Chemoradiotherapy as adjuvant treatment of gastric cancer

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Historically, radiotherapy has been occasionally used in the treatment of gastric cancer. More recently, the results of INT-0116 trial have shown an improvement of disease-free and overall survival by chemoradiation with a significant impact on the management of this tumor. Based on these data, there has been an increasing interest in radiotherapy and its association with chemotherapy for patients with locoregional disease as a part of an adjuvant treatment after surgery in high-risk patients. However, many questions remain to evaluate; first of all the toxicity of this approach and its efficacy after adequate surgery.

Introduction

Worldwide, gastric cancer is the fifth most common malignancy and the second leading cause of cancer death. A significant geographic variation exists, with high-risk areas including Japan, Central and South America, and Eastern Asia and low-risk areas including Kuwait, Israel, and the United States [1, 2].

According to the Surveillance, Epidemiology, and End Results database, 5-year survival rate for all gastric cancer patients treated in the United States from 1995 to 2001 was 23.2%. This represents an improvement from 15.3% respect to the period from 1974 to 1976. As expected, patients with localized disease have a higher 5-year survival rate (59%) compared to patients with regional (21.9%) or distant metastases (3.1%). Unfortunately, only 25%–40% of the patients have localized disease at diagnosis [3].

Outcome for patients in high-risk countries such as Japan are generally better than outcomes in low-incidence countries. This variation is likely due to earlier diagnosis (due to aggressive screening programs) and greater clinical experience in high-risk countries, as well as differences in the etiology and biology of tumors in high versus low countries. The relative contributions of these factors to outcome and the implication for therapeutic decisions remain ill defined [4].

Surgical resection of the primary tumor and regional lymph nodes is the treatment of choice for gastric cancer. Several prospective randomized trials have assessed the role of D1 (includes perigastric lymph nodes along the lesser and the greater curvature) versus D2 (includes lymph nodes along the left gastric artery, the common hepatic artery, the celiac trunk, the splenic hilum, and the splenic artery) resection in the management of gastric cancer and they did not show any advantage in terms of overall survival (OS) in favor of extended surgery [5–8]. Of note, Maruyama et al. [9] reported an improvement in 5-year OS from 20.3% with D0 dissection to 41.2% with D1 dissection to 63.8% with D2 dissection.

Unfortunately, >50% of the patients will have locoregional recurrence after receiving curative resection. This evidence supports the need for optimal surgery and also for the evaluation of complementary strategies aiming at decreasing local relapse as well as distant metastasis.

The role of chemotherapy (CT) as adjuvant treatment is controversial. Three randomized trials and a meta-analysis concluded that postoperative CT did not add a survival benefit to surgery [10–13]. Also, our trial in which Etoposide, l-leucovorin and fluorouracil (ELF) regimen was compared to surgery alone did not show a relevant advantage in terms of OS for CT-treated patients [14].

The MAGIC trial demonstrated an improvement in OS and disease-free survival when epirubicin, cisplatin, and 5-FU are added before and after surgery; 5-year OS was improved from 23% to 36% (P = 0.009) [15]. Although this encouraging results, only adequately powered prospective randomized trial could evaluate this issue.

Adjuvant radiotherapy alone

The role of radiation therapy (RT) alone as adjuvant treatment was reported in one randomized trial in which 145 patients received surgery alone, 138 postoperative CT (mitomycin C, adriamycin, and 5-FU), and 153 postoperative RT. No survival difference was reported, but RT offered an advantage in terms of reduction in local recurrence (27% with surgery alone versus 10% with surgery and RT). Forty percent of the patients had gross or microscopic residual disease following surgery and
24% of the patients on radiation arm did not received any RT [16].

**adjuvant chemoradiotherapy**

The importance of RT combined with CT in the adjuvant setting was first evaluated by the Mayo Clinic study that randomized 62 patients to surgery versus surgery plus rate for patients randomized to adjuvant CT and RT was 23% compared to 4% for patients who did not receive adjuvant therapy, evaluating this data by actual treatment received these benefits were not statistically significant. Although local control favored the chemoRT arm, it did not reach the statistical difference [17].

