Future strategies and adjuvant treatment of gastric cancer

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The most recent meta-analyses of adjuvant chemotherapy in resected gastric cancer suggest that systemic treatment may achieve a small, but statistically significant and probably clinically relevant, reduction in risk of death. However, this still needs confirmation in a large, prospective, well-designed phase III study. The recent Intergroup 0116 study, conducted in USA, of combined post-operative chemoradiotherapy demonstrated significantly improved disease-free and overall 5-year survival compared with an observation-only arm. However, 54% of patients appeared to have had suboptimal surgery. The fact that adjuvant therapy reduced locoregional (and not distant) relapse suggests that its benefit may lie in compensating for inadequate dissection. Combined modality therapy was associated with moderate toxicity, but a high requirement for changes in radiation planning. Therefore, the role and feasibility of adjuvant radiotherapy needs to be confirmed in patients operated on in Western Europe. Several approaches to the development of early systemic therapy in gastric cancer are being pursued. These include the evaluation of cisplatin-based adjuvant regimens, the use of neoadjuvant treatment, the incorporation into adjuvant and neoadjuvant regimens of newer cytotoxics such as docetaxel and irinotecan, and the assessment of novel, molecularly targeted agents such as the epidermal growth factor receptor and angiogenesis inhibitors.

Introduction

In cancer of the stomach and distal esophagus, surgical resection remains the primary treatment. Although stage I–IV M0 gastric carcinoma is potentially curable, there is considerable debate about the most appropriate procedure to undertake, and, in particular, whether a D2 resection confers survival benefit or results simply in more accurate pathological staging [1–7]. These issues are reviewed by Alberts et al. elsewhere in this volume [7].

Irrespective of the operation performed, there is a high recurrence rate following surgery. Even with stage II gastric cancer, the majority of patients will relapse and die of their disease. There is thus a clear rationale for adjuvant therapy aimed at eradicating micrometastases.

Meta-analyses of adjuvant chemotherapy in gastric cancer

In 1993, Hermans et al. [8] published a meta-analysis of data from 2096 patients involved in 11 randomized trials of adjuvant chemotherapy, predominantly 5-fluorouracil (5-FU) based, that had been conducted over the previous decade. The overall 0.88 odds ratio for death in treated patients was not significant [95% confidence interval (CI) 0.78–1.08]. The study therefore concluded that postoperative chemotherapy could not be considered standard treatment.

A year later, Hermans and Benekamp [9] published a letter qualifying their previous analysis. The inclusion of 318 patients from two trials that had erroneously been omitted reduced the odds ratio of death in treated patients to 0.82, which then became significant (95% CI 0.68–0.98). It was concluded that there was evidence of a benefit of adjuvant chemotherapy, but that the evidence was insufficient to make such treatment a standard of care.

In 1999, Earle and Maroun [10] reported a meta-analysis of 13 randomized trials conducted outside Asia and published between 1980 and 1996. Among these 13 trials, the adjuvant treatment consisted of a 5-FU + anthracycline-containing regimen in six, and seven other regimens contained 5-FU and/or mitomycin C and/or a nitrosourea. A total of 1990 patients were included. This demonstrated an odds ratio for death of 0.80 in treated patients (95% CI 0.66–0.97), representing an absolute reduction in death rate of 4%. The benefit in node-positive patients was larger than in those who were node negative. The conclusion was that adjuvant chemotherapy may produce a small, but significant, survival benefit.

More recently, a third meta-analysis was conducted by Mari et al. [11] in Milan. This analysis included 20 studies undertaken between 1983 and 1999: in seven the adjuvant treatment consisted of a 5-FU + anthracycline-containing regimen, and 13 other regimens contained 5-FU and/or mitomycin C and/or a nitrosourea. Data from the 3568 patients analyzed showed a hazard ratio of death of 0.82 (95% CI 0.75–0.89; P <0.001). This represented an 18% reduction in the relative risk of death. The reduction in risk of death was no greater after polychemotherapy regimens that included an anthracycline than after treatment with those that did not.

The most recent meta-analysis is that of Gianni et al. [12]. This study (which used strict selection criteria) analyzed data from 2913 patients enrolled in 17 randomized trials (including those conducted in Asia) that had been published over the period 1981–1999. A statistically significant reduction in the risk of death was confirmed, the odds ratio in treated patients being 0.72 (95% CI 0.62–0.84; P <0.001).
The 0116 study of adjuvant chemoradiotherapy

Findings over the last 15 years have suggested that a combination of radiotherapy with chemotherapy can result in the apparent cure of small amounts of residual or recurrent disease [13–16]. In esophageal cancer, this approach has led to prolongation of disease-free survival. Encouraged by these data, the US Intergroup 0116 study evaluated the effects of combining 5-FU/leucovorin (5-FU/LV) with radiation in patients with resected stage IB–IV gastric adenocarcinoma [17].

