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# Current questions for the treatment of advanced gastric cancer

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ABSTRACT

*Background:* Gastric cancer remains a major health problem worldwide. Treatment of advanced gastric cancer is controversial and there is no standard regimen for first- or second-line chemotherapy (CT). This review aims to give an overview of the hot topics concerning treatment, prognostic factors and new strategies in advanced gastric cancer.

*Material and methods:* Seven questions of special clinical interest have been formulated previously to the literature review. With the aim of answering each of these questions, a specific search of the relevant trials and meta-analyses published or communicated from 1990 to date was performed.

*Results:* Patients treated with CT have a survival benefit over those treated with only best supportive care (BSC). Such active cytotoxic drugs as cisplatin or docetaxel and targeted agents as trastuzumab showed superiority in randomized trials. Other agents such as oxaliplatin, oral fluoropyrimidines and irinotecan showed non-inferiority or less toxic results, positioning them as valuable alternatives to classical schedules. Combination regimens seem to be an improvement over single agent therapy. However, increased toxicity of some regimens makes their general use difficult. Second-line CT is of value for selected patients with good performance status. Trastuzumab is the only targeted agent showing better survival when added to chemotherapy in HER2-driven tumors.

*Conclusions:* With the introduction of new agents, management of advanced gastric cancer has experienced important changes. First and second-line CT improve survival in patients with good performance status. Future trials should address how to better select patients for new, targeted agents, based upon validated predictive biomarkers.



Gastric cancer is a major health problem. Predictions for the year 2011 add up to 989,600 new cases and more than 738,000 deaths worldwide.[1] In just the European Union (EU), 55,896 deaths from gastric cancer are estimated for this year.[2] As a consequence of more accurate diagnostic and therapeutic strategies, however, adjusted mortality rates could be decreasing. In the early 1980s gastric cancer was the second cause of death in men and the third in women. In 2011 gastric cancer is the fifth cause of death in men and the sixth in women.

Patients presenting at early stages are often treated with surgery plus perioperative or adjuvant CT with curative intent. Nevertheless, many of them will relapse, with a proportion of long-term survivors of around 25%. When the disease is detected at an advanced stage, which is the case for approximately two thirds of the patients at diagnosis, the outcome is disappointing.[3] The optimal regimen for first-line CT has yet to be clearly established. Whether a three-drug regimen is more effective than a potentially less toxic doublet is a point of controversy.

Treatment decisions in advanced gastric cancer have to consider more than just the potential benefit of CT. Patients with advanced gastric cancer may frequently have nutritional deficiencies, be frail or present symptoms derived from high tumour burden. The main aim of treatment is palliation. A balance between CT benefit and minimization of toxicities is critical.

In this review we aimed at answering some questions in the management of advanced gastric carcinoma.

## Should patients with advanced gastric cancer receive CT?

The real impact of palliative CT on survival has been clearly demonstrated. Two studies[4,5] addressed the question of whether or not CT has an impact on survival. Patients were randomized to receive palliative CT plus BSC versus BSC alone. Most patients recruited in the CT arm of these trials received a three-drug combination with at least anthracyclines and 5-Fluorouracil (5FU). Separately, all these studies demonstrated a benefit of CT versus BSC. Unfortunately, important design limitations, mainly related to poor accrual or to cross-over, have made it difficult to draw any solid conclusions.

Wagner et al. performed a meta-analysis of these randomized clinical trials (RCT) including 184 patients (103 in the CT arm

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versus 81 in the BSC arm). The median hazard ratio (HR) for survival was 0.37 (95% Confidence Interval (CI): 0.24–0.55) in favour of palliative CT. A second sensitivity analysis according to the quality score of the trials, including only studies with adequate allocation concealment, did not change the overall HR (HR 0.37, 95% CI 0.19–0.70). This was the first unequivocal demonstration that CT was able to improve survival in advanced gastric cancer. A more updated Cochrane review performed by the same authors confirmed these findings.[6,7]

The study by Glimelius et al.,[8] not included in the Wagner meta-analysis due to cross-over, reported an interesting comparison of quality of life (QoL) for both arms. This study confirmed a significant improvement in QoL favoring CT with 45% of patients in the CT arm vs 20% in the BSC with a high QoL for at least 4 months ($p < 0.005$).

In Table 1, most relevant trials in this setting are summarized.

