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FIELD OF VISION

Advanced gastric cancer: Is there enough evidence to call second-line therapy standard?

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Abstract

Gastric cancer and cancer of the gastro-oesophageal junction (GOJ) are the 4th most common cancer diagnoses worldwide with regional differences in incidence rates. The treatment of gastric and GOJ cancers is complex and requires multimodality treatment including chemotherapy treatment, surgery, and radiotherapy. During the past decade considerable improvements were achieved by advanced surgical techniques, tailored chemotherapies/radiotherapy and technical innovations in clinical diagnostics. In patients with advanced or metastatic gastric/GOJ cancer systemic chemotherapy with fluoropyrimidine/platinum-based regimens (+/-human epidermal growth factor receptor-2 antibody) is the mainstay of treatment. Despite these improvements, the clinical outcome for patients with advanced or metastatic disease is generally poor with 5-year survival rates ranging between 5%-15%. These poor survival rates may to some extent be related that standard therapies beyond first-line therapies have never been defined. Considering that this patient population is often not fit enough to receive further treatments there is an increasing body of evidence from phase-2 studies that in fact second-line therapies may have a positive impact in terms of overall survival. Moreover two recently published phase-3 studies support the use of second-line chemotherapy. A South Korean study compared either, irinotecan or docetaxel with best supportive care and a German study compared irinotecan with best supportive care-both studies met their primary endpoint overall survival. In this "Field of Vision" article, we review these recently published phase-3 studies and put them into the context of clinical prognostic factors helping to guide treatment decisions in patients who most likely benefit.

Key words: Gastric cancer; Cancer of the gastro-esophageal junction; Second-line chemotherapy; Best supportive care; Survival

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INVITED COMMENTARY ON HOT ARTICLES

Background

Gastric cancer and cancer of the gastro-esophageal junction are one of the most common cancers in the world with significant impact on health resources[1]. Extensive

surgery is the therapy of choice in early disease stages and often accompanied by neo-adjuvant and/or adjuvant chemotherapy[2]. However, a significant number of patients relapse after initial surgery and a large proportion of patients (30%) present with advanced disease. In this setting systemic 5-fluoropyrimidine/platinum based chemotherapy [+/-human epidermal growth factor receptor 2 (HER-2) antibody] has shown to be an effective first-line therapy[3]. Although first-line therapy is effective in the majority of patients a large proportion has no or limited benefit and may merit further treatment. Over the last decade second-line therapy has been controversially debated as clinical evidence, mostly generated from small, single centre or retrospective studies, was sparse. In this "Field of Vision", we review the results of two recently published trials reporting the benefit of second-line therapy for patients with advanced gastric cancer and put this into the context of current treatment algorithms.

"Field of Vision" commentary

We followed with great interest two recently published papers addressing the use of second-line therapy in patients with advanced gastric cancer.

Briefly, the Arbeitsgemeinschaft Internistische Onkologie (AIO) trial was a prospective, randomised, multicentre, open-label phase-3 study of 40 patients which compared irinotecan (n = 21; 250 mg/m^2 first cycle and 350 mg/m^2 subsequent cycles, *qw* 3) *vs* best supportive care (BSC; n = 19) where crossover into the irinotecan arm was not allowed[4]. Restaging was performed every 6 wk and toxicity assessed based on the common toxicity criteria version 2.0 (CTCv2.0). Patients were well balanced for performance status (0-$\leqslant$ 2), pretreatment, primary tumour type, number of metastatic sites, age, however, there was an imbalance in the male:female-ratio in both arms. In total a median number of two cycles was administered (range: 0-9) and 37% of patients in the chemotherapy treatment arm were dose-escalated to 350 mg/m^2 irinotecan. Irinotecan was generally well tolerated and the main grade 3/4 toxicity was diarrhea (26% of patients)-no treatment related deaths were observed. There was no objective tumour response, however disease stabilisation > 6 wk was documented in 53% of patients and a significant proportion of patients reported improvement of symptoms while on treatment (n = 9, 50%). The progression free survival for patients on treatment was 2.5 mo (95%CI 1.6-3.9 mo) with a median overall survival (OS) of 4.0 mo compared to a 2.4 mo OS in the BSC arm [hazard ratio (HR) 0.48, 95%CI 0.25-0.92, P = 0.012; one-sided log-rank test]. As a result and supported by evidence from phase-2 studies the German Gastric Cancer national guideline committee approved the use of second-line chemotherapy in patients with advanced gastric cancer.

The second study was recently reported from a group in South Korea where second-line therapy was historically more widely used despite level 3 evidence.

