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New horizons for gastric cancer: commentary

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Gastric cancer is a significant global problem. Recent figures indicate that 1.4 million new cases of gastro-oesophageal cancer are diagnosed annually and 1.1 million deaths are attributed to the disease [1]. While the rate of fundic and distal gastric cancers (which are often associated with *Helicobacter pylori* infection) has declined over past decades, the incidence of adenocarcinomas of the gastric cardia and gastro-oesophageal junction continues to rise. Areas with a particularly high incidence of gastric cancer include parts of Asia, Eastern Europe and South America.

As with other malignancies, treatment for gastric cancer varies depending on the stage of the disease. For patients with early gastric cancer, the primary treatment is surgery. Although this treatment approach is usually effective in the short term, many patients who undergo resection experience some form of recurrence [2]. Multiple clinical studies have therefore looked at whether adjuvant chemotherapy can improve patient outcomes. Unfortunately, many of the studies have been underpowered for survival and the majority have used 'old' chemotherapy regimens. Nevertheless, meta-analyses of these studies suggest a small (12% to 28%) reduction in the risk of death with adjuvant therapy versus no treatment [3–7]. Due to the lack of high quality, prospective data, adjuvant chemotherapy has not yet become accepted as the standard of care for resectable gastric cancer.

Data from the large SWOG 9008/INT 0116 Phase III trial suggest that adjuvant chemoradiotherapy can significantly improve survival compared with surgery alone (median overall survival [OS]: 35 vs. 26 months, respectively, with >6 years median follow-up [$P = 0.01$]) [8,9]. Although the trial was powered adequately to detect survival differences in the overall patient population, the results are somewhat confounded by the methodology (select patient group, lack of control for surgical procedure, use of old radiotherapy treatment/planning methodology, use of an old chemotherapy regimen [bolus 5-fluorouracil (5-FU)/leucovorin]) and uncertain benefit in D2/adequately resected patients. Adjuvant chemoradiotherapy appears to be a reasonable treatment option for some resected patients, especially those whom may have had inadequate surgery, have a high risk of relapse, or both. Studies are currently examining the efficacy of new regimens (newer drug combinations and radiotherapy techniques) and schedules (including neoadjuvant strategies), as well as exploring the value of chemoradiotherapy in D2 and adequately resected patients. A further Phase III trial (the MAGIC study) has shown that combined pre- and post-operative chemotherapy with epirubicin–cisplatin–5-FU (ECF) can improve survival compared with surgery alone (median OS: 24 vs. 20 months, respectively; hazard ratio for death: 0.75; 5-year survival: 36% vs. 23%, respectively), suggesting that peri-operative therapy is another treatment option for early gastric cancer [10].

Frequently, patients with gastric cancer present with large, unresectable tumours at the time of diagnosis. For these patients, treatment is palliative and, in most cases, options are limited to systemic chemotherapy and supportive care. While conventional cytotoxic chemotherapy can improve survival compared to best supportive care [11], no single agent or combination has become accepted as the gold standard. A recent meta-analysis showed that combination regimens achieve better survival outcomes than 5-FU monotherapy and that regimens containing 5-FU, anthracyclines and cisplatin are the most effective [11]. Cisplatin–5-FU (CF) and ECF have been used as reference regimens for regulatory purposes because they have been widely investigated in clinical studies and have demonstrated favourable survival outcomes [12–20] (Fig. 1).

The introduction of a new generation of cytotoxic agents (docetaxel [Taxotere®], oxaliplatin [Eloxatin®], irinotecan, capecitabine and S-1) has renewed hope for more effective and better tolerated chemotherapy regimens. One of the most promising of these new agents is docetaxel, which has demonstrated encouraging activity both as monotherapy and in combination with conventional drugs. The recent TAX

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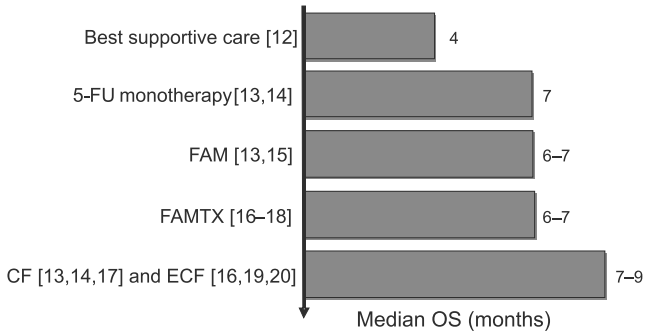

Fig. 1. Median overall survival (OS) in advanced gastric cancer with conventional chemotherapeutic regimens. 5-FU, 5-fluorouracil; CF, Cisplatin–5-FU; ECF, Epirubicin–cisplatin–5-FU; FAM, 5-FU–doxorubicin–mitomycin-C; FAMTX, 5-FU–doxorubicin–methotrexate.

325 and SAKK 42/99 studies established the docetaxel–cisplatin–5-FU (TCF) triplet as a new first-line reference therapy in advanced gastric cancer [21,22]. In the large Phase III TAX 325 study, TCF demonstrated significantly improved efficacy compared to CF (median time to progression [primary endpoint]: 5.6 vs. 3.7 months, respectively [$P = 0.0004$]; median OS: 9.2 vs. 8.6 months, respectively [$P = 0.02$]; 2-year survival 18 vs. 9%, respectively), whilst also preserving patients' quality of life [22,23]. Although the toxicity profile of TCF is not insignificant, toxicities can be managed with appropriate interventions and seem acceptable in relation to the potential benefits of treatment. In particular, primary G-CSF prophylaxis is recommended to prevent febrile neutropenia, in line with new practice guidelines [24–26] that advocate its use in conjunction with chemotherapy regimens associated with a >20% risk.

TCF clearly represents a significant step forward in gastric cancer chemotherapy, but there is still room for improvement, in terms of both efficacy and toxicity. Studies are therefore looking at ways in which docetaxel-based chemotherapy may be improved. Experimental approaches include modification of the TCF dosing schedule and the use of different platinum and/or fluoropyrimidine agents. The recently completed Phase III REAL-2 study showed that oxaliplatin and capecitabine are viable alternatives to cisplatin and continuously infused 5-FU, respectively, and confer benefits in terms of tolerability (oxaliplatin) and convenience (capecitabine) [27]. Further planned and ongoing studies will investigate combinations of the novel cytotoxic agents with docetaxel (e.g., docetaxel–oxaliplatin, docetaxel–oxaliplatin–5-FU and docetaxel–oxaliplatin–capecitabine). Once the optimal cytotoxic backbone has been established, molecularly targeted biological therapies have the potential to improve efficacy further. As well as benefiting patients with advanced gastric cancer, it is hoped that the new cytotoxics and combination regimens will one day prove beneficial in the adjuvant and neoadjuvant settings.

This proceedings supplement provides an insightful and informative review of the evolution of docetaxel-containing chemotherapy for advanced gastric cancer, focusing on past, present and future studies aimed at establishing the most favourable docetaxel-based regimen.

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