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Review

Ethical issues related to chemotherapy in patients with gastric cancer

J.K. Triantafillidis[1], G. Peros[2]

SUMMARY

Postoperative chemotherapy and radiation therapy is standard care in high risk patients who had undergone a curative resection of the primary tumor. Best survival results are achieved with three-drug regimens containing FU, an anthracycline, and cisplatin (ECF), although the recently presented REAL-2-trial, demonstrated a significant survival benefit for EOX (epirubicin, oxaliplatin, capecitabine) over ECF. Consequently, chemotherapy could be offered to some proportion of patients with advanced gastric cancer taking into account the results of the available clinical trials. Neo-adjuvant chemotherapy has the ability to downsize gastric tumours. It remains unclear however, how the neoadjuvant therapy may be integrated into the multimodality management of localized gastric cancer. According to recent studies, adjuvant chemotherapy resulted in a significant survival benefit in patients with gastric cancer. However, others did not recommend adjuvant chemotherapy as routine therapy. A lot of case reports with metastatic cancer treated with S-1 plus cisplatin have appeared in the recent literature with promising results. Therefore, such treatment could be offered to some patients with metastatic gastric cancer as a last hope. Patients with peritoneal dissemination should be submitted to chemotherapy after full explanation of the expected results. The use of chemotherapy in patients with linitis plastica remains controversial. Chemotherapy should be offered to patients with gastric cancer at advanced age. Nutrition therapy in advanced gastric cancer might offer improved quality of life especially to those with gastric outlet obstruction despite the associated increased cost. Other parameters related to the decision to give chemotherapy or not to gastric cancer patients are related to the role of patient relatives, the doctors' training and availability, the psychological support of the patient, the doctor's-patient relationships, and the right of the patient to receive the best available medical treatment. These parameters must be taken into account where dealing with a patient with gastric cancer who is a candidate for chemotherapy.

Key words: Gastric cancer, Chemotherapy, Ethics

[1]Department of Gastroenterology "Saint Panteleimon" General Hospital, Nicea, [2]4th Surgical Unit "Attikon", Hospital, University of Athens, Athens, Greece

Author for correspondence:

Professor John K. Triantafillidis, MD, Iera Odos 354, Haidari, Greece, Tel: 0030-210-5819481, Mobile: 6944432917, Fax: 0030-210-5810970, e-mail: jkt@panafonet.gr

INTRODUCTION

Although the incidence of gastric cancer is decreasing, it remains a leading cause of death in the world. Gastric cancer is considered to be a very challenging malignancy given that it presents late, and has complex pathogenetic mechanisms.

Postoperative chemotherapy and radiation therapy is standard care in high risk patients who have undergone a curative resection of the primary tumor. The favourable results obtained with application of different preoperative approaches need to be further explored in the near future. During years we have become witnesses of promising recent results obtained with a number of new agents.[1]

But the question remains: Should chemotherapy be offered to all patients with gastric cancer or do we have to exclude some of them? What are the factors that could influence our decision to apply chemotherapy or not?

In the following discussion we will try to answer these questions the light of recently published data.

ADVANCED GASTRIC CANCER

The most important question that should be answered

from both the scientific and economic point of view is: Should chemotherapy be offered to patients with advanced gastric cancer? It is well established that although responses to chemotherapy have been reported in up to 60% of patients in phase II trials, most patients could develop drug resistance and the median survival of treated patients has been reported to fluctuate between 7 and 9 mo. These results prompted the investigators to evaluate the benefit of chemotherapy in terms of survival and/or quality of life compared with best supportive care alone. Randomized phase III studies, showed a survival advantage in favour of chemotherapy of about 6 mos. It seems therefore that chemotherapy should be offered to patients with metastatic gastric cancer and good general condition.

In a meta-analysis aiming to assess the efficacy and tolerability of chemotherapy in patients with advanced gastric cancer, randomized phase II and III clinical trials on first-line chemotherapy in advanced gastric cancer were analyzed.[2] The analysis of chemotherapy versus best supportive care and combination versus single agent, mainly fluorouracil-based chemotherapy showed significant overall survival regimens benefits in favor of chemotherapy and combination chemotherapy, respectively. In addition, comparisons of FU/cisplatin-containing regimens versus regimens without anthracyclines and FU/anthracycline-containing combinations and versus regimens without cisplatin both demonstrated a significant survival benefit for the three-drug combination. Comparing irinotecan-containing versus nonirinotecan-containing combinations (mainly FU/cisplatin) resulted in a non-significant survival benefit in favor of the irinotecan-containing regimens, but they have never been compared against a three-drug combination. Best survival results are achieved with three-drug regimens containing FU, an anthracycline, and cisplatin. Therefore chemotherapy could be offered to a large proportion of patients with advanced gastric cancer taking into account the above mentioned results. However, results for ECF have been challenged by a recent trial, which demonstrated a significant survival benefit for EOX (epirubicin, oxaliplatin, capecitabine) over ECF.[3]

ADJUVANT CHEMOTHERAPY

Gastric cancer seem to be an ideal setting to test adjuvant cytotoxic regimens, as there are multiple significantly active chemotherapy drugs and combinations that show antitumoral activity in the metastatic disease. However, over the last three decades multiple phase III studies failed to demonstrate a clear improvement in survival, and therefore, this strategy is far from being the standard management following curative surgery.

