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What have we learned and where are we going in the treatment of colorectal and gastric cancer?

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Abstract

Clearly increasing knowledge of the timing of administration of new chemotherapy combinations coupled with an improvement in technical skills in the surgical setting has improved the outcome for patients with colorectal and gastric cancer. Of the newer cytotoxic chemotherapy agents irinotecan in particular represents the cornerstone of the new treatment regimens that are leading to a better prognosis for patients with colorectal and gastric cancer. The systematic study of agents like irinotecan and the integration of novel targeted agents into combination chemotherapy regimens can only serve to improve still further the benefits we are beginning to see for the treatment of these patients.

Keywords: Adjuvant; Colorectal; Irinotecan; Gastric; Metastatic

1. Introduction

Colorectal and gastric cancers between them represent a major public health problem [1,2]. In the case of CRC more effective treatment strategies both in terms of chemotherapy regimens and an increase in the number of patients being referred for resection have lead to an improvement in overall survival. However, in the case of gastric cancer there has been no major change in prognosis over the last 10–20 years. The need for effective systemic chemotherapy in these patients is therefore an urgent necessity.

2. Colorectal cancer patients

Irinotecan in combination with 5-fluorouracil (5-FU) and folinic acid (FA) has been shown to be more effective than 5-FU/FA alone [3,4] and has been approved for the treatment of advanced and metastatic CRC first-line in both Europe and the US since 2000. More recently oxaliplatin in combination with 5-FU/FA has been approved first-line in Europe. Both these combination regimens have been shown to prolong survival and improve quality of life (QoL). The use of combination chemotherapy, in the palliative setting, consistently results in response rates of around 50% and median survivals of between 16 and >20 months [3–7]. Thus it is clear that patients with metastatic CRC should be given 5-FU/FA in combination with one of these newer agents, although the level of evidence is highest for irinotecan in combination with 5-FU/FA first-line (Köhne, this supplement). The optimal sequence of administration of these two active regimens has been the subject of much discussion and the results of the recently published GERCOR study showed both FOLFIRI (irinotecan/5-FU/FA [de Gramont]) followed by FOLFOX (oxaliplatin/5-FU/FA [de Gramont]) and FOLFOX followed by FOLFIRI to achieve similar first-line responses and long-term survivals [8]. However, although an increasing number of patients receive

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second-line chemotherapy, this study emphasised that there is still a high proportion of patients that do not, making the choice of first-line chemotherapy very important. Another important observation from this study was the distinctive toxicity profile of oxaliplatin when used first-line, that forced some patients to stop oxaliplatin therapy first-line before tumour resistance developed.

What is also clear is that combining agents such as irinotecan with oral fluoropyrimidines such as capecitabine [9,10] and the new targeted biological agents [11,12] should lead to improvements in survival for patients with inoperable disease. Cetuximab, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody that blocks the binding of the natural ligands (EGF and TGF-alpha) to the EGFR, showed activity both alone and in combination with irinotecan in patients with metastatic CRC that had failed on previous irinotecan-based therapy [13,14]. More recently, the randomised BOND study has confirmed that both cetuximab alone and cetuximab in combination with irinotecan are active in heavily pretreated patients, with irinotecan in combination with cetuximab being significantly more effective than cetuximab alone in terms of response rate, time to progression, and overall tumour growth control [11]. Significantly, more than 40% of patients in this study had received more than two lines of chemotherapy. Promising results have also been shown for irinotecan-5-FU/FA in combination with cetuximab first-line [15,16]. There was also evidence that this combination facilitated the performance of complete, potentially curative resections of CRC hepatic metastases in some patients. Results have also been obtained first-line for irinotecan plus bolus 5-FU/FA in combination with the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab [12]. Bevacizumab was shown to prolong survival by an impressive almost 40% and prolong time to progression by 70%.

Clearly the treatment for patients with CRC is improving and importantly there is clear evidence that irinotecan containing regimens can be safely administered to elderly patients [17–19], a group of patients that is under treated and under represented in clinical trials. Furthermore, there is clear evidence that not only oxaliplatin but also irinotecan in combination with 5-FU/FA can facilitate the resection of colorectal liver metastases [20–22] and that the treatment of patients with colorectal liver metastases should be conducted within the framework on multidisciplinary teams.

