Editorial

Neoadjuvant chemotherapy for gastric cancer

Kate Young, Anna Minchom, David Cunningham, Ian Chau

Department of Medicine, Royal Marsden Hospital, London and Surrey, UK

Corresponding to: Dr. Ian Chau. Department of Medicine, Royal Marsden Hospital, Downs Road, Sutton, Surrey, United Kingdom. Email: ian.chau@rmh.nhs.uk.

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Surgery remains the cornerstone of curative treatment for gastric cancer (GC). However, randomised controlled trials (RCTs) have established a multi-disciplinary approach in the treatment of resectable GC. Interestingly, trials conducted in different parts of the world have given rise to varying standards of care. Generally, except patients with T1N0 or intramucosal tumour, all patients with resectable GC should be considered for a multi-modality treatment plan, preferably decided by a multi-disciplinary team.

Three treatment strategies are now considered standard treatment options - adjuvant chemotherapy, adjuvant chemoradiation (CRT) and peri-operative chemotherapy. Whereas several studies evaluated the use of neoadjuvant chemotherapy alone in gastric cancer, RCTs that demonstrated a survival benefit utilised both pre-operative and post-operative chemotherapy. Nevertheless, as the delivery of post-operative chemotherapy was generally suboptimal, due to patients' poor tolerance, clinicians often interpreted these studies as proof of concept for neoadjuvant chemotherapy for gastric cancer. Nevertheless one could not clearly separate out the proportional benefit of each treatment component, thus one should not exclude the routine use of post-operative chemotherapy after neoadjuvant chemotherapy.

For peri-operative chemotherapy, two RCTs demonstrated almost identical survival benefit with the use of cisplatin, 5-fluorouracil (5-FU) ± epirubicin resulting in an absolute improvement in 5-year survival of 13%. The MAGIC trial used epirubicin, cisplatin and 5-FU (ECF) (1) whereas the FNLCC ACCORD 07- FFCD 9703 trial utilised cisplatin and 5-FU (FP) (2). Both studies included GC and oesophagogastric junction (OGJ) cancers, therefore this treatment strategy is employed in both GC and OGJ cancers. Oral fluoropyrimidines have been shown to be non-inferior in survival compared to infused 5-FU in advanced GC (3) and they have also been tested in the adjuvant setting in the CLASSIC (4) and ACT-GC trials (5), thus capecitabine is readily used in the peri-operative setting.

To improve on the efficacy of neoadjuvant chemotherapy, two main avenues have been pursued - (I) addition of post-operative CRT and (II) newer drugs such as biologicals. However, one needs to stress the importance of quality control for surgery in the pursuit of better efficacy from neoadjuvant chemotherapy. With D2 dissection, 5-year survival rate in the Japanese ACT-GC study was 61.1% for surgery alone (5) and in the Dutch study this was only 47% (6). Better baseline staging, establishment of high volume surgical centres and incorporation of surgical protocols in current RCTs are supposed to mitigate against poor surgical outcome. It would be interesting to see the adherence to surgical protocols in the current generation of RCTs for pre-operative therapy in gastric cancer. One concerning observation from the recently reported CALGB 80101 (7) was that the survival outcome from the control arm, bolus 5-FU/leucovorin plus radiation, was identical to that of Intergroup 0116 published more than a decade ago (8). Although no details on surgery are available yet for CALGB 80101 study, it appeared that no progress has been made in the last 10 years despite better staging and focus on high volume surgical centres. These factors will all come under close scrutiny with the recently completed UK OEO5 as well as the ongoing UK STO3 and Dutch CRITIC trials.

The addition of post-operative CRT is currently being evaluated in the Dutch CRITIC study where 788 patients will be randomly allocated to either peri-operative epirubicin, cisplatin plus capecitabine (ECC) or pre-operative ECC followed by post-operative CRT. Aside from surgical quality control, radiation quality assurance will also be of importance in this study. Indeed in the recently reported CALGB 80101 study, 15% of the radiotherapy treatment plans were found to contain major deviations (7).

The integration of biologicals is currently being assessed in the UK STO3 study. One thousand and one hundred patients will be randomised to peri-operative ECC ± bevacizumab. Maintenance bevacizumab is given for a further 18 weeks after the completion of post-operative chemotherapy. Some reservations have been made about the likely success of the STO3 study based on the negative overall survival results of the AVAGAST study in advanced gastric cancer (9) as well as the adjuvant trials in colon cancer including NSABP-C08 (10) and AVANT (11) studies. In the AVAGAST study there was a statistically significantly improved radiological response rate and progression free survival with the addition of bevacizumab. This may allow more curative surgery to be performed and this is often cited as the important secondary outcome leading to the success of the MAGIC and the FFCD studies (1,2). Furthermore, the relapse rate after gastric cancer surgery is considerably higher than colon cancer surgery. Potentially there may be more established micrometastatic disease to gain benefit from the use of bevacizumab, more akin to the setting of ovarian cancer after optimal debulking surgery (12,13). Safety results from the first 200 patients recruited into STO3 study did not demonstrate any clinically increased bevacizumab-related toxicities. Perforation rates were similar between the two treatment arms. Cardiac monitoring within the study also alleviated the concern of combined cardiac toxicity of epirubicin and bevacizumab with recovery of cardiac function after cessation of trial drugs (14).

The recent introduction of trastuzumab in metastatic HER2 positive gastric cancer calls for evaluation of HER2 targeted agents in the peri-operative setting (15). Lapatinib, TDM-1 and pertuzumab are other clinically proven HER2 targeted agents in breast cancer. However, recent studies suggested that <15% of resected gastric cancer was indeed HER2 positive. Furthermore, often the magnitude of benefit over standard treatment is less pronounced in the operable compared to the metastatic setting. The implication would potentially be a screening requirement in excess of 5,000 operable gastric cancer patients to recruit into an adequately powered RCT to evaluate HER2 targeted agents. Such trials will likely require multi-national collaboration.

Whereas the traditional TNM staging allows some selection of patients based on pre-treatment characteristics, much more individualised biomarkers are required. This does not necessarily apply to the novel biologicals only and indeed, if possible, this should also be applicable to the standard platinum/fluoropyrimidine that we are currently using for neoadjuvant chemotherapy. Recent genomic profiling of gastric cancer cell lines identified two major intrinsic subtypes: G-INT and G-DIFF (16). This gene signature was then mapped onto two independent cohorts of gastric cancer patients and was found to have prognostic significance with G-DIFF having a poorer survival. More importantly, G-INT was found to be more sensitive to 5-FU and oxaliplatin where G-DIFF was more sensitive to cisplatin. This may pave the road for the future to better select patients for neoadjuvant chemotherapy based on pre-treatment biomarkers.

In view of the poor prognosis after surgery alone and poor tolerance to post-operative therapy, neoadjuvant chemotherapy appears to be an attractive option for gastric cancer. Integration of biologicals and radiotherapy may improve survival further. However, pre-treatment biomarkers, either tissue-based or imaging-based, would be key to identify patients who would benefit most from this treatment strategy.

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