Irinotecan or oxaliplatin for first-line treatment of advanced colorectal cancer?

In this issue of *Annals of Oncology*, two studies by the Southern Italy Cooperative Oncology Group (SICOG) and the Hellenic Cooperative Oncology Group (HECOG) are presented in which treatment with irinotecan and oxaliplatin, both in combination with 5-fluorouracil/leucovorin (5-FU/LV), is compared in patients with advanced colorectal cancer [1, 2]. The choice of the first-line regimen may be important, since not all patients are eligible for salvage treatment, which obviously provides a rationale to first administer the most effective treatment. The study by Goldberg et al. [3], which showed an overall survival benefit for FOLFOX when compared with IFL, has convinced many colleagues that oxaliplatin should be the preferred choice. However, both the fact that in this study a bolus 5-FU regimen (IFL) was compared with a prolonged 5-FU infusion regimen (FOLFOX), and the fact that salvage treatment in the IFL arm was inferior to the FOLFOX arm, do not allow such a straightforward conclusion [4]. The GERCOR study in which irinotecan and oxaliplatin were compared using the same schedule of prolonged 5-FU infusion and LV with both drugs did not show any significant differences in response rates or survival [5].

The originality of the current studies lies in the fact that a bolus 5-FU regimen was used with both drugs. This has the advantage that central venous access devices and ambulatory pumps are not required. Both studies had response rate as the primary end point, and are comparable in the patient selection criteria and baseline patient characteristics. Yet, the authors come to different conclusions. Some important study characteristics and results are as follows. The SICOG study [1] used a 2-weekly schedule, with irinotecan or oxaliplatin administered on day 1 and 5-FU/LV on day 2. The rationale to administer these drugs on consecutive days as opposed to administration on the same day is unclear. The oxaliplatin arm showed superior results in terms of response rate (44% versus 31%; *P* = 0.029), failure-free survival (7 versus 5.8 months; *P* = 0.046) and overall survival (18.9 versus 15.6 months; *P* = 0.032). This caused the authors to select the oxaliplatin schedule as the regimen of choice. The dose of oxaliplatin was decreased after a planned interim analysis, without apparent detrimental effect on efficacy.

The HECOG [2] used a weekly schedule for 6 weeks followed by 2 weeks of rest, and no difference between the oxaliplatin and irinotecan arm was found in terms of response rate (unconfirmed 32% versus 33%, confirmed 22% versus 23%), time to progression (7.6 versus 8.9 months) and overall survival (17.4 versus 17.6 months). The main problem with this study lies in its design: with response rate as the primary end point, a scheduled interval between tumour evaluations of 16 weeks is simply too long. Moreover, confirmation of response had to wait for another 16 weeks. This is most probably the explanation for the lower response rate when compared with the SICOG study while the overall survival in both studies was in the same range. Likewise, results on time to progression are likely to be less accurate when such a long interval is used for tumour evaluation.

What other remarks can be made on these studies? First, despite the comparable results on overall survival between the two studies the dose intensity for the used drugs was lower in the HECOG study, most markedly for irinotecan: the planned total irinotecan dose over an 8-week period was 800 mg/m² in the SICOG study versus 420 mg/m² in the HECOG study. Results from small studies have suggested a dose–response relationship for irinotecan [6, 7]. As mentioned, the response rates are not comparable between the current studies, and any relationship between irinotecan dose and survival based on these studies should be interpreted with caution in any case, since only a direct comparison between the regimens would allow a definite conclusion. Secondly, a difference in the occurrence of severe diarrhoea between the study arms was only observed in the SICOG study, with a higher incidence in the irinotecan arm. The incidence of diarrhoea in the irinotecan arm was higher compared with the HECOG study (28% versus 12.3%), which may be related to the lower dose of irinotecan in the latter study. As expected, neurotoxicity was observed more frequently in the oxaliplatin arms of both studies. Together with the comparable results on efficacy, the increased incidence of neurotoxicity caused the authors of the HECOG study to select the irinotecan schedule as the regimen of choice.

How do the results of the current studies contribute to the ongoing discussion of which drug is to be preferred for first-line treatment? When only comparative studies between irinotecan and oxaliplatin are taken into account in which the 5-FU/LV schedule was similar in both arms, only the SICOG study [1] shows a benefit for oxaliplatin. The HECOG [2] and GERCOR [5] studies, as well as the preliminary results from a randomized phase II study in which capecitabine was used instead of 5-FU/LV [8], do not show significant differences in efficacy between irinotecan and oxaliplatin. It is not clear why the SICOG study stands out in this respect. The median number of cycles, as well as the percentage of patients receiving salvage treatment, was comparable between the two study arms.

This shifts the focus towards the toxicity of the regimens. Results of a phase III study comparing a 3-weekly with a weekly irinotecan schedule when given as a single agent showed comparable efficacy but significantly less diarrhoea and fewer dose reductions for the 3-weekly schedule [9].
In a randomised phase II study with irinotecan plus capecitabine, 3-weekly administration of irinotecan also resulted in less diarrhea compared to weekly irinotecan administration, and a clinical benefit was suggested for the 3-weekly schedule as well [10]. These results show that irinotecan should probably not be scheduled as a weekly administration. Compared with oxaliplatin, treatment with irinotecan produces more severe diarrhoea with a bolus 5-FU schedule [1], but not with a prolonged 5-FU infusion schedule [5]. The incidence of irinotecan-induced severe diarrhoea was 28% with bolus 5-FU in both the SICOG study [1] and the study by Goldberg et al. [3], and 14% with prolonged 5-FU infusion in the GERCOR study [5]. These results suggest a preference to combine irinotecan with prolonged infusion instead of bolus 5-FU. For oxaliplatin, the 5-FU schedule appears to have less impact, since the incidence of severe toxicities are comparable between studies using a 5-FU bolus or prolonged infusion schedule. However, there are no data available on a direct comparison between bolus and prolonged 5-FU infusion in combination with oxaliplatin.

Lastly, has the concomitant use of novel targeted therapies any impact on the choice? This is not yet clear, since irinotecan and oxaliplatin in combination with agents that target the VEGF or EGF pathways have not been studied vigorously in randomized studies. However, current results in colorectal cancer patients do not suggest that the efficacy of targeted therapy is dependent on the choice of chemotherapy, although some of these data are still preliminary.

In conclusion, with all published data taken into account, an outright choice cannot be made for either irinotecan or oxaliplatin in first-line combination schedules for the treatment of advanced colorectal cancer. The choice between these agents remains to be made on an individual basis, in which the medical history as well as the preference of the patient should be taken into account. Pharmacogenetic/genomic studies hold the promise to provide additional selection criteria. As to the 5-FU/LV schedule in combination therapy, it is unlikely that schedules with bolus versus prolonged 5-FU infusion will be compared in prospective randomized trials, since other study designs have a higher priority. Given the better overall survival of ~21 months for both irinotecan and oxaliplatin in patients with comparable baseline characteristics [5], as well as the lower incidence of diarrhoea with irinotecan, prolonged infusion appears to be the preferred way to administer 5-FU in combination treatment. This results in a higher incidence of febrile neutropenia, vomiting and alopecia with irinotecan, and of neutropenia and neurotoxicity with oxaliplatin [5]. The promising phase II results on response rates of irinotecan and oxaliplatin in combination with capecitabine may solve the issue of 5-FU scheduling [4, 11, 12]. Phase III studies on combination therapy with capecitabine are ongoing.

References