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Salvage chemotherapy in gastric cancer – more than a straw?

Florian Lordick

The benefit of salvage chemotherapy in gastric cancer refractory to first-line platinum and fluoropyrimidine therapy was previously unknown. A randomised multicentre study has shown that irinotecan or docetaxel administered as single agents improved survival compared with best supportive care alone. Hence, salvage chemotherapy is now a proven option in pretreated gastric cancer.

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Gastric cancer is one of the most common and fatal malignancies. Despite a decreasing incidence in Western civilisations,[1] gastric cancer accounts for approximately 700,000 deaths every year worldwide.[2] Cure can only be achieved in the early stages, and the treatment of metastatic disease pursues only palliative goals. First-line chemotherapy with platinum compounds and fluoropyrimidines had a proven role in prolonging survival and controlling disease-related symptoms in advanced stages,[3] but the role and benefit of second-line or further-line chemotherapy was undefined.

Now, a prospective randomised multicentre study called 'salvage chemotherapy', conducted by Korean investigators, has unravelled the value of further-line chemotherapy following failure of first-line or second-line chemotherapy.[4] Kang and colleagues selected patients with advanced-stage gastric cancer who had not responded to one or two prior chemotherapy regimens involving both fluoropyrimidines and platinum. Eastern Cooperative Oncology Group performance status was 0 or 1. Patients were randomly assigned in a ratio of 2:1 to receive salvage chemotherapy plus best supportive care or best supportive care alone. Choice of salvage chemotherapy – either docetaxel 60 mg/m^2 every three weeks or irinotecan 150 mg/m^2 every two weeks – was left to the discretion of the investigators. The primary endpoint was overall survival. Median overall survival was 5.3 months among the 133 patients in the chemotherapy arm and 3.8 months among the 69 patients in the best supportive care arm (HR=0.657, 95%CI 0.485–0.891; one-sided P=0.007). Overall survival benefit for salvage chemotherapy was consistent in most of the prospectively defined subgroups, which included age, performance status, number of prior treatments, metastatic sites, haemoglobin levels, and response to prior chemotherapy. Salvage chemotherapy was generally well tolerated, and adverse events were similar in both arms. No difference in overall survival was found

between docetaxel and irinotecan (5.2 months vs 6.5 months; P=0.116). In summary, the study by Kang and colleagues[4] proves the value of salvage chemotherapy in pretreated advanced-stage gastric cancer. Single-agent chemotherapy improves survival when added to best supportive care and, as single agents, irinotecan and docetaxel are equivalent options.

Both regimens showed good safety profiles, manageable toxicity and good feasibility. Although haematological toxicities were more common in patients treated with chemotherapy, non-haematological adverse events were seen in both arms, indicating that symptoms may have been disease related, rather than treatment related.

The investigators should be commended for the conduct of this informative trial. Do the results come as a surprise and will they alter our daily clinical practice? I feel that both questions can be negated. The results match our expectations and, as clinical oncologists, we have been using second-line chemotherapy for advanced-stage gastric cancer for quite a while.

Experiences from East Asia suggested a clear benefit of sequential treatment for advanced-stage gastric cancer.[5] Relatively long intervals have been reported between the failure of first-line chemotherapy and death in studies in which consecutive lines of chemotherapy were administered in the majority of patients. For example, in a Japanese study that compared the drug S-1 administered as first-line alone or in combination with cisplatin, 75% of patients received post-progression chemotherapy. This treatment administered on disease progression consisted mainly of taxane-based (or irinotecan-based) regimens. Progression-free survival of first-line treatment was four months and six months, respectively, whereas survival following first progression was seven months in both arms.[5] It must be assumed that a much shorter post-progression survival would have been observed if less 'salvage chemotherapy' had been given in the post-progression phase of this study.