A meta-analysis published in 2002 showed that adjuvant chemotherapy resulted in a significant survival benefit in patients[4] though the authors suggested that this conclusion should be confirmed in large prospective randomized trials. Nevertheless, others did not recommend adjuvant chemotherapy as routine therapy in this setting.[5]

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant treatment, chemotherapy or chemoradiotherapy, has been tested in small studies. Preoperative chemotherapy may allow to improvement in the R0 rate due to tumour down-staging, and also may contribute to eradication of micrometastasis. At present, neoadjuvant treatment is being tested in locally advanced non-resectable tumours and in those resectable tumours with a high risk of recurrence.

However, it seems that patients with early gastric carcinoma (stages 0 and I) could be over-treated, and among stage II-IV non-metastasic gastric cancers, the response to the preoperative therapy could be unsatisfactory; therefore, some patients could be exposed to unnecessary morbidity, and furthermore, the success of surgical resection could be hampered. In this context, efforts to identify prognostic factors and more active and less toxic preoperative regimens are being sought.

In a relevant study, 503 patients with potentially resectable gastric cancer were randomized to both preoperative and postoperative EFC chemotherapy *versus* surgery alone. EFC regimen consisted of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) administered on day 1, and protracted venous infusion of 5-FU (200 mg/m^2 per d) on days 1 to 21, administered every 3 wk for three cycles before and after surgery. The results demonstrated statistically significant improvement of the study arm in disease-free survival and a strong trend towards better overall survival compared to surgery alone[6]. Although in the study group, the number of patients who underwent surgery was slightly lower the rate of pathological complete response was significantly better in this group and the surgical morbidity and mortality were not compromised. However, it remains unclear how the neoadjuvant therapy may be integrated into the multimodality management of localized gastric cancer. Consequently, ongoing randomized controlled trials are evaluating this issue. According to the results of the UK MAGIC trial, perioperative treatment with ECF (3 cycles prior to and post surgery) results in a significantly reduced risk of death for patients with resectable gastric cancer as compared to surgery alone.[7]

METASTATIC GASTRIC CANCER

The prognosis of patients with metastatic gastric cancer is extremely poor. It has been estimated that fewer than 10% of these patients live more than 24 months. Based on the absence of many randomized clinical trials on metastatic gastric cancer, a large proportion of medical oncologists do not wish to treat such patients. In these cases chemotherapy should only be administered as a palliative modality. However, a lot of case reports with metastatic cancer treated with S-1 plus cisplatin appeared in the recent literature with promising results.[8] Therefore, such a treatment could be offered to patients with metastatic gastric cancer as a last hope after fully informing of the patients and their relatives.

Comparison of chemotherapy and support care treatment was made in patients diagnosed with gastric adenocarcinoma, regardless of their age, gender or place of treatment. Five studies fulfilled the inclusion criteria, for a total of 390 participants, 208 (53%) receiving chemotherapy, 182 (47%) receiving support care treatment and 6 losses (1.6%). The 1-year survival rate was 8% for support care and 20% for chemotherapy; 30% of the patients in the chemotherapy group and 12% in the support care group attained a 6-month symptom-free period. Quality of life evaluated after 4 months was significantly better for the chemotherapy patients with tumor mass reduction. Chemotherapy increased the 1-year survival rate of the patients and provided a longer symptom-free period of 6 months and an improvement in quality of life.[9]

PERITONEAL DISSEMINATION OF GASTRIC CANCER

Peritoneal dissemination is the most frequent form of evolution of a patient with gastric cancer after curative resection. The prognosis is poor with poor survival and poor quality of life. Since 1990s intraoperative hyperthermic peritoneal chemotherapy combined with cytoreductive surgery would improve prognosis.[10]

Published studies on the use of intraperitoneal chemotherapy are few and not conclusive regarding efficiency and safety. Therefore this kind of treatment is only justified in controlled clinical trials.

However, during the last few years the efficacy of new anti-cancer therapy such as TS-1 system was tested (especially in Japan) in patients with gastric cancer and peritoneal dissemination, and seems to be quite satisfactory. A number of recently published case reports demonstrated that oral TS-1 combined with docetaxel and cisplatin could prolong life, offering concurrently a satisfactory level of quality of life[11]. It seems reasonable to conclude that patients with peritoneal dissemination of gastric cancer should be submitted to chemotherapy after full explanation of the expected results.

PLASTIC LINITIS

In patients with linitis plastica longer survival time can be expected from chemotherapy including TS-1 compared to conventional chemotherapy. In a relevant study involving 19 patients who received TS-1 and 43 patients receiving chemotherapy mainly with 5-FU, cisplatin, methotrexate and mitomycin C it was found that patients of the first group had significant overall response and significantly longer survival time compared to the second group.[12] Again patients with plastic linitis should be subjected to chemotherapy with ST-1.

