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Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO)

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ABSTRACT

Background: The value of second-line therapy for metastatic gastric cancer is unclear. So far there are no randomised phase III data comparing second-line chemotherapy to best supportive care (BSC). In this prospective, multicenter, open label, randomised phase III study we compared irinotecan to BSC to evaluate the impact on survival of second-line chemotherapy.

Methods: Eligible patients (pts) had metastatic or locally advanced gastro-oesophageal junction or gastric adenocarcinoma, objective tumour progression during or within 6 months after first-line chemotherapy and ECOG performance status 0–2. Stratification for time of progression after first-line therapy, ECOG PS and pretreatment secured even distribution of important prognostic factors.

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Treatment: Arm A: Irinotecan 250 mg/m^2 q3w (first cycle) to be increased to 350 mg/m^2, depending on toxicity. Arm B: BSC.
Findings: Between 10/2002 and 12/2006 40 pts were randomised. The study was closed prematurely due to poor accrual. *Response for arm A* (19 pts evaluable): No objective responses, SD 53%, PD 47%. Improvement of tumour related symptoms: Arm A 50% of pts, arm B 7%. *Overall Survival*: (all events in 40 pts have occurred): The hazard ratio for death was reduced to 0.48 (95%CI 0.25–0.92) in the irinotecan-arm ($p = 0.012$). Median survival arm A: 4.0 months (95% CI 3.6–7.5), arm B: 2.4 months (95% CI 1.7–4.9).
Interpretation: Irinotecan as second-line chemotherapy significantly prolongs overall survival compared to BSC in the studied pts. Second-line chemotherapy can now be considered as a proven treatment option for metastatic or locally advanced gastric cancer.
Funding: The study was supported by a research grant from Aventis and Pfizer.

1. Background

Gastric cancer is a significant global problem with more than 0.93 million new cases diagnosed annually.[1] As resection is curative in only about 30% of patients[2] the aim of therapy is mostly palliative. Four randomised trials demonstrated a statistically significant prolongation of survival achieved with first-line chemotherapy as compared to best supportive care (BSC),[3–6] although all of these studies only included a small number of patients (37, 40, 41 and 61 patients).

The availability of more active chemotherapeutics and targeted therapies opened the option for second line chemotherapy. The attitude towards second line chemotherapy differs dramatically between countries and between physicians. In the most recent first-line phase III trials subsequent use of second-line chemotherapy differed between 14% (REAL-2-study),[7] 42% in the ToGA Trial[8] and 75% in the SPIRITS study.[9] Therefore, it is important to answer the question whether second-line chemotherapy benefits the patient and prolongs survival.

So far, there is no published phase III study comparing second line chemotherapy to best supportive care in gastric cancer.

Several small phase II studies demonstrated second-line activity of taxanes and irinotecan as a monotherapy or in combination with fluropyrimidines.[10–15] ECOG performance status, progression free interval following first-line chemotherapy and platinum based first-line chemotherapy were suggested as factors to identify patients with the highest chance of a benefit from second line chemotherapy.[16,17]

In the current AIO-trial pretreated patients were randomised between irinotecan as second-line chemotherapy and BSC. The primary end-point of the study was overall survival. The trial focused on patients with a progression during or within 6 months after first-line chemotherapy. It, therefore, selects patients who are resistant to first-line chemotherapy. A possible benefit in patients with chemoresistant tumours should translate even more for patients with chemoresponsive disease and longer treatment free intervals after first-line.[16] To assure an even distribution of the most relevant prognostic variables patients were stratified for ECOC PS, pretreatment and timing of progression under first-line treatment. Irinotecan monotherapy was selected due to its lack of cross-resistance to common first-line regimens containing cisplatin/fluoropyrimidine or docetaxel. Irinotecan has proven activity in gastric cancer first-line therapy administered in a 3 weekly monotherapy regimen[18] or in combination with 5-fluorouracil.[19,20] Administration of irinotecan in a 3-weekly regimen starting the first cycle in a reduced dose and escalate to full dose depending on individual tolerability was based on published experience for optimal efficacy and tolerability.[21,22]

This is the first randomised trial which investigates whether second-line chemotherapy can prolong survival in gastric cancer.

2. Material and methods

This randomised multicenter open label investigator initiated phase III study of the AIO was approved by the local ethics committee, registered with the health authorities, published in http://www.clinicaltrials.gov (number NCT00144378) and performed according to the guidelines of good clinical practise and the Declaration of Helsinki.

2.1. *Patient eligibility*

Eligible patients had to have written informed consent, histologically proven adenocarcinoma of the stomach or gastro-oesophageal junction, metastatic or locally advanced with surgical incurability, no pretreatment with more than one prior palliative regimen of chemotherapy (neoadjuvant or adjuvant chemotherapy or radiation was permitted), documented objective imaging proven progression during or within 6 months after the end of a first-line chemotherapy. Further criteria were age $\leqslant$75 years, adequate bone marrow function, (leucocytes >3.0 Gpt/l, thrombocytes >100 Gpt/l), liver function (bilirubin <1.5 times the upper limit of normal (ULN), AST and ALT $\leqslant 3 \times$ ULN), kidney function (serum creatinine <1.25 ULN and creatinine clearance >60 ml/min (calculated according Cockroft-Gault), ECOG performance status $\leqslant$2, measurable or evaluable disease and adequate contraception. Exclusion criteria were prior second malignancy, uncontrolled infection, central nervous system metastases, other severe medical illness, major operation within the last 2 weeks, pretreatment with irinotecan, chronic diarrhoea,