In this prospective phase-3 study, 202 patients with advanced gastric cancer who received at least one prior therapy were randomised in a 2:1 fashion and received either chemotherapy (irinotecan 150 mg/m^2, *qw* 2 or docetaxel 60 mg/m^2, *qw* 3) or best supportive care[5]. Restaging was performed every 6 wk and toxicity assessed based on the CTCv3.0. Patients were well balanced for performance status (0-1), pretreatment, primary tumour type, number of metastatic sites, age, however, there was an imbalance in the male: female-ratio in both arms. The treatment was generally well tolerated (66 patients, docetaxel; 60 patients, irinotecan; 62 patients BSC). Grade 3/4 toxcities included anemia (30 and 32%), neutropenia (15% and 18%) and fatigue (26% and 10%) in the docetaxel and irinotecan arm, respectively. Anemia, fatigue and anorexia were the most common grade 3/4 toxicities in the BSC arm. After a median follow-up of 20 mo the intention to treat analysis showed an increase in OS form 3.8 mo in the BSC arm (95%CI 3.1-4.5 mo) to 5.3 mo (95%CI 4.1-6.5 mo) with a HR of 0.657 (95%CI 0.485-0.891, P = 0.007; one-sided log rank test). There was no difference in the treatment effect of docetaxel and irinotecan; P = 0.116. Further exploratory analysis showed that PS (0 *vs* 1), prior chemotherapy (1 *vs* $\geqslant$ 2) and chemotherapy-free interval (< 3 mo *vs* > 3 mo) were prognostic factors in the uni- and multivariate analyses.

Both phase-3 studies have shed light into a field which has been discussed controversially for the last few years (Table 1). Despite several limitations in design and recruitment there are several factors which we feel are important to highlight.

First, the two trials showed comparable clinical benefit in two different patient populations[6]-both, the Western World and Asian population, tolerated treatments generally well and had had similar outcomes in terms of survival.

Second, the different choice of chemotherapy, e.g., weekly docetaxel or irinotecan as seen in the South Korean study, did not impact on outcome and therefore offers treatment choices in this setting. These results were recently supported in abstract format by a Japanese phase-3 study (WJOG4007) including 223 patients with advanced gastric cancer. Patients received either weekly docetaxel (80 mg/m^2) or irinotecan (150 mg/m^2, *qw* 2) and were followed up until progression[7]. In terms of toxicity both treatment regimens were comparable with grade 3/4 toxicities being: neutropenia (39% *vs* 29%), anemia (17% *vs* 7%) and fatigue (13% *vs* 7%), respectively.

Third, the multivariate analysis in the South Korean study identified clinical important prognosticators (performance status, number of prior chemotherapies and chemotherapy-free interval) which could serve physicians to make adequate treatment decisions. In this context, a recent retrospective study by Hasegawa *et al*[8] identified additional clinical factors which could support treatment decision, namely PS (0-1 *vs* 2), albumin (> 35 mg/dL *vs* < 35 mg/dL) and time to progression on first-line therapy (> 170 d *vs* < 170 d). According to a prognostic model patients with two or more of these factors would not

Table 1 Clinical decision tool for second-line therapy

Prognostic marker	Treatment action	
	Support treatment	Caution-poor outcome
Albumin (mg/dL)	> 35	< 35
Performance status	0-1	2
Chemotherapy free interval (mo)	> 3	< 3
Time to progression on 1st-line therapy (mo)	> 6	< 6

benefit from second-line therapy.

Fourth, improved understanding of gastric/GOJ tumour biology have opened new avenues in combining chemotherapy with novel molecular targeted agents. For example, expression of the HER-2 has been associated with poor prognosis. Targeting this receptor *via* the monoclonal antibody trastuzumab (Herceptin) has shown improved outcome in the first-line setting in terms of response rates, progression free and overall survival[9]. Other approaches in targeting the human epidermal growth factor family are *via* tyrosine kinase inhibitors such as lapatinib. Although lapatinib in the second-line setting had limited benefits as single agent the combination with taxanes is thought to have synergistic effects and several phase-2 and a randomised phase-3 trial (TYTAN-Study) are ongoing to test this hypothesis[10]. Other molecular target drugs currently in the clinical arena are directed against the epidermal growth factor receptor (EGFR)-although results of early trials were ambiguous in unselected patient populations there are signs that selected patients with EGFR over-expression may have better outcome. For example, in pretreated patients the combination of irinotecan with cetuximab or nimotuzumab have resulted in trends towards better outcomes in those patients where EGFR was over-expressed[11]. Other targets of interest are the oncogene c-Met which encodes the hepatic growth factor receptor and the insulin growth factor receptor-1-both receptors are often over-expressed in gastric/GOJ cancer and are thought to play a critical role in chemotherapy resistance[12]. An increasing field of interest is the study of biomarker and molecular signatures predicting clinical outcome. For example, an increasing body of evidence suggests that downstream mutations in the Kirsten rat sarcoma viral oncogene or loss of the phosphatase and tensin homolog tumour suppressor gene are associated with poor prognosis and moreover predict inferior outcome in patients who are treated EGFR/HER2 targeted therapies[13]. Other studies suggest that expression of the pro-apoptotic protein Bcl-2-associated protein X is associated with improved clinical outcome for a variety of chemotherapies including irinotecan and others[14].

In summary, there is now increasing high-level evidence to support the use of second-line therapy in advanced gastric cancer. In addition easily derived clinical prognostic factors in combination with molecular signatures should guide us in our attempt to rationalise the decision-making process to improve patient outcome.

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