Re: Adjuvant Treatment of High-Risk, Radically Resected Gastric Cancer Patients with 5-Fluorouracil, Leucovorin, Cisplatin, and Epidoxorubicin in a Randomized Controlled Trial

We read with great interest the recent article by Cascinu et al. (1). The authors compared an 8-week intensive platinum, epirubicin, leucovorin, fluorouracil regimen (PELFw) with a much less intensive "control" 5-fluorouracil/leucovorin regimen in patients with radically resected locally advanced gastric cancer (1) and reported no difference in terms of overall survival and disease-free survival. The negative results of this trial could be due to several reasons, including the lack of new drugs in the experimental arm and inadequate sample size. Nevertheless, the take-home message of the authors is that intensive adjuvant chemotherapy is ineffective and uselessly toxic, and, therefore, they suggest a move toward a preoperative setting of investigation.

Other trials have revealed the problems of postoperative intensive chemotherapy; among them, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial (2) showed that perioperative

chemotherapy with ECF (epirubicin, cisplatin, 5-fluorouracil) improves survival compared with surgery alone, although we cannot know if this advantage derives from preoperative or postoperative treatment or both. Based on the report of Cascinu et al. (1), we cannot know if the PELFw chemotherapy regimen is equally effective as the 5-fluorouracil/leucovorin regimen or if both are totally ineffective, given the lack of an observation-only arm. We agree with the authors that the unexpectedly high survival rate observed could be due to adequate nodal dissection, as previously shown in the Italian Trials of Medical Oncology trial (3), where the surgery-alone arm produced a 48% 5-year survival rate after D2-dissection.

Another important message from the study of Cascinu et al. (1) is the uselessness of radiotherapy after high-quality surgery, as suggested by the low local recurrence rate. This is a further demonstration that the American standard option of adjuvant chemoradiotherapy, derived from the study of Macdonald et al. (4), is not applicable to the Italian reality.

The authors' conclusions confirm our experimental approach of some years ago, when we designed a randomized trial comparing preoperative versus postoperative therapy with a taxotere/cisplatin/5-fluorouracil combination in radically resected locally advanced gastric cancer patients. This study, born from a cooperation between the Swiss Group for Cancer Research and the European Institute of Oncology in Milan, found that preoperative therapy was better tolerated and more feasible compared with postoperative therapy (unpublished data) but did not furnish useful information on relative efficacy because it was prematurely stopped due to slow accrual. Neoadjuvant studies are much more difficult than adjuvant ones, requiring a high level of multidisciplinary management. This is demonstrated by the fact that the conclusions from the trial of Cascinu et al. (1) were not applied even by the same investigative institutions involved in the trial. Indeed, many of them preferred to participate in an ongoing two-arm adjuvant Italian intergroup trial with a large accrual goal of 1100 patients to obtain statistical evidence in favor of an intensive new drug postoperative chemotherapy that was missing in the PELFw trial. In conclusion, given the increased investigative focus toward a preoperative setting in resectable gastric cancer, the time is ripe to conduct a large, international multicentric randomized phase III trial of a new-drug neoadjuvant chemotherapy regimen involving all major reference groups.

NICOLA FAZIO
ROBERTO BIFFI
GIUSEPPE CURIGLIANO
KATIA LORIZZO
MARIA GIULIA ZAMPINO
FILIPPO DE BRAUD
ANTONIO CHIAPPA
ARNAUD ROTH
ARON GOLDHIRSCH

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Notes

Affiliations of authors: European Institute of Oncology, Milan, Italy (NF, RB, GC, KL, MGZ, FDB, AC, AG); Geneva University Hospital, Geneva, Switzerland (AR).

Correspondence to: Nicola Fazio, MD, Department of Medicine, Division of Medical Oncology, European Institute of Oncology, Via Ripamonti 435, 20141 Milano, Italy (e-mail: nicola.fazio@ieo.it).

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Response

We have read with interest the correspondence regarding the role of pre- and postoperative chemotherapy in gastric cancer in response to our recent report of an intensive adjuvant chemotherapy in gastric cancer (1). The idea that preoperative chemotherapy may be a more suitable treatment approach for locally advanced gastric cancer is, in fact, now widely shared. Our data, along with those deriving from the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, seem to indicate that a better tolerability profile of a perioperative treatment approach is responsible, at least in part, for the improved outcome (2). However, when our trial was designed, about 10 years ago, this was not a widespread opinion. At about the same time, the Swiss Group designed a clinical trial comparing a preoperative versus a postoperative chemotherapeutic approach with a regimen that included docetaxel. Unfortunately, at that time definitive data about activity and tolerability of docetaxel as a treatment for gastric cancer were largely lacking, making the trial design somewhat problematic. In fact, it was only last year that a randomized trial clarified the role of docetaxel in gastric cancer (3). Furthermore, our trial was designed before the MAGIC trial, when data from published literature seemed to largely support a postoperative approach (4). However, we believe that even positive results obtained with a preoperative approach may require cautious interpretation. It is important to consider that the 5-year survival in the MAGIC trial was only 23% in the control arm and 36% in the treatment arm, whereas the 5-year survival approached 50% in the control arms, both in our study and in the Italian Trials of Medical Oncology trial (5). Once again, potentially positive results may depend on the quality of surgery, and adjuvant treatment may be useful only in patients not likely to receive an optimal surgical treatment. We note that a similar interpretation was applied to results obtained with adjuvant radiotherapy in the trial of MacDonald et al. (6).

Finally, Fazio et al. seem to question the choice by the Italian Intergroup to carry out a new postoperative therapy with a chemotherapy including 5-fluorouracil, cisplatin, irinotecan, and docetaxel in a sequential manner. Although we agree with most of the comments and concerns raised in the letter, we think that this new trial is exploring a novel treatment strategy in gastric cancer by allowing the administration of several drugs but, at the same time, limiting their toxic effects. The sequential multidrug approach is biologically different from the intensive approach evaluated in our study and could not be explored with a

neoadjuvant design. Preliminary safety data from this trial are encouraging. If this approach also fails to show any advantage, preoperative chemotherapy would be the only viable treatment strategy to pursue in the future.

STEFANO CASCINU
MARIO SCARTOZZI
CARLO BARONE
ROBERTO LABIANCA
ARMANDO SANTORO
CARLO CARNAGHI
GIORDANO D. BERETTA
VINCENZO CATALANO
SANDRO BARNI
LUCIANO FRONTINI

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Notes

Affiliations of authors: Clinica di Oncologia Medica, Universita' Politecnica delle Marche, Ancona, Italy (SC, MS); Oncologia Medica, Universita' Cattolica del Sacro Cuore, Policlinico A. Gemelli, Roma, Italy (CB); Oncologia Medica, Azienda Ospedaliera "Ospedali Riuniti di Bergamo," Bergamo, Italy (RL, GDB); Oncologia Medica, Istituto Clinico Humanitas, Milano, Italy (AS, CC); Oncologia Medica, Azienda Ospedaliera S. Salvatore, Pesaro, Italy (VC); Oncologia Medica, Azienda Ospedaliera di Treviglio, Treviglio, Bergamo, Italy (SB); Clinical Trials Unit, GISCAD, Milano, Italy (LF).

Correspondence to: Stefano Cascinu, MD, Clinica di Oncologia Medica, Universita' Politecnica delle Marche, Ospedali Riuniti di Ancona. Via Conca, 60020 Ancona, Italy (e-mail: cascinu@yahoo.com).

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