The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: A randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+) ★

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Abstract Background: We evaluated the feasibility and tolerability of triple- versus double-drug chemotherapy in elderly patients with oesophagogastric cancer.

Methods: Patients aged 65 years or older with locally advanced or metastatic oesophagogastric cancer were stratified and randomised to infusional 5-FU, leucovorin and oxaliplatin without (FLO) or with docetaxel 50 mg/m² (FLOT) every 2 weeks. The study is registered at ClinicalTrials.gov, identifier NCT00737373.

Findings: One hundred and forty three (FLO, 71; FLOT, 72) patients with a median age of 70 years were enrolled. The triple combination was associated with more treatment-related National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3/4 adverse events (FLOT, 81.9%; FLO, 38.6%; \( P < .001 \)) and more patients experiencing a ≥10-points deterioration of European Organization for Research and Treatment of Cancer Quality of Life (EORTC QoL) global health status scores (FLOT, 47.5%; FLO 20.5%; \( p = .011 \)). The triple combination was associated with more alopecia (\( P < .001 \)), neutropenia (\( P < .001 \)), leukopenia (\( P < .001 \)), diarrhoea (\( P = .006 \)) and nausea (\( P = .029 \)). No differences were observed in treatment duration and discontinuation due to toxicity, cumulative doses or toxic deaths between arms. The triple combination improved response rates and progression-free survival in the locally advanced subgroup and in the subgroup of patients aged between 65 and 70 years but not in the metastatic group or in patients aged 70 years and older.

Interpretation: The triple-drug chemotherapy was feasible in elderly patients with oesophagogastric cancer. However, toxicity was significantly increased and QoL deteriorated in a relevant proportion of patients.

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1. Introduction

The global incidence of oesophagogastric cancer was estimated to be nearly 1.5 million in 2008. The majority of these patients, nearly two-thirds, are over the age of 65 years; however, older patients are generally underrepresented in clinical trials, and many elderly patients do not receive effective combination therapies most probably due to concerns with tolerability.

Systemic chemotherapy as palliative treatment of patients with advanced oesophagogastric cancer is widely accepted. Doublet combinations with a fluoropyrimidine and a platinum have been considered standard treatment based on improved survival and response rates for many years. The addition of docetaxel to cisplatin and 5-FU (DCF regimen) has been shown to improve efficacy in a recent phase III trial. The improvement, however, was achieved on the cost of substantial toxicity. National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3/4 neutropenia and complicated neutropenia were observed in 82% and 29% of patients receiving DCF, respectively, and severe stomatitis, diarrhoea and lethargy were in the 20% range. Median age was 55 years, with only 24% of patients aged ≥65 years. This has raised doubts about whether older patients will be able to tolerate a docetaxel-based triplet.

Oxaliplatin has been shown to be more tolerable than cisplatin, especially in older patients, and has proven efficacy in combination with fluorouracil. In a randomised phase III trial of 220 patients with previously untreated advanced adenocarcinoma of the stomach or oesophagogastric junction, the combination of 5-FU, leucovorin and oxaliplatin (FLO) every two weeks was associated with significantly less adverse events compared to 5-FU, leucovorin and cisplatin (FLP) with comparable efficacy. Furthermore, elderly patients treated with FLO had significantly higher ORR (41.3% versus 16.7%; \( P = .012 \)), median PFS (6.0 versus 3.1 months; \( P = .029 \)) and a trend towards an improved OS (13.9 versus 7.2 months) compared to those treated with FLP.

The addition of docetaxel at 50 mg/m² every two weeks to the FLO regimen was shown to be active and tolerable in a cohort of 59 patients with a median age of 60 years, with metastatic gastric or oesophagogastric junction cancer, yielding a response rate of 58%. Grade 3/4 neutropenia occurred in 48% of patients, but febrile neutropenia in only 3.8%, which were favourable compared to DCF.

The aim of this present study was to determine if the docetaxel-based triplet regimen FLOT is feasible in elderly patients. Since information on tolerability and feasibility of FLOT was required for both, the locally advanced and metastatic setting, patients with locally advanced or metastatic disease were eligible to enrol in this phase II trial after prospective stratification.
2. Methods

2.1. Patient eligibility

Patients aged \( \geq \) 65 years with histologically confirmed and measurable locally advanced or metastatic adenocarcinoma of the stomach or oesophagogastric junction were eligible. Patients with locally advanced disease (as determined by CT scans and endoscopic ultrasound) had to have lymph node involvement (>2 cm) in order to enable adequate response evaluation. Patients must have had no prior chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, sufficient bone marrow and kidney function, and no concurrent uncontrolled medical illness. Participants gave written informed consent, which was approved by the ethics committees of the participating institutions.

