Impact of pathologic complete response on disease-free survival in patients with esophagogastric adenocarcinoma receiving preoperative docetaxel-based chemotherapy

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Background: The aim of this study was to evaluate the impact of pathologic complete response (pCR) on outcome in patients with gastric or esophagogastric junction (EGJ) adenocarcinoma after neoadjuvant docetaxel/platin/fluoropyrimidine-based chemotherapy.

Patients and methods: Patients received at least one cycle of chemotherapy for potentially operable disease. Pretreatment clinicopathologic factors and pCR were investigated. Disease-free survival (DFS), overall survival (OS) and tumor-related death were correlated with pCR.

Results: One hundred twenty patients were included in this analysis. Eighteen patients (15%) achieved a pCR. Tumor localization in the EGJ was identified as the only significant predictor of pCR (P = 0.019). Median follow-up was 41.1 months. Median DFS and OS for all patients were 24.1 and 48.6 months, respectively. Median DFS for patients with a pCR was not reached versus 22.1 months non-pCR patients (hazard ratio, HR 0.38; 3-year DFS: 71.8% and 37.7%, respectively, P = 0.018). While OS was not significantly different, the risk for tumor-related death was significantly lower for pCR patients compared with non-pCR patients (3-year cumulative incidences of 6.4% and 45.4%, respectively, P = 0.009).

Conclusion: A pCR following preoperative docetaxel/platin/fluoropyrimidine indicates favorable outcome in patients with gastric or EGJ adenocarcinoma. Tumor location in the EGJ is associated with a higher pCR rate.

Key words: docetaxel, esophagogastric adenocarcinoma, pathologic complete response, preoperative

introduction

Despite the increasing use of perioperative chemotherapy for locally advanced esophagogastric cancer, 5-year survival rates remain <40%, which underlines the need for exploration of more potent chemotherapeutic regimens [1, 2].

In patients with metastatic esophagogastric cancer, improved outcomes in terms of significantly increased response and survival rates have been reported when docetaxel was added to cisplatin and 5-fluorouracil (5-FU). However, the classic docetaxel, cisplatin, fluorouracil (DCF) regimen leads to considerable therapy-associated toxicity [3]. In order to improve tolerability by maintaining efficacy, DCF was modified and tested in different phase II studies [4, 5]. Based on phase III studies, oxaliplatin can substitute for cisplatin and capecitabine for 5-FU [5–7]. DCF modifications proved feasible and efficacious in the perioperative setting in patients with resectable esophagogastric cancer [4, 8, 9]. While there is strong evidence that perioperative chemotherapy can improve survival in general, the most efficacious regimen is not yet known and indicators for an individual treatment benefit are lacking.

Histopathologic regression, following preoperative chemotherapy, has been shown to be prognostic [10]. Pathologic complete response (pCR) after neoadjuvant chemotherapy correlates with a favorable long-term outcome in gastric cancer [11–13]. The value of pCR in patients treated with neoadjuvant chemotherapy has, to the best of our knowledge, not yet been investigated in a separate analysis.
The histopathologic complete remission rate has been low (<5%) in large randomized trials with standard cisplatin and 5-FU-based chemotherapy regimens [1, 2, 14]. Addition of docetaxel to a platinum/5-FU combination may increase the pCR rates to 13%–19% [4, 8, 9]. We performed a pooled analysis of patients treated with DCF modifications; docetaxel, cisplatin, capecitabine (DCX), docetaxel, cisplatin, 5-FU (T-PLF) and 5-FU, oxaliplatin, docetaxel (FLOT), in order to:

1) Assess the histological response rate after docetaxel-based triple chemotherapy.
2) Identify predictive markers for histopathologic response.
3) Compare disease-free survival (DFS) in patients with and without pCR.

