Short Communication

Gastric cancer: toward a cisplatin-free disease?

Fausto Petrelli[1], Sandro Barni[1], Stefano Cascinu[2], Alberto Zaniboni[3]

[1]Oncology Department, Medical Oncology Unit, Azienda Ospedaliera Treviglio, Treviglio (BG), Italy; [2]Medical Oncology, Università Politecnica delle Marche, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I, Ancona, Italy; [3]UO Oncologia, Dipartimento Oncologico, Istituto Ospedaliero Fondazione Poliambulanza, Brescia, Italy

Correspondence to: Dr. Fausto Petrelli. Oncology Department, Medical Oncology Unit, Azienda Ospedaliera Treviglio, Piazzale Ospedale 1, 24047 Treviglio (BG), Italy. Email: faupe@libero.it.

Abstract: Historically, the cornerstone of treatment of advanced gastric cancer (GC) is 5-fluorouracil (5-FU)-based chemotherapy that increases median overall survival (OS) compared to best supportive care by some months. The addition of cisplatin (CDDP) to chemotherapy doublets showed a limited but significant benefit in term of OS according to a Cochrane meta-analysis. However, the recent individual patient-data GASTRIC meta-analysis, confirms this benefit in term of progression-free survival (PFS) but not OS, in randomized eight trials that include or not CDDP. The substitution of CDDP with a modern agent (oxaliplatin, irinotecan or taxanes) has been poorly evaluated in the literature. The REAL-2 phase III trial confirmed the equivalence of oxaliplatin and CDDP-based triplets, and a meta-analysis of three oxaliplatin-based randomized trials demonstrated that these combinations are better that CDDP-based doublets or triplets, improving both PFS (HR =0.88) and OS (HR =0.88). In particular, oxaliplatin-based chemotherapy was associated with less neutropenia and thromboembolic events, but with worse neurotoxicity. Given that the role of chemotherapy in advanced GC is palliative, CDDP-free regimens, and in particular oxaliplatin-based chemotherapy, may be considered for both CDDP-fit and unfit patients (that are those with poor renal function, older age, bad performance status or who cannot tolerate forced hydration for example). The limited absolute survival benefit of chemotherapy in advanced GC (few weeks at best), the cumbersome vascular toxicity of CDDP and the activity of several new drugs such irinotecan, oxaliplatin, taxanes and oral fluoropyrimidines make nowadays possible to consider CDDP-free regimens for the treatment of this incurable disease.

Keywords: Cisplatin (CDDP); gastric cancer (GC); oxaliplatin; overall survival (OS); toxicity; first line

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The treatment of advanced gastric cancer (GC), including gastro-esophageal junction cancer, has evolved little over the years, with the exception of the treatment of human epidermal growth factor receptor-2 (HER-2) positive disease. Historically, the cornerstone of treatment of advanced GC is 5-fluorouracil (5-FU)-based that increases median overall survival (OS) compared to best supportive care by some months (1-3).

The combination of continuos infusion of 5-FU + cisplatin (CDDP) was investigated extensively since three decades ago, and it remains still now a reference regimen of almost all contemporary investigations, in metastatic disease (4,5).

In 2006, a meta-analysis of advanced GC (6), published in the *Journal of Clinical Oncology*, established the role of multidrug combinations (triplets) including CDDP, compared to two-drug combinations with significant survival benefit [hazard ratio (HR) for survival 0.83]. The addition of one or two agents to monochemotherapy obviously added toxicities to single-agent arms. Overall, treatment-related side effects, although not significantly different in the individual trials, were greater in combinations arms. Three studies, adopted a platinum-free combination of irinotecan-5-FU, which was compared to CDDP-5-FU or etoposide-leucovorin-5-FU (ELF).

The pooled HR for OS was 0.88 in favor of the irinotecan-containing regimens that translated into an insignificant benefit in median OS of approximately 1 month for the irinotecan-containing regimens.

The Cochrane meta-analysis of 2010 (7) confirmed the survival benefit with the addition of CDDP to 5-FU/anthracyclines doublets. However, both irinotecan- (HR 0.86; 95% CI, 0.73 to 1.02; 639 participants) and docetaxel-containing regimens (HR 0.93; 95% CI, 0.75 to 1.15; 805 participants) showed a not significant OS gain in favor of the not-irinotecan and not-docetaxel-containing regimens.

