Editorial

Quality of life versus survival benefits in patients with HER-2 negative metastatic gastric cancer: exploration of the randomized trials from the patient's perspective

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Despite the significant advances in diagnosis and therapy of gastric cancer (GC), and well developed screening programmes in countries such as Japan and South Korea, this tumor remains the fifth most common malignancy and the third leading cause of cancer mortality worldwide (1,2). Most of the cases are diagnosed in advanced stages with a 5-year survival rate ranging from 20% to 27% (2,3) and median survival of 6–15 months in metastatic cases (4). Moreover, even in patients with early gastric cancer cancer (EGC), aberrant metastatic behaviour and occurrence of skip metastasis are reported (5-7). Other changes related on the GC are the following: increase proportion of cases located in the upper third of the stomach, especially for young patients (1,5), changing spectrum of the histogenetic pathways (8), and progressive augmentation of the poorly-cohesive/diffuse type carcinomas and neuroendocrine variants (1,3,7-10). All of these characteristics and resistance of GC cells upon most of the target chemotherapic agents increase the therapeutically difficulty.

In the last years, few clinical trials were performed to identify the best therapeutically approach of patients with HER-2 negative advanced GC with distant metastases. The first randomised controlled trial that examined the survival benefit of additional gastrectomy over chemotherapy alone in incurable GC was published in *Lancet Oncology* in January 2016 (11). Fujitani *et al.* (11) performed an open-label, randomised, multicentric phase 3 trial (REGATTA) that taken into account patients from 44 centres or hospitals in Japan, South-Korea, and Singapore, diagnosed with HER-2 negative advanced GC with a single non-curable factor. Patients aged 20–75 years with hepatic, peritoneal, or distant lymph node metastases were randomly assigned to chemotherapy alone (oral S-1 and cisplatin) or gastrectomy followed by chemotherapy. No survival benefits were observed between the two groups, the authors concluding that gastrectomy is not justified for thes patients, except cases with life-threatening complications such bleeding, obstruction, etc. (11).

Other ongoing trial is the GYMSSA trial that, based on the studies showing that complete removal of both the gastric primary and peritoneal metastases combined with intraperitoneal chemotherapy associates improved survival, included patients assigned to gastrectomy with metastasectomy plus systemic chemotherapy *vs.* systemic chemotherapy alone with the FOLFOXIRI regimen (4).

The main weak point of the recently trials is the quality of life of the patients that is not usually taken into account to evaluate the success or failure of a certain intervention, as the main point of result. The trials are mostly concentrated upon the overall survival and progression-free survival (4,10), although some of them include patients with short survival rate. In the REGATTA trial the median overall survival was 16.6 for patients assigned to chemotherapy alone and 14.5 months for those that underwent gastrectomy followed by chemotherapy (11). In the GYMSSA trial the included patients was supposed to have a median survival of 6–11 months (4).

In the REGATTA trial which results have been published

in 2016 (11), we performed a statistical analysis of Table 3 and observed that the following chemotherapy induced adverse effects were more frequent in patients assigned to gastrectomy followed by chemotherapy compared with those receiving chemotherapy alone: grade 3–4 leucopenia (29% *vs.* 12%, P=0.0007), grade 3 anorexia (19% *vs.* 2%, P=0.01), grade 3 nausea (15% *vs.* 5%, P=0.02), grade 1–2 diarrhea (45% *vs.* 22%, P=0.03). On the other hand, grade 1–3 sensory neuropathy was slightly more frequent in the patients receiving chemotherapy alone (26% *vs.* 8%, P=0.05). Based on the fact that anorexia, diarrhea, risk for infections, and the perioperative status significantly affect the quality of life (especially for those with upper-third tumors), and also on the previously reported decreased physical function and increased fatigue and poor body image post-gastrectomy (2), the idea of no performing gastrectomy in these patients can be accepted. However, the patient should choose the best therapeutically approach based on its desire (longer life *vs.* qualitative life). In the REGATTA trial, 41% of the patients refused enrolment and 25% did not receive any explanation of the study (11).

Assessment of the quality of life can be done, in patients with GC, based on the international-validated questionnaires such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Stomach (EORTC QLQ-STO22), mostly used in Europe, the Functional Assessment of Cancer therapy-Gastric (FACT-Ga) that is more disposed in Asia and North America, and the Postgastrectomy Syndrome Assessment Scale-45 (PGSAS-45) recently created by the Japanese researchers (2,12). They include evaluation of physical, psychological, and social aspects but few than 20 representative studies were published till January 2016 (2), based on the use of these questionnaires in the clinical trials that included patients with GC. The main evaluated criteria were diarrhea/constipation, dysphagia, dietary restriction, dumping, indigestion, body weight loss, pain, reflux, anxiety, fatigue, iatrogenic-induced effects, and emotional status (dry mouth, body image, taste problems) (2,12).

In summary, in patients with advanced GC and distant metastases the best therapeutically approach should be established based on a specific questionnaire which results should be evaluated after a detailed discussion with the patient. In metastatic cases with a predicted short overall survival the therapy should be mainly based on the quality of life, not only on the overall survival and progression-free survival. The decision should be based on the Hippocratic Oath principles which paraphrasing can be adapted in the following conclusion: "*Do not harm, do not overtreat, look at the patient in a sympathetic but scientific way, do not play at God, and plan the beginning of a trial conceiving that you can one day be included in your trial*".

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Footnote

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