2.1. Adjuvant chemotherapy

The survival benefit of using adjuvant chemotherapy in the treatment of patients with stage III disease is well established [23]. Currently the most commonly used regimen is bolus or infusional 5-FU/FA administered for a period of 6–8 months post-surgery. The jury still out on the use of adjuvant chemotherapy for CRC patients with stage II disease [24]. However, the clear benefit of adding irinotecan to infusional or bolus 5-FU/FA for the treatment of metastatic CRC indicated the likely efficacy of this combination in the adjuvant setting. Irinotecan is therefore well represented in a number of large randomized studies. These include the ACCORD 2 trial comparing bolus and infusional 5-FU/FA with or without irinotecan in patients with high-risk Stage III disease. Irinotecan is also being investigated in combination with continuous infusion 5-FU/FA [PETACC-3] and in combination with weekly administered bolus 5-FU/FA (CALGBC89803). In addition, the QUASAR II study is comparing the combination of irinotecan and capecitabine with bolus 5-FU/FA in stage III disease. Furthermore, in addition to the use of conventional chemotherapy agents there is clearly the potential for clinical benefit with certain biological agents e.g. cetuximab (anti-EGFR) and bevacizumab (anti-VEGF), and irinotecan/capecitabine in combination with bevacizumab is being included as a third arm in the QUASAR II adjuvant trial. The efficacy results of these trials are eagerly awaited.

Thus the future for patients with CRC looks potentially very exciting. However, for patients with gastric cancer we still have to wait for a significant change.

3. Gastric cancer

Gastric cancer is a debilitating, aggressive disease that is frequently not diagnosed until it has reached an advanced stage. Surgery is the only curative treatment option for patients with resectable gastric cancer. The data indicate that chemotherapy has a good symptomatic benefit and prolongs survival compared with best supportive care in advanced non-resectable and metastatic gastric cancer [25,26]. In the control group the median survivals were 3–5 months whilst in the chemotherapy arms the median survivals were in the range of 7–9 months. Moreover, if chemotherapy is given early to asymptomatic patients the benefit in terms of clinical control and prolongation of survival is better than if administered late to patients who already have symptoms. The problem is however that the benefit and the responses are often of short duration and the complete response rates very low. Also, these patients in poor general condition often find it difficult to tolerate chemotherapy. A plethora of different chemotherapy regimens have been investigated which have typically yielded response rates of between 25% and 40% and median overall survivals of 7–9 months. However, there is still no single agent or combination regimen that is accepted as standard treatment.

The data presented in this supplement (Wilke *et al.*, and Van Cutsem) clearly demonstrate roles for irinotecan and docetaxel at the forefront of new chemotherapy treatment combinations. Both have been shown to be active alone in this setting [27–29] and in combination with cisplatin [27,30–32] and 5-FU [33–35]. In a recent randomised phase II study the efficacy and toxicity profile of irinotecan/5-FU/FA was found to be preferable to that of 5-FU/FA alone and 5-FU/FA/cisplatin [34]. A randomised phase III trial comparing irinotecan/5-FU/FA with cisplatin plus 5-FU is ongoing [35]. A two part, multinational phase II/III trial has been initiated to evaluate the efficacy of docetaxel-based treatment in gastric cancer. Based on encouraging results achieved with the combination of docetaxel/cisplatin, the first part of the trial investigated whether the addition of continuous infusion 5-FU to this regimen (DCF), would further improve the response rate. The results showed that DCF was associated with a higher response rate than docetaxel/cisplatin (43% versus 26%). As a result DCF was chosen for the phase III trial to be compared with a standard treatment regimen, cisplatin/5-FU. The results of the planned interim analysis of the phase III trial show the DCF arm to be associated with a significantly higher overall response rate (39% versus 23%; $p = 0.012$) and a significantly longer median time to tumour progression (5.2 months versus 3.7 months; $p = 0.0008$). However, the longer median overall survival for patients treated with the DCF regimen (10.2 versus 8.5 months) did not reach statistical significance in the interim analysis, compared with cisplatin/5-FU alone [36]. The results of the full study population are awaited eagerly.

In the case of patients with operable gastric cancer the roles of neoadjuvant and adjuvant chemotherapy, and adjuvant chemoradiotherapy are also changing. The US intergroup has shown a clear benefit for post-operative chemoradiotherapy in patients who undergo curative resections for gastric cancer. Both the disease-free survival and overall survival were significantly longer. The UK MAGIC trial has shown that patients treated with both pre- and post-operative chemotherapy compared to surgery alone had a better disease free survival. The curative resection rate was also higher in patients who were treated with pre-operative chemotherapy (ECF regimen). The survival difference in patients treated with pre- and post-operative chemotherapy did, however, not reach significance. Pre-operative radiation alone is ineffective, whilst chemoradiation is promising but still investigational.

Clearly large randomized trials are required to detect the clinically relevant differences in the metastatic and advanced, adjuvant and neoadjuvant settings for these patients, but at last it seems that chemotherapy is being seen to confer a real benefit.

4. Conclusion

New developments, especially in the treatment of metastatic colorectal cancer, and more recently in the treatment of gastric cancer, seem to be having an impact on the management of patients with these frequently occurring cancers.

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