lower than expected.[27,28] Two trials in USA (IG/NCCTG-N0147) and in Europe (PETACC-8) are currently under way to investigate cetuximab in combination with FOLFOX.

At present, the clinical-pathologic stage represents the only surrogate marker for the risk of distant micrometastatic disease, but it has major limitations, as exemplified by the not homogeneous prognosis of stage II as well as stage III patients. The use of agents that target biological pathways of tumour cell or of its environment further reinforces the need of carefully investigating on molecular prognostic factors. Most ongoing trials planned a detailed study of potential biological markers based on the existing knowledge. However, only few trials have a design based on some known clinical–biological prognostic/predictive factor. One of these studies is the ECOG protocol E5202 which is enrolling patients with stage II colon cancer with at least eight lymph nodes examined to exclude metastases. In this protocol, the patients considered as having high-risk disease on the basis of microsatellite instability (MSI) and 18qLOH are randomised between OXA-based chemotherapy with or without bevacizumab, whereas low risk patients are assigned to observation only. At present, however, the prognostic value of MSI is still debated; therefore,

it is uncertain whether this study will really allow us to identify the subgroup of high-risk patients.

In future, more precise predictive markers are expected from the pharmacogenomic as well as prognostic grouping would result from gene expression signature by means of DNA-microarray that may allow to distinguish genetic profiles associated with prognosis and therapeutic outcome.

Conflict of interest statement

Prof. Barone has received honoraria from Sanofi-Aventis, Merck KGA, AstraZeneca, and Roche and has been a member of advisory boards for Amgen, Pfizer, Merck KGA, and Roche.

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