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EDITORIAL – GASTROINTESTINAL ONCOLOGY

Neoadjuvant Chemotherapy for Gastric Cancer: What are we Trying to Accomplish?

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Gastric cancer remains the second leading cause of cancer death in the world and is the most common cancer in Japan.[1] Although surgery is the mainstay of curative treatment, even after complete resection, more than half of patients with locally advanced tumors recur, and fewer than 40 % survive beyond 3 years. Accordingly, investigators around the world have explored a variety of adjuvant and neoadjuvant multimodality treatment approaches to this disease. In North America, the standard approach has long been upfront surgery followed by adjuvant chemoradiotherapy based on the findings of the Intergroup 0116 trial, which showed that postoperative 5-fluorouracil (5-FU)/leucovorin-based chemoradiation increases overall survival compared with surgery alone.[2] However, another standard of care for resectable gastric cancer in North America and Europe emerged with the publication of the MAGIC trial a few years later and the FNCLCC/FFCD multicenter phase III trial a few years after that. The MAGIC trial reported an improvement in overall survival with perioperative epirubicin, cisplatin, and 5-FU (ECF) compared with surgery alone, and the FNCLCC/FFCD trial showed an improved R0 resection rate and survival with perioperative 5-FU and cisplatin.[3,4]

In Japan, the standard approach to patients with T2 N^+ or T3 gastric cancers is upfront surgery with D2 lymphadenectomy followed by 1 year of S-1 chemotherapy, based on the ACTS trial, a large phase III trial demonstrating a significant survival benefit to this approach over surgery alone.[5] Nonetheless, even with adjuvant S-1 chemotherapy, the prognosis of Japanese patients with stage III gastric cancers in particular remains unsatisfactory, and so investigators in Japan recently have been evaluating various regimens of neoadjuvant chemotherapy followed by extended surgery in multiple phase II trials, including one to three courses of S-1 and cisplatin, two to three courses of irinotecan and cisplatin, and two to four courses of paclitaxel and cisplatin.[6–9] The optimal duration and regimen of neoadjuvant chemotherapy has not yet been established.

In this issue, Yoshikawa et al.[10] report the early results of the COMPASS trial, a randomized, multi-institutional phase II trial comparing two and four courses of neoadjuvant S-1/cisplatin (SC) and paclitaxel/cisplatin (PC), followed by surgery and postoperative S-1 chemotherapy, for macroscopically resectable locally advanced gastric cancer. A total of 83 patients were enrolled based on power calculations assuming a 10 % absolute improvement in 3-year overall survival in the four-course PC arm. The primary endpoint of the study is the 3-year overall survival rate, and the secondary endpoints include the clinical and pathologic response rates, chemotherapy-related toxicities, R0 resection rates, and surgical morbidity and mortality. This report summarizes only the early outcomes—that is, these secondary endpoints—because the data are not mature enough to report on the survival outcomes. Unfortunately, the eligibility criteria for this trial included patients with "resectable minimal peritoneal metastases confirmed by laparoscopy," which is considered M1 (metastatic) disease in all staging systems and not "locally advanced" disease. In fact, 13 (16 %) of the 83 enrolled patients had M1 disease on initial staging as manifested by either gross peritoneal metastases ($n = 5$) or positive peritoneal cytology ($n = 8$) and thus did not have a realistic chance for cure at the outset. Accordingly, the 3-year overall survival rates for this trial are likely to be low, and

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given the small numbers of patients in each treatment arm, none of the regimens are likely to demonstrate a significant survival benefit. As the authors point out, this will require a much larger phase III trial, choosing the regimen showing the greatest activity based on the secondary endpoints of this phase II trial.

In terms of the tolerability of the regimens studied in this trial, the toxicities in all four arms were quite modest and were understandably higher in the four-course regimens compared with the two-course regimens. The rates of completion of all intended courses of neoadjuvant chemotherapy ranged from only 60 % in arm B (4 courses of SC) to 100 % in arm C (2 courses of PC), and the overall completion rate was a reasonable 83 % (69/83). This compares favorably with the completion rates of the preoperative courses in the MAGIC (86 %) and FNCLCC/FFCD (87 %) trials. Only six (7 %) patients did not proceed to surgery due to early disease progression on chemotherapy; this is a fairly low percentage given the biologic aggressiveness of the gastric cancers included in this study. Furthermore, the surgical morbidity rates were remarkably low in all four treatment arms, especially in light of the fact that a significant percentage of patients underwent extended surgical resections.