In recent years, oxaliplatin, which is more extensively studied in colorectal cancer, emerged as a valid alternative option in lieu of CDDP in stage IV GC (8). In 2011, Montagnani and colleagues published a meta-analysis of three trials comparing CDDP to oxaliplatin regimens in advanced GC (9). Two phase III and one smaller phase II trials were included. Oxaliplatin significantly improved progression-free survival (PFS) (HR =0.88, P=0.02) and OS (HR =0.88, P=0.04). In particular, oxaliplatin-based chemotherapy was associated with less neutropenia and fewer thromboembolic events, but with worse neurotoxicity. This analysis confirms that a CDDP-free chemotherapy could represent a less toxic approach, and may be more active as a first-line treatment for advanced GC. Recently, the first results of a phase III trial comparing S-1 + CDDP (SP) to S-1 + oxaliplatin (SOX) were presented at the 2013 Gastrointestinal Cancer Symposium (10). Six hundred eighty-five patients with advanced or recurrent GC were randomized to SOX (oral S-1 40 mg/m^2 bid. for 14 days plus oxaliplatin 100 mg/m^2 iv on day 1, q3 weeks) or SP (oral S-1 40 mg/m^2 bid for 21 days plus CDDP 60 mg/m^2 iv on day 8, q5 weeks). The study confirmed the noninferiority of PFS between the two platinum-based combinations. However, serious adverse events occurred in 29.3% of patients for SOX and 37.9% of patients for SP. Eight treatment-related deaths were reported in SP (2.4%) and four in SOX (1.2%). Overall, this study confirmed once again that oxaliplatin plus an oral fluoropyrimidine represents one of the referent regimens for the treatment of this disease.

With the present data in mind, it can be affirmed that oxaliplatin, irinotecan and eventually taxanes, could be adequate substitutes for CDDP in multidrug combination according to four considerations.

First, the 3-drug combination TCF, whose use is substantially limited for the toxicity profile, could be resumed by replacement of CDDP with oxaliplatin. For example, in the randomized phase II trial GATE, led by Van Cutsem *et al.* (11), the triplet combination of docetaxel, oxaliplatin and 5-FU (TEF) obtained a 46% response and more than 14 months of OS; Second, oxaliplatin has been demonstrated to be equivalent and even not cross resistant with CDDP *in vitro* (12); Third, the FOLFOX-regimen, for example, is now worldwide one of the preferred choices as an up-front treatment for both esophageal and GC (with or without radiotherapy) with similar, if not even better, outcome and safety compared to CDDP/fluoropyrimidine schedules (13,14); Fourth, a systematic review and meta-analysis (15) of randomized controlled trials (1,837 patients included from ten trials) demonstrated that irinotecan-containing regimens significantly improved OS (HR 0.86; 95% CI, 0.78-0.94; P=0.002) and PFS (HR =0.82; 95% CI, 0.69-0.97; P=0.026) compared to not-irinotecan-containing ones.

Recently, an individual patient-data meta-analysis was published (16), which included 22 out of 55 potentially eligible trials. Compared to control arms, chemotherapy reduced overall the hazard of death by 12% and of progression by 19%. When analyzing the contribution of individual agents, only CDDP (eight trials included) and irinotecan led to a benefit in PFS but not in OS. On average, the benefit with palliative chemotherapy from this meta-analysis is limited to about 3-4 months for both PFS and OS.

A confirmatory meta-analysis, published by Petrelli and colleagues, confirmed the goodness of non-CDDP over CDDP polychemotherapy in advanced disease (17). Among 14 randomized trials, including about 3,000 patients, chemotherapy regimens without CDDP significantly improved OS (HR 0.79; 95% CI, 0.68-0.92; P=0.003), PFS (HR 0.77; 95% CI, 0.66-0.90; P=0.001), and response rate (RR) (OR 1.25; P=0.004) when compared to CDDP-containing regimens.