Other studies published almost exclusively in the Japanese literature mainly in the form of case reports, have produced similar results. However, the use of chemotherapy in patients with linitis plastica remains controversial.

AGE OF PATIENTS WITH GASTRIC CANCER

It is well known that over 60% of the total number of patients with GI cancer in Europe and USA occurs in patients aged 65 or more. On the other hand it is well established that the incidence of gastric cancer in this particular group of patients is increasing.

Elderly patients are generally under-represented in clinical trials. It has been suggested that only 22% of patients enrolled in clinical trials phase II are over the age of 60. There is a general belief that elderly patients would not tolerate anticancer therapy as well as patients of younger age. However, clinical data demonstrate that age alone is not a sufficient reason to exclude patients from therapeutic trials.[13]

The prognostic value of age in patients with gastric cancer remains elusive. In a relevant study involving 1473 patients with gastric cancer who had undergone curative gastrectomy, it was found that chemotherapy was carried out in non-elderly more frequently than in elderly patients. Multivariate analysis showed that age was an independent prognostic factor of survival.[14] It could be supported that chemotherapy should be offered to patients with gastric cancer at an advanced age.

PATIENT'S INFORMED CONSENT

It is generally believed that we must fully informe the patient with cancer about the kind and duration of treatment, the expected results, the side-effects of the drugs that we are going to administer and the quality of life during and after treatment.

The informed consent is an integral element of ethical medical practice. However, it seems that informed consent is often viewed as a legal necessity rather than as an expression of patient's autonomy. Published medical literature documents numerous deficiencies in the informed consent process. Some patients do not read consent forms carefully and some do not even understand the content. Probably the most important point for the doctors to improve the meaning of informed consent is to understand the patients' needs and perceptions.[15]

In a currently performed study of the relevant cancer literature concerning the informed consent process of cancer patients, it was found that there is not enough information regarding the ways in which treatment and clinical trial details are explained by oncologists to patients[16]. However, all studies and authors agree that personal interaction between doctors and patients is critical to maintaining the ethical standards necessary to achieve informed consent.

QUALITY OF LIFE OF PATIENTS WITH GASTRIC CANCER

The influence of chemotherapy on quality of life in advanced gastric cancer has been reported in only a few studies. It seems that about 50% of the patients have a clinically relevant relief of tumor-related symptoms and thereby improved quality of life. It was reported that quality-adjusted survival was estimated to a median of six months in the treated patients compared with two months in the controls. In a recent study, an improvement from baseline in quality of life measures and hospital anxiety and depression scale scores in patients with advanced gastric cancer treated with second-line chemotherapy was demonstrated. So, chemotherapy should be applied in patients with gastric cancer bearing in mind the parameter "Quality of life".[17]

COST-BENEFIT OF CHEMOTHERAPY

In spite of the fact that chemotherapy has been extensively used in advanced gastric cancer, only a few studies focus on the economic cost of such treatment[16]. It seems that we urgently need studies dealing with this so important parameter.

PARTICIPATION IN CLINICAL TRIALS

It has recently been suggested that the Declaration of Helsinki cannot be applied to cancer trials as patients do not and perhaps cannot give fully informed consent to participate in the clinical trials. It has also been suggested that the results of clinical trials do not translate into daily practice in a way that patients might expect.[17] One concern regarding informed consent in research is the confusion between therapeutic intervention and experimental treatment, a fact certainly leading to barriers in informed consent.[18]

NUTRITIONAL ASPECTS

The provision of nutrition in patients with advanced gastric cancer (especially in patients with gastric outlet obstruction) is a matter of discussion by doctors, patients and administrators. Generally there is no agreement on this topic possibly because of the involvement of medical, ethical, emotional, economical and legal considerations that they can not easily be overcome. The results of the available studies concerning the benefits of nutritional therapy in gastric cancer patients are controversial. It has been suggested that decision-making should be addressed on an individual basis considering also the role of the patient's family. It is a general belief that nutrition therapy in advanced gastric cancer might offer improved quality of life especially to those with gastric outlet obstruction despite the associated increased cost.[19]

TELLING THE TRUTH

Telling terminally ill gastric cancer patients the truth about their diagnosis and prognosis is probably the most painful of all the physicians responsibilities to fulfill. According to many authors the moral obligation is to give the patient information and offer directions according to clinical situation and patient's desires.[20]

OTHER ISSUES

Other parameters related to the question of offering chemotherapy or not to gastric cancer patients is related to the role of patient' relatives (they some times raise financial claims), the doctor's training and availability, the psychological support of the patient, the doctor-patient relationship, and the right of the patient with gastric cancer to receive the best available medical treatment, a fact directly related with the availability of treatment. All these parameters must be taken into account when dealing with

a patient with gastric cancer who is a candidate for chemotherapy.

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