

Progress in the treatment of gastrointestinal cancer

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Colorectal cancer (CRC) is common and is associated with a high mortality, due principally to the tendency of the disease to spread to other organs, notably the liver. While adjuvant chemotherapy has been shown to improve survival in stage III patients, its role in stage II disease has not yet been established [1]. The incorporation of new and active cytotoxic agents such as irinotecan into adjuvant regimens may further benefit survival, as may the introduction of novel cytostatics targeted at processes promoting malignant spread. On the neoadjuvant front there are also encouraging prospects: use of chemotherapy that achieves major responses is enabling certain patients with initially unresectable disease to proceed to potentially curative surgery.

However, in the foreseeable future there will continue to be a massive need for palliative chemotherapy among patients with advanced disease. Fortunately, there is a history of progress here on which we can build [2–5]. Through a series of innovations in therapy, each of them having a small impact by itself but a large impact in aggregate, we have reached a situation in which clinical trials consistently achieve response rates exceeding and median survival durations in excess of 17 months. Essential to this progress has been the development of irinotecan, which remains the only drug to have shown significant survival advantage when added to an optimum 5-fluorouracil/folinic acid (5-FU/FA) regimen [6–9].

Oxaliplatin is also an active drug in this disease, producing good rates of response and extending time to progression when added to 5-FU/FA [10, 11]. This means that patients can now benefit from two regimens: FOLFOX (oxaliplatin, 5-FU, leucovorin) and FOLFIRI (irinotecan, 5-FU, leucovorin). How best to sequence these treatments has been an important question addressed in a phase III randomized controlled trial, which is about to be published [12].

In parallel with work on sequencing, there is active investigation of dose-intensified irinotecan and of the combination of irinotecan with oxaliplatin, with oral 5-FU prodrugs, raltitrexed and molecularly targeted agents such as the anti-epidermal growth factor receptor antibody cetuximab. The advent of novel cytostatic agents may improve our ability to tailor treatment to the biological and molecular characteristics of individual tumors.

In CRC, several important issues have been at least partially resolved: we know that adjuvant chemotherapy benefits stage III patients; irinotecan is clearly an integral part of standard first- and second-line care; and there is a logical way to decide on how to sequence active combination regimens. In gastric cancer, however, there are still many more questions than answers in all aspects of management, and indeed in epidemiology, since the

recent rise in adenocarcinomas of the gastro-esophageal junction is striking.

The extent of surgical dissection required remains hotly debated. The randomized D1 versus D2 trial conducted in The Netherlands did not provide support for routine radical resection [13]. Nevertheless, the need for surgery to be sufficient to provide good regional control is clear. In practice, a limited D2 (or 'D1.5') resection is frequently advocated for patients who do not have significant co-morbidities. In major centers, the operative mortality is now down to a few percent and central node staging in early gastric cancer may avoid unnecessarily extensive lymphadenectomy.

Recent meta-analyses have shown an overall small but statistically significant benefit for adjuvant chemotherapy in gastric cancer [1]. However, such studies do not guide us towards any one regimen that may be particularly beneficial in this context, and there have recently been well-conducted adjuvant studies that failed to show improved survival.

Despite a clear rationale for adjuvant radiotherapy, its role in patients who have received optimum surgery remains unresolved [14]. The need for further randomized studies of adjuvant chemoradiotherapy is clear, but the appropriate control for such a study is not. Should it be surgery only, or chemotherapy with a cisplatin or epirubicin/5-FU combination, or a 'modified Macdonald' combination of chemotherapy and radiation? We must also note that the fact that many gastric cancer patients are not sufficiently fit for post-operative chemotherapy may shift the focus to the neoadjuvant arena. In this situation, it is mandatory that surgeons and oncologists (and indeed radiotherapists) work together. Each speciality needs the others.

In metastatic gastric cancer, there are clear signs of progress, with median survival durations of 8–10 months in patients receiving chemotherapy, compared with 3–4 months in those who do not. There is no one agreed standard of care, although there is a consensus that some form of cisplatin/5-FU combination provides an appropriate reference regimen, and it is against cisplatin/5-FU that the promising combination of irinotecan/5-FU is now being tested in the phase III setting.

Along with irinotecan, docetaxel is proving to be of considerable interest in gastric cancer, and can achieve single-agent responses in ~20% of patients, even when used as second-line therapy [15]. Combinations of docetaxel with cisplatin and 5-FU are being actively pursued, both in advanced disease and in the neoadjuvant settings. It is to be hoped that progress in the chemotherapy of gastric cancer will in time at least match that already achieved in CRC.

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