Three-year DFS has shown to be a good surrogate for 5-year overall survival (OS) [15] and was chosen as the primary end point.

patients and methods studies
We pooled data from three multicenter phase II studies of the Arbeitsgemeinschaft Internistische Onkologie (AIO) [4, 8, 9]. All patients received preoperative modified DCF chemotherapy followed by resection. Patient selection was comparable in the three studies. All patients, irrespective of tumor localization in the gastroesophageal junction or the gastric body, received initial staging, including CT scan of the thorax and abdomen and endoscopy with endosonography. Only patients with at least stage II (Union for International cancer control; UICC) [16] T2N+ or T3 were included. All data collections were approved by relevant ethics committees and were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

patients
In total, 120 patients were analyzed. All patients had undergone resection of the tumor in curative intent.

The first trial assessed the efficacy of split-dose docetaxel 40 mg/m², cisplatin 40 mg/m² on days 1, 15 and 29, leucovorin 200 mg/m² and 5-FU 2000 mg/m² weekly in patients with metastatic and locally advanced esophageal cancer [4].

The second trial evaluated the efficacy of perioperative docetaxel 75 mg/m² and cisplatin 60 mg/m² (day 1) followed by capcitabine 1875 mg/m² daily (days 1–14) every 3 weeks (DCX) [9].

In the third trial, patients were treated with biweekly oxaliplatin 85 mg/m² (day 1), docetaxel 50 mg/m² (day 2) and continuous infusion 5-FU 2600 mg/m² (days 1–2) (FLOT) [8].

Pretreatment characteristics of the patients and tumor-related parameters are listed in supplementary Table S1, available at Annals of Oncology online. Based on an AIO study, which suggests that resection of limited metastases may be beneficial [17], we did not exclude patients with resected metastases from this pooled analysis.

follow-up
Patients were followed every 3 months in year 1–3 and every 6 months thereafter until disease progression by abdominal and thoracic CT scans in the case of esophagogastric junction (EGJ) cancer. DFS was measured from the date of resection until disease progression or death of any cause. OS was calculated from the day of surgery until death of any cause.

histopathologic work up and response evaluation
Histopathologic evaluation was done by standardized protocols including the pTNM (postsurgical histopathological classification) categories, tumor localization, subtype according to Lauren’s classification and resection margins, as demanded in the guidelines of the UICC 2002 [16]. R0 resection was defined as no tumor identified on microscopic examination of proximal, distal or circumferential margins.

Patients with tumors located in the EGJ were classified as esophageal carcinoma in case that the major tumor mass was located in the esophagus including all patients with Siewert I tumors. All other tumors of the EGJ including patients with Siewert II–III tumors were classified as gastric tumors.

Tumor regression was assessed semiquantitatively according to a previously published scoring system by Becker et al. [18], looking at the proportion of residual tumor cells in relation to the macroscopically identifiable tumor bed. All patients with no residual tumor (regression score 1a) were classified as pathologic complete responders (pCR). All other patients were classified as nonresponders (non-pCR), including grade 1b (subtotal remission) <10% residual tumor/tumor bed, grade II (partial remission), 10%–50% residual tumor/tumor bed and grade III (minor/no remission) >50% residual tumor/tumor bed [11, 18].

statistical analysis
Categorical data are described by absolute and relative frequencies, quantitative data by medians, minima and maxima. Frequencies of pCR between groups were compared by using Fisher’s exact test, quantitative data by Mann–Whitney U-tests. Distributions of OS and DFS were estimated using the Kaplan–Meier method. Hazard rates were compared using the log-rank test. Cox proportional hazards models were fit to the data to estimate hazard ratios (HRs) and corresponding 95% confidence intervals. Cumulative incidence functions were estimated for time to tumor-related death treating deaths from other causes as competing events.

To assess the influence of pCR on DFS adjusted for possible confounders, a multiple Cox regression model including these covariates was fit to the data.