Despite the progress in the treatment of advanced-stage gastric cancer that has been observed by the Korean investigators, we must not overlook the purely palliative character of any chemotherapy in this disease. For me, the term 'salvage chemotherapy' is unfortunate. The word 'salvage' is based on the Latin word 'salvare', which means that someone can be rescued and that lives can be saved. But, what is more inapplicable to chemotherapy-refractory advanced-stage gastric cancer than the promise of rescue and cure by offering further chemotherapy? The metaphor that would come closer to the reality is the drowning man who will clutch at a straw. We must not forget that the battle of patients with chemotherapy-refractory advanced-stage gastric cancer is inevitably lost and death will usually arrive at short term. The chance of inducing a new 'response' – whatever that means for the prognosis – is no more than 10% according to the Korean data.[4] The realistic achievements of second-line irinotecan or docetaxel are a transient deferral in tumour progression, a moderate prolongation of the remaining survival time and, possibly, a better control of disease-related symptoms (which has not been assessed in the Korean study). We must learn to talk honestly with our patients. We must be aware that the early communication of the palliative nature of all treatment efforts is beneficial if, in addition, we also support patients in making their decisions and finding their way not out but through the disaster of suffering from a malicious disease and facing death. Jennifer S. Temel and colleagues recently demonstrated that an early palliative intervention following new diagnosis of metastatic non-small-cell lung cancer – a disease with many similarities to gastric cancer – led to improved survival, better quality of life, improved mood and less use of chemotherapy in the last two months of lifetime compared with patients who received standard care.[6] This is not meant as a plea against second-, and further-, line chemotherapy in advanced-stage gastric cancer. Rather, I clearly vote for a frank communication with our patients about realistic treatment goals, for shared and informed decision making, and for palliative support that goes beyond second-line chemotherapy and standard (undefined) best supportive care.

Is irinotecan or docetaxel the only medical option that there is for treating post-progression gastric cancer?

> **"The metaphor that would come closer to the reality is the drowning man who will clutch at a straw"**

Key points

- Second-line chemotherapy improves outcome in advanced-stage gastric cancer
- Irinotecan or docetaxel administered as single agents are proven options in pretreated gastric cancer

Certainly not; more potentially active drugs are available, including other taxanes and alternative platinum compounds that are probably not completely cross-resistant to cisplatin, which is most commonly used in the first-line setting. Even anthracyclines or mitomycin may show benefit in further treatment lines. To date, single-agent irinotecan, given in a biweekly (150 mg/m²) or three-weekly (250–350 mg/m²) schedule has the best evidence to improve survival and symptom control in post-progression advanced-stage gastric cancer. A smaller randomised German study of the Arbeitsgemeinschaft Internistische Onkologie (AIO) showed a consistent benefit for second-line treatment with irinotecan that resulted in a reduction of the hazard ratio for death to 0.48 (95%CI 0.25–0.92, *P*=0.012) in the irinotecan arm compared with best supportive care alone.[7] Beyond chemotherapy, medicinal pain management, nutritional support, psycho-social support and many other interventions do not yet have proven benefit for patients with advanced gastric cancer.[3]

A consistent benefit of 'salvage chemotherapy' has been observed in most of the prospectively defined subgroups of the Korean study.[4] Nevertheless, in the era of personalised medicine and increasing disease stratification, the benefit of specific medicinal interventions must be challenged in future studies that may assess whether this benefit might be the same for different ethnic subgroups,[8] for different histological phenotypes,[9] and for different gastric cancer genotypes.[10]

In summary, irinotecan or docetaxel significantly prolonged overall survival compared to best supportive care in the studied patients. Second-line chemotherapy can now be considered as a proven treatment option for pretreated advanced-stage gastric cancer and this option should be integrated into a comprehensive palliative care strategy.

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Competing interests

Florian Lordick declares associations with the following companies: Pfizer, Sanofi-Aventis

Manufacturer sponsorship bias in economic analyses matters

➜ David Kerr and Ahmed Elzawawy

A qualitative study indicates that there is a positive selection bias towards favourable economic analysis of targeted therapies when these are funded by the manufacturer. At a time of increasing budgetary constraints and public scrutiny of the relationship between industry and the professions, we need a more mixed economy of funding for this field.

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In terms of the history of medicine and health care, the 19th century may be regarded as the century of Public Health, clean water, sewerage and understanding the basis of infection; the 20th century might be regarded as the century of knowledge, when systematic clinical and laboratory research yielded extraordinary insights into the mechanism of disease; we predict that the 21st century will be driven by value. Considering the spiralling costs of healthcare and an often confused approach to how we define value in a societal