Following surgery, 603 patients were randomized to one of two groups. These consisted of an observational control arm and an interventional arm in which patients received a course of 5-FU/LV with radiation in patients with resected stage IB–IV gastric adenocarcinoma [17].

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The local relapse rate was 19% in the chemoradiotherapy arm and 29% among control patients. There was no difference between groups in the risk of distant metastases. This may be explained by the nature of the surgery performed. Fully 54% of surgical procedures (based on 551 cases) involved less than a D1 dissection (Table 2). This would generally be judged inadequate. It is therefore possible that chemoradiotherapy had benefit only because it compensated for the effects of suboptimal surgery.

Future strategies

Based on the data reviewed above, it would be reasonable to conclude that the body of evidence for the efficacy of adjuvant chemotherapy has changed since 1993. Recent meta-analyses suggest that post-operative systemic treatment may confer a small, but probably clinically significant, improvement in survival. However, this still needs confirmation in a large, prospective, well-designed phase III study. The role of additional radiotherapy has been demonstrated in a large randomized US trial; however, the efficacy and feasibility of post-operative chemoradiotherapy needs to be confirmed in patients operated on in Western Europe.

Three inter-related strategies for the further development of early systemic treatment in gastric cancer can be identified.

Cisplatin-based adjuvant regimens

First is the evaluation of cisplatin-based adjuvant regimens. Three such studies have already been closed to accrual. These are the Italian studies comparing surgery alone against surgery followed by four cycles of PELF (cisplatin, etoposide, leucovorin, 5-fluorouracil; FU, 5-fluorouracil; LV, leucovorin; ECF, epirubicin, cisplatin, 5-fluorouracil).

Table 1. SWOG 9008/INT 0116: survival [17]

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<thead>
<tr>
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<th>Surgery</th>
<th>Surgery and chemo-radiotherapy</th>
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<tr>
<td>Median disease-free survival (months)</td>
<td>19</td>
<td>30 &lt;0.001</td>
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<tr>
<td>Median survival (months)</td>
<td>27</td>
<td>36 0.005</td>
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Figure 1. SWOG 9008/INT 0116: study design [17].

Table 2. SWOG 9008/INT 0116: surgical procedures (551 cases) [17]

<table>
<thead>
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<th>Surgical procedure</th>
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<tr>
<td>&lt;D1</td>
<td>54</td>
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<tr>
<td>D1</td>
<td>36</td>
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<td>D2</td>
<td>10</td>
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Figure 2. Cisplatin-based adjuvant chemotherapy (closed studies). PELF, cisplatin, etoposide, leucovorin, 5-fluorouracil; FU, 5-fluorouracil; LV, leucovorin; ECF, epirubicin, cisplatin, 5-fluorouracil.
study is comparing surgery alone versus three cycles of ECF (epirubicin, cisplatin, 5-FU) followed by surgery, and then three more adjuvant ECF cycles.

Neoadjuvant therapy

The MAGIC trial therefore has a neoadjuvant element, and the second approach to early treatment is indeed to assess the role of pre-operative chemotherapy. This approach has a potential advantage in that patients are generally better able to tolerate cytotoxics before their operation. In the EORTC 40954 study, patients will be randomized either to surgery or to surgery preceded by cisplatin/5-FU/LV (Figure 3). In the French FNCLCC trial, the design is the same, but the neoadjuvant regimen is with cisplatin plus 5-FU alone. The Swiss SAKK study is interesting because it compares the neoadjuvant approach against the adjuvant strategy. Patients will receive the TCF combination of docetaxel, cisplatin and 5-FU, either before or after surgery.

New agents

The SAKK study also breaks new ground in that it uses the third strategy of incorporating a new cytotoxic into an established regimen. This approach is also being adopted in the Italian ITMO trial in which surgery is followed either by adjuvant mitomycin C × 6 or by sequential treatment with three cycles of irinotecan/5-FU/LV and three cycles of docetaxel/cisplatin. A similar combination of irinotecan and docetaxel is likely to form part of a forthcoming Italian Intergroup study.

Novel agents such as the epidermal growth factor receptor, angiogenesis inhibitors and others, which attack specific molecular targets underlying malignancy, should also be assessed in gastric cancer, as they are in other tumor types.

Finally, the ability to tailor treatment to patients most at risk of relapse may be aided by increased understanding of aspects of tumor behavior and biology that predict outcome. Among factors potentially predictive of the efficacy of adjuvant treatment are thymidilate synthase, topo-1, ERCC-1, microsatellite instability and epidermal growth factor.

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References