In terms of the effectiveness of the various regimens, there was no clear winner; however, there were higher pathologic complete response (CR) rates (10 vs. 0 %) in the four-course arms compared to the two-course arms. The authors claim that a 10 % pathologic CR rate is "high," and indeed for neoadjuvant regimens of chemotherapy alone, a 10 % pathologic CR rate is reasonable, but I would hesitate to say it is "high." If a high pathologic CR rate is a primary goal of any neoadjuvant regimen, and indeed it is a worthy goal based on the knowledge that the degree of pathologic tumor response (and not clinical parameters) determines outcome, then perhaps neoadjuvant chemoradiotherapy regimens, which engender much higher pathologic CR rates of 20–30 %, are more appropriate for locally advanced gastric cancer patients.[11–13] The R0 resection rates ranged from 67 % in arm C to 81 % in arm A, for an overall rate of 75 %, which is better than that reported in the MAGIC trial (69 %) but worse than that reported in the FNCLCC/FFCD trial (84 %). Of course, the R0 resection rate would have been significantly higher if patients with peritoneal metastases were excluded from this trial, as two such patients underwent palliative bypasses, five underwent R2 resections, and eight (all with positive cytology) R1 resections.

In summary, this phase II trial shows that four courses of neoadjuvant chemotherapy is probably better than two in terms of tumor response and that four courses can be administered safely in terms of toxicity and similar R0 resection rates with the regimens studied. Ultimately, the real question is what are we trying to accomplish with the administration of chemotherapy before surgery for gastric cancer? As physicians, our obligations are to help people be cured more often, live longer, and/or feel better. In any adjuvant setting, our goal is the first of these three obligations: to cure people more often. Therefore, when we are designing clinical trials of neoadjuvant therapy in gastric cancer, the goal is to cure more patients. So, are neoadjuvant trials attempting to move all of the systemic therapy upfront, before surgery, because we know that preoperative chemotherapy is better tolerated than postoperative chemotherapy, and in so doing ensure that more patients actually receive systemic therapy and its associated 10 % survival benefit? Or are we trying to generate more R0 resections, converting patients with unresectable disease to resectable disease, and in so doing offer them a chance for cure?

The major flaw with this phase II study and others like it is that the study design is unlikely to help answer either of these questions. By effectively mandating that all patients also receive 6–12 months of postoperative S-1 chemotherapy, it is unlikely that two or four cycles of preoperative doublet therapy will move the survival curve in a positive direction, and it will definitely not make patients feel better. By including patients with metastatic disease to the peritoneum and by choosing therapies with little differences between them and with fairly low pathologic response rates, this trial fails to demonstrate support for the other major rationale for neoadjuvant chemotherapy—increased rates of potentially curative, R0 resections. Hopefully, those designing future trials of neoadjuvant chemotherapies for gastric cancer will first and foremost ask the question, "What are we trying to accomplish with this therapy?" and then set forth to design a trial that will in fact answer whether that goal was achieved.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer.* 2010;127:2893–2917.
2. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med.* 2001;345:725–730.
3. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med.* 2006;355:11–20.
4. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol.* 2011;29:1715–1721.
5. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer

with S-1, an oral fluoropyrimidine. *N Engl J Med.* 2007;357:1810–2180.
6. Inoue K, Nakane Y, Kogire M, Fujitani K, Kimura Y, Imamura H, et al. Phase II trial of preoperative S-1 plus cisplatin followed by surgery for initially unresectable locally advanced gastric cancer. *Eur J Surg Oncol.* 2012;38:143–149.
7. Yoshikawa T, Omura K, Kobayashi O, Nashimoto A, Takabayashi A, Yamada T, et al. A phase II study of preoperative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study). *Eur J Surg Oncol.* 2010;36:546–551.
8. Yoshikawa T, Sasako M, Yamamoto S, et al. Phase II study of neoadjuvant chemotherapy and extended surgery for locally advanced gastric cancer. *Br J Surg.* 2009;96:1015–1022.
9. Tsuburaya A, Nagata N, Cho H, Hirabayashi N, Kobayashi M, Kojima H, et al. Phase II trial of paclitaxel and cisplatin as neoadjuvant chemotherapy for locally advanced gastric cancer. *Cancer Chemother Pharmacol.* 2013;71:1309–1314.
10. Yoshikawa T, Tanabe K, Nishikawa K, Ito Y, Matsui T, Kimura Y, et al. Induction of a pathological complete repsonse by four courses of neoadjuvant chemotherapy for gastric cancer: early results of the randomized phase II, COMPASS trial. *Ann Surg Oncol.* 2013.
11. Ajani JA, Mansfield PF, Crane CH, Wu TT, Lunagomez S, Lynch PM, et al. Paclitaxel-based chemoradiotherapy in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. *J Clin Oncol.* 2005;23:1237–1244.
12. Ajani JA, Mansfield PF, Janjan N, Morris J, Pisters PW, Lynch PM, et al. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. *J Clin Oncol.* 2004;22:2774–2780.
13. Ajani JA, Winter K, Okawara GS, Donohue JH, Pisters PW, Crane CH, et al. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. *J Clin Oncol.* 2006;24:3953–3958.