A two-sided level of significance of α = 0.05 was used for all statistical tests.

results
One hundred twenty patients were analyzed [4, 8, 9]. Fifteen patients (13%) had distant metastases (M1) at diagnosis. The median follow-up for all patients was 41.1 months (range 0.4–89.6) from the date of operation. At last follow-up, 49 (41%) patients had died from recurrent gastric cancer and 8 (7%) patients had died of other causes.

histopathologic response
Eighteen patients (15%) achieved a pCR. The remainder (n = 102; 85%) had evidence of residual disease and are defined as the non-pCR group. The pCR rates ranged from 11% (3/27) to 14% (7/49) to 18% (8/44) in the individual studies. The median follow-up was 53.4 months (range 17–90 months) for the pCR and 41.1 months (range 0.4–90 months) for the non-pCR group.

predictive factors for histopathologic response
Table 1 shows the association of clinicopathological factors at baseline with histopathologic response. There were no significant differences between the pCR and non-pCR groups with respect to patient age and pretreatment T and N category.
Patients with tumor localization in the stomach were more likely to be histopathologic nonresponders compared with patients with EGJ tumors [49/52 (94.2%) versus 53/68 (77.9%); \( P = 0.02 \)]. Patients with diffuse type gastric cancer were also more frequently histopathologic non-responders (39/42; 92.9%) compared with patients with intestinal type according to Lauren’s classification (46/60; 76.7%; \( P = 0.075 \)).

### Efficacy and survival

The median DFS and OS for the whole population were 24.1 and 48.6 months, respectively. For patients with a pCR, the median DFS was not reached and for non-pCR patients the median DFS was 22.1 months (HR 0.38; 95% CI 0.16–0.87; 3-year DFS probability: 71.8% ± 10.7% and 37.7% ± 5.1%, respectively, \( P = 0.018 \); Figure 1A).

We observed a decreased relative risk of death of almost 50% for patients with pCR compared with non-pCR (HR 0.53; 95% CI 0.23–1.23). The difference in survival time was not statistically significant \( (P = 0.131 \); Figure 1B). If only tumor-related death was analyzed, pCR was a significant predictor of survival. Four patients in the pCR and four patients in the non-pCR group had died noncancer related. Supplementary Figure S1, available at Annals of Oncology online summarizes the cumulative incidence of tumor-related death. Estimated cumulative incidence for tumor-related death at 3 years was 45.4% in the non-pCR group compared with 6.4% in the pCR group \( (P = 0.009 \).

Supplementary Figure S2, available at Annals of Oncology online shows the DFS according to the Becker regression score. The difference between Ia and Ib patients as well as the difference between Ib and II or III patients was not statistically significant in pair wise comparisons \( (P = 0.158 \) and \( P = 0.297 \), respectively), as the number of grade Ib patients was rather small \( (n = 20 \).

Table 2 is showing the DFS in association of pretreatment characteristics with DFS. In the multiple regression model for DFS, including pCR, ECOG performance status, tumor localization, histopathologic subtype and initial M-status, considering all patients with complete observations regarding these parameters \( (n = 107 \), pCR was a significant predictive marker for longer DFS \( (HR = 0.304; 95\% \ CI 0.125–0.742; \ P = 0.009 \). Additionally, intestinal subtype, according to Laurens classification, and tumor localization in the stomach were significantly associated with prolonged DFS. Of note, non-pCR patients with stomach cancer had better 3-years DFS

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<th>Table 1. Association of clinicopathological factors at baseline with histopathologic response</th>
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*Thirteen patients not specified were excluded from univariate analysis.

*Mann–Whitney U-test was used.

**Fisher’s exact test was used.

ECOG, Eastern Cooperative Oncology Group; EGJ, esophagogastric junction.
and OS (49.9% ± 7.7% and 64.8% ± 7.5%) compared with non-pCR patients with tumor localization in the EGJ (26.6% ± 6.6% and 41.0% ± 7.0%).

In total, 15 patients (13%) had initial distant metastases (M1) (2 patients achieving a pCR and 13 patients remaining non-pCR). These patients were included in the survival analysis. Excluding these patients from the survival analysis did not lead to any changes in the results (data not shown).

surgical complications and postoperative mortality
The 30-day postoperative mortality was 1.7% with one patient dying due to septic complication and one patient dying due to pulmonary embolism. Postoperative morbidity in the immediate (30-day) postsurgical period was observed in 33% of patients. Common (>5%) causes of postsurgical morbidity were pneumonia (n = 11, 9.2%), anastomotic insufficiency (n = 8, 6.7%) and pancreatic fistula and infection (n = 6, 5.0%).

discussion
This pooled analysis reports, to our knowledge, on the largest series of preoperative docetaxel-based chemotherapy in esophagogastric adenocarcinoma. It shows that a high pCR rate of 15% can be achieved and that pCR is associated with a better DFS. The observed pCR rate with a triple-drug regimen containing docetaxel clearly exceeds the 0%–7.7% pCR rates reported from other cisplatinum-based regimens [1, 18].