## Does primary tumor location matter?

The importance of primary tumor location is a matter of debate. Cancers detected earlier in the lower third of the esophagus were considered to have a better prognosis when compared with those from around the cardias and stomach. Still, the relevance of this hypothesis remains unclear. That notwithstanding, these three locations may represent different diseases with diverse epidemiological, biological and clinical factors. Pooling these three conditions together may make our trials underpowered in an attempt to detect relevant location-dependent aspects. Historically, most of the clinical trials in locally advanced or metastatic adenocarcinoma included mostly gastric cancer and distal esophagus or esophago-gastric junction (EGJ) carcinoma were frequently underrepresented in these studies. In 2009, Chau et al.,[9] performed an analysis of the individual data for 1775 patients from four RCT: 485 patients with esophageal adenocarcinoma, 457 with adenocarcinoma of EGJ and 833 with gastric cancer. The objective of this study was to assess the role of the primary tumor location on prognosis and response to therapy. Despite a slightly better outcome in the esophageal or EGJ adenocarcinoma, no statistical differences were found in terms of OS or response rates (RR) in the three groups. Median overall survival (OS) was 9.5 months for esophagus, 9.3 months for EGJ and 8.7 months in gastric cancer. These data support the current strategy of lumping together the three tumor locations in CT trials for advanced disease.

Recently, Shah et al.[10] defined a new classification of localized gastric cancer according to a differentiated genetic expression. Three different subtypes have been defined: proximal non-diffuse (type 1), diffuse (type 2) and distal non-diffuse (type 3). This classification may require further validation, and its potential relationship with anti-cancer agent sensitivity needs to be defined.

## Which are the main prognostic factors?

Prognosis assessment is a major concern in every advanced malignancy. Advanced gastric cancer is frequently associated with a deterioration in the overall state of health or with the elderly.

In 2004 Chau et al.[11] studied the individual data of 1080 patients from three different randomized trials to identify baseline patient- and tumour-prognostic factors. Four factors were significantly deleterious for survival: PS $\geqslant$ 2, liver metastases, peritoneal metastases, and alkaline phosphatase $\geqslant$ 100 UI/L. A prognostic index was constructed with these factors by classifying patients as good (no risk factor) moderate (one or two factors) and poor prognoses (three or four risk factors). One year survival rates were 48.5%, 25.7% and 11% respectively for these three prognostic groups, with these differences being highly significant ($p < 0.00001$).

This prognostic index was later validated in the population of 1002 patients enroled in the REAL-2 trial.[12] All the previously mentioned prognostic factors remained significant in the multivariate analysis in this population with the exception of alkaline phosphatase. PS of 2 or more was the most highly significant with a HR of 2.044 (99% CI 1.533–2.725). This prognostic model of Royal Marsden remained effective for discriminating different survival groups. In the good prognosis group, the response to CT was identified as a strong survival predictor with 70.9% and 37.8% 1 year survival rate for responders and non-responders respectively.

## Are combination regimens better than single agent CT?

The meta-analysis by Wagner et al.[7] demonstrated a significant benefit for survival for the combination schedules. Data from 11 randomized trials in the 1980s and 1990s of doublet/triplet CT versus single agent were examined, with a final sample size of 1472 patients. In the majority of these trials, the single-agent arm was 5FU, administered either by bolus or continuous infusion. Median survival was 8.3 months for combination and 6.7 months for single agent therapies (HR = 0.82, CI 95% 0.74–0.90). The benefit observed was marginal, however, with an increase in the weighted mean average OS of 1.6 months. Moreover, an overestimation of the effect of combination CT cannot be excluded, as an intention-to-treat analysis was not performed in a relevant number of studies. As expected, toxicity was increased in the combination schedules. Despite the statistical benefit achieved, combination CT should only be considered in patients with good performance status.

## Which are the active drugs and the effective combination regimens?

Although there is not a single standard of care in advanced gastric cancer, there is some evidence coming from meta-analyses and a few trials that should be underscored. Commonly, RCTs of first-line combinations showed significant differences in terms of response, with only a few of them demonstrating an unequivocal benefit toward survival.[13] Fig. 1 chronologically summarizes important steps or achievements in the treatment of advanced gastric cancer. Drugs related to increased survival in phase III trials are cisplatin, docetaxel and trastuzumab. Table 2 shows the most relevant trials with a superiority design. Other drugs showing benefits similar to standard therapies, some of them in non-inferiority designed trials, are S1, capecitabine, oxaliplatin and irinotecan (see Table 3).

**Table 1**
Summary of selected phase III trials of chemotherapy versus best supportive care (BSC) in first- and second-line for advanced gastric cancer.

| Study | Setting | Treatment | No. of patients | Response rate (%) | Median survival (months) |
|---|---|---|---|---|---|
| Murad el al. (Ref. 4) | 1st line | FAMTX vs BSC | 30 | 50 | 9 vs 3 ($p = 0.001$) |
| Pyronen et al. (Ref. 5) | 1st line | FEMTX vs BSC | 41 | 29 | 12.3 vs 3.1 ($p = 0.0006$) |
| Glimelius et al. (Ref. 8) | 1st line | ELF vs BSC | 61 | NR | 8 vs 5 (NS) |
| Thuss-Patience et al. (Ref. 53) | 2nd line | Irinotecan vs BSC | 40 | 0 (58 stable disease) | 4 vs 2.4 ($p = 0.0023$) |
| Park et al. (Ref. 54) | 2nd line | Irinotecan or Docetaxel vs BSC | 193 | NR | 5.1vs 3.8 ($p = 0.004$) |