The largest trail which evaluated the role of chemorRT as adjuvant treatment was the U.S. Intergroup 0116. In this study, 556 patients with resected adenocarcinoma of the stomach or gastroesophageal junction were randomized to surgery alone or plus postoperative chemorRT. The adjuvant treatment consisted of 425 mg/mq 5-FU (bolus infusion) per day plus 20 mg/mq of leucovorin (LV) for 5 days, followed by 45 Gy in 25 fractions of 1.8 Gy >5 weeks with bolus 5-FU and LV during the first and last week of RT. Two cycles of 5-FU/LV followed RT 4 weeks later. Surgical margins required to be negative. The survival at 3 years was 50% versus 40% in favor of patients treated with postoperative chemorRT. After 5 years of follow-up, compared with surgery alone, the OS was improved by 11.6% (28.4% versus 40%; P < 0.001) and the relapse-free survival was increased from 25% to 31% in favor of patients treated with postoperative chemorRT. Local regional relapse was decreased from 29% to 19%. Toxicity was significantly higher with chemoradiation; the three-quarter of patients experienced grade 3/4 toxicity, and the 17% of patients were unable to complete the treatment due to toxic effects. Treatment-related mortality was low (1% in the chemoradiation arm versus 0% in the surgery arm alone) [18].

Although this is the only trail which clearly demonstrated the advantage for chemoradiation treatment after surgery, it is to note that the CT used for this study is not considered the more active in gastric cancer and also that the benefit are clearly evident when a adequate surgery, such as D2 dissection, has been performed.

In 2005, a phase II study conducted by the AIO/ARO/ACO was published with the aim of developing novel regimen for adjuvant chemoradiation in cancer patients undergoing potentially curative resection. Eighty-six patients were randomized to receive 5-FU/folinic acid/cisplatin with or without paclitaxel. Radiation with 45 Gy plus concomitantly applied 5-FU 225 mg/mq/24 h was scheduled in between the two cycle of CT. Both chemoradiation regimen appears feasible with an acceptable toxicity represented by granulocytopenia, anorexia, nausea and diarrhea. The projected 2-year progression-free survival was 64% (95% CI 56% to 68%) for nonpaclitaxel arm and 61% (95 CI 42% to 78%) for paclitaxel-containing arm. The authors concluded that treatment should be given in experienced centers in order to avoid unnecessary toxicity [19].

Advanced gastric cancer remains incurable, and patients have a median survival of 6–9 months. While CT can prolong survival and improve quality of life when compared with best supportive care alone, no one agent or combination regimen has become accepted as the standard of treatment [20, 21]. Among the single agents with proven activity in the first-line setting are 5-FU, cisplatin, etoposide, irinotecan, mitomycin C, paclitaxel, 5-Fluorouracil and uracil/tegafur. With these agents, response rates (RRs) ranging from 14% to 44% have been reported. 5-FU, cisplatin, paclitaxel and irinotecan have also been used as single agents second line, achieving RRs of 12% to 26% [22, 23].

Different regimens have been tested in advanced gastric cancer patients: to date, some second-generation regimens, such as weekly platinum, epirubicin, LV, 5-fluorouracil and ECF (epirubicin, cisplatin, 5-fluorouracil), have produced high-objective RRs of >50% [24, 25] and, in one randomized phase III trial, ECF was demonstrated to be superior to the traditional fluorouracil, adriamycin, high-dose methotrexate, both in terms of overall RR and median OS [26]. Unfortunately, about half of the patients treated in first-line are unresponsive.

While prognosis of these patients is poor, RT with or without CT sometimes results in long-term survival (5-year survival of 5%–15%). Most phase III trials for unresectable or residual gastric cancer show an advantage for combined modality.

When RT alone is compared to chemoradiation, the OS and the residual disease after resection favored the combination arm [27, 28].

A study by GITSG randomized 90 patients to received RT plus 5-FU followed a maintenance 5-FU/MeCCNU or 5-FU/ MeCCNU alone. The RT consisted of 50 Gy given in a split course. Radiation and CT resulted in a statistically significant improvement in 4-year survival compared with CT alone (18% versus 6%) [29].

The treatment of gastric cancer has improved modestly over time. RT has a role in adjuvant setting improving the OS and the local control of the disease and also in the unresectable cancer which provides effective palliation either alone or in combination with CT. These encouraging results have to be confirmed by larger trials.

**references**