The amount of cardiovascular risk linked to CDDP administration was revealed by a meta-analysis that compared patients with neoplastic diseases, treated or not, with CDDP (18). The incidence of venous thromboembolic events (VTEs) was 1.92% in patients treated with CDDP-based chemotherapy *vs.* 0.79% in patients not treated with CDDP-containing chemotherapies. Patients receiving CDDP-based regimens suffered from significantly increased risk of VTEs (relative risk 1.67; 95% CI, 1.25 to 2.23; P=0.01). In the setting of GC, the REAL-2 study showed an overall rate of thromboembolic events significantly lower in the oxaliplatin grvoups than in the CDDP groups (7.6% *vs.*

15.1%, P<0.001).

If we consider the activity of oral agents [capecitabine (X) and S-1] and the administration of agents such as oxaliplatin, paclitaxel, docetaxel and irinotecan, whose infusion duration and possibly worrisome toxicities could be reduced compared to CDDP, the treatment of this disease can be more convenient and feasible for patients by using CDDP-free regimens. In addition the described regimens, and in particular oxaliplatin-based chemotherapy, may be likely offered to both CDDP-fit and unfit patients (that are those with poor renal function, older age, bad performance status or who cannot tolerate forced hydration for example)

In HER-2 positive disease, however, the registration of trastuzumab, according to TOGA trials, limits the use of doublets other than CDDP-5-FU or CDDP-X (19). However, some literature evinces significant activity of oxaliplatin-based chemotherapy plus trastuzumab (20,21). The case of breast cancer is emblematic; in this setting, in fact, trastuzumab is effective and synergic (or additive) when coupled with various cytotoxic agents (e.g., vinorelbine and gemcitabine) but more cardiotoxic when associated with the most active agents taxanes and anthracyclines (22,23).

Is the paradigm of GC treatment shifting to a new era where old and toxic drugs (e.g., CDDP, anthracyclines, mytomicin C) replaced by modern and more effective agents? Is the cost of toxicities and time spent well balanced by a significant and clinical therapeutic effect of CDDP-based regimens in GC? We are not sure of this. OS of stage IV GC is near 12 months; a true gain in survival has not been demonstrated up to today with the addition CDDP as opposed to no CDDP in addition to other agents, and quality of life should still remain one of the co-primary endpoints of palliative treatments.

The duration of treatment in responders with advanced GC has not been specifically studied. There are no data about the discontinuation of a treatment regimen prior to disease progression. In general, chemotherapy is given until the patient has a progressive disease or cannot tolerate further treatment. In this case, the potential cumulative toxicity of platinum salts (allergic reaction and neurotoxicity) has to be carefully taken into account when deciding on a first-line regimen. As for now, cumulative sensorial neuropathy due to oxaliplatin can be safely attenuated without compromising efficacy, with calcium/magnesium infusions (24).

Finally, in neither an adjuvant nor a neoadjuvant setting has a clear (CDDP-based) winner regimen been declared. Platinum-based chemotherapy still remains the cornerstone of treatment in this setting, but a referent regimen has not been discovered. In locally advanced settings, ECF-like regimens are the most frequently implemented in Western countries according to MAGIC trial (25). In advanced settings, however, the REAL-2 phase III trial affirmed the superiority of X-based and the equivalence of oxaliplatin-based schedules. In the adjuvant setting, a limited but significant benefit has been demonstrated with adjuvant polychemotherapy according to GASTRIC meta-analysis (26). Most of the post operative randomized trials were mitomycin C/5-FU plus or minus anthracyclines regimens, and limited data exist with CDDP-based schemes. One of the larger trials comparing chemotherapy to no chemotherapy after D2 gastrectomy adopted however an X + oxaliplatin regimen that obtained a 44% lower risk of progression or death (27).

In conclusion, as in other neoplastic conditions (ovarian or small cell lung cancer) other platinum analogues and some new drugs, have obtained the recognition of less toxic and equi-effective systemic agents. In a GC setting, other potentially active chemotherapies have been demonstrated to safely replace CDDP as the cornerstone of up-front treatment of metastatic or unresectable disease.

A correct selection of patients and their preference, coupled with the judicious application of the more effective agents, can probably, step by step, extend a benefit to those with this incurable disease.

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