There was no significant relationship between pCR and age, gender, ECOG performance status and clinical stage at diagnosis. In contrast, carcinomas of the EGJ as well as adenocarcinomas of the intestinal-type histology were more likely to achieve a pCR. These findings are in line with other studies demonstrating a less frequent complete histopathologic regression in tumors of the stomach and tumors of the nonintestinal subtype [11]. Our data show that intensive preoperative chemotherapy is feasible and particularly effective in EGJ tumors. Retrospective analysis have shown, that adenocarcinoma of the EG junction are more likely to respond to preoperative chemotherapy than distal gastric cancer [1, 2, 17]. The high pCR rate achieved with a taxane-based triplet shown in our study supports the possible role of preoperative chemotherapy in particular for EGJ tumors (22% versus 6% in stomach cancer). Despite the higher pCR rate, EGJ tumors seem to have in general, a worse prognosis compared with gastric tumors [17, 19].

Histopathologic response to preoperative chemotherapy has been shown to correlate with long-term survival [12] in esophagogastric cancer. As demonstrated in other studies [20, 21], patients, who achieved a pCR following preoperative therapy, had a significantly improved DFS when compared with non-pCR patients. Therefore, our study supports the potential role of pCR as a surrogate marker for outcome following preoperative chemotherapy. A worse DFS and OS was observed for patients achieving only a subtotal remission (Ib) with <10% tumor cells compared with patients with a total remission Ia. This finding is in contrast to the suggestion that patients with complete and subtotal regression should be regarded as responding tumors [22]. As the number of patients with Ia (n = 18) and Ib (n = 20) regression in our analysis is small, these results needs to be confirmed. However, based on our data, we still suggest that only a complete remission is a strong predictive marker for a long-term survival.

The prognostic value of pCR achievement could be demonstrated in univariate analysis, and was also maintained in multivariate analysis. However, while other investigators could identify pCR as a prognostic factor in univariate analysis, these associations did not persist in multivariate analysis [12, 21]. Of note, most of these analyses correlated histological response and survival after preoperative chemoradiation.

Histopathologic regression was achieved independently of metastatic status at resection, which might
explain, that rather tumor biology than tumor load is predictive for long-term survival.

However, we have to admit that by including only patients into the analysis who underwent tumor resection with curative intent after preoperative chemotherapy, we are potentially selecting for patients with a more favorable prognosis. Therefore, our results may not be valid in populations not fulfilling the inclusion criteria of our analysis.

We acknowledge that our observations are based on a small number of patients with a pCR (n = 18). Larger trials and longer follow-up periods are necessary to clearly define the role for the use of histopathologic complete response as an independent predictor of long-term survival after neoadjuvant docetaxel-based chemotherapy.

In conclusion, our data demonstrate that the achievement of a pCR to preoperative docetaxel-based chemotherapy may serve as a predictor of favorable outcome in patients with gastric or EGJ adenocarcinoma. The high rate of pCR achieved with this triplet warrants a direct comparison to standard ECF/ECX, a phase III trial, which is currently recruiting patients (Clinical-Trial.gov number NCT01216644).

disclosure

The authors have declared no conflicts of interest.

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Circulating levels of immune and inflammatory markers and long versus short survival in early-stage lung cancer

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Background: Some patients diagnosed with early-stage lung cancer and treated according to standard care survive for only a short period of time, while others survive for years for reasons that are not well understood. Associations between markers of inflammation and survival from lung cancer have been observed.

Materials and methods: Here, we investigate whether circulating levels of 77 inflammatory markers are associated with long versus short survival in stage I and II lung cancer. Patients who had survived either <79 weeks (~1.5 years)

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