2.2. Stratification and treatment

Patients were stratified by centre, tumour status (locally advanced versus metastatic), ECOG status, presence of liver metastases and pharmacogenetic risk (as determined by analysis of specific genetic variants). The pharmacogenetic risk profile was an experimental stratification; the results will be published separately. The dose of oxaliplatin 85 mg/m\(^2\), leucovorin 200 mg/m\(^2\) and docetaxel 50 mg/m\(^2\), each as an intravenous infusion followed by 5-FU 2600 mg/m\(^2\) as a 24-h continuous infusion (FLOT) or the same regimen without docetaxel 50 mg/m\(^2\) (FLO). Treatment was administered on day one of two weekly cycles. Antiemetic prophylaxis was given according to local protocols. Prophylactic dexamethasone 8 mg was administered orally (days −1 to +2) to prevent fluid retention and allergic reactions. The prophylactic use of growth factors was not permitted. Patients received eight cycles of FLOT or FLO, which could be extended to a maximum of 12 cycles upon investigator’s decision. Patients in the locally advanced stratum were reevaluated for operability after four cycles (8 weeks). Treatment in both arms was continued until disease progression, unacceptable toxicity, patient’s refusal, physician’s decision or until eight cycles (or 12 cycles upon investigator’s decision) were completed.

The dose of 5-FU and docetaxel was reduced by 25% for diarrhoea or mucositis exceeding NCI-CTC grade 2. In cases of paresthesia or dysesthesia persisting between cycles, oxaliplatin was reduced by 25%. In cases of paresthesia or dysesthesia accompanied by pain or functional impairment, oxaliplatin was reduced by 50% or omitted in further cycles until recovery (if persisting between cycles). Treatment was continued if blood leucocytes were \( \geq 3000/\mu l \) independent of the granulocyte count and in the absence of thrombocytopenia or any other non-haematological toxicity >NCI-CTC grade 1.

2.3. Toxicity assessment

For the assessment of toxicity, patients were interviewed using a standardised set of questions and were evaluated by physical examination and laboratory tests, including complete blood count, blood chemistry and urine analysis, every week. Toxic effects were graded according to NCI-CTC version 3.0. Peripheral sensitive neuropathy was graded according to an oxaliplatin-specific scale.\(^{10}\)

2.4. Quality of life assessment

Quality of life (QoL) was evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ C30). QoL was assessed within seven days prior the first cycle and at eight, 16 and 24 weeks thereafter. According to EORTC guidelines, patients filled out the QoL questionnaires before the tumour assessment was performed.

2.5. Evaluation of efficacy outcomes

Responses were classified according to the World Health Organization (WHO) criteria\(^{11}\) to ensure comparability to previous studies.\(^8,9\) Computed tomography scans of the chest, abdomen and pelvis were carried out within 3 weeks before the start of treatment and were repeated every eight weeks. Patients who discontinued the study were evaluated every 2 months.

2.6. End-points and statistical analysis

The primary objective of the study was tolerability and feasibility, defined as per group differences in toxic effects, serious adverse events, treatment durations, treatment withdrawals or discontinuations for toxicity or patient’s request and the proportions of patients with a \( \geq 10\)-point change of QoL global health status at eight weeks compared to baseline.\(^{12}\)

Since this primary objective was exploratory and consisted of multiple parameters, with no preexisting assumptions, we chose the response rate for sample size calculation. Based on historical response rates observed for FLO (32%)\(^8\) and FLOT (58%),\(^9\) we assumed response rates of 30% and 50% with FLO and FLOT, respectively. The resulting sample size was 140 patients, using an 80% power at one-sided significance level of 0.05. Further end-points were progression-free survival (PFS) and overall survival (OS).

PFS was measured from the date of randomisation until disease progression or death of any cause. OS was measured from date of randomisation until death of any cause.
2.7. Role of the funding source

The Institute of Clinical Research at Krankenhaus Nordwest University Cancer Center Frankfurt is the legal sponsor of the study according to European Law. The study design, protocol writing and the conduct of the trial were performed by the staff of the Institute of Clinical Research and AIO. The Institute of Clinical Research has received partial funding from Sanofi Aventis, Germany. However, the funder had no role in the conduct of the trial or collection, analysis and interpretation of the data. The funder also had no role in writing or reviewing this manuscript.

3. Results

3.1. Patient characteristics

Between August 2007 and October 2008, 143 patients (FLOT, 72; FLO, 71) were recruited from 28 centres in Germany. One patient was excluded from the safety analysis because of consent withdrawal before study treatment. Therefore, all 143 patients (FLOT, 72; FLO, 71) were eligible for the efficacy analysis on an intent-to-treat basis and 142 patients (FLOT, 72; FLO, 70) were eligible for the safety analysis (Fig. 1). The treatment arms were well balanced for pretreatment characteristics (Table 1).

3.2. Treatment

In both treatment arms, median of applied chemotherapy cycles was 8 (range, FLOT, 1–13; FLO, 0–15). Treatment durations were comparable for both regimens, with 32% of FLOT and 33% of FLO patients receiving between 0 and 4 cycles; 39% and 38% receiving 5–8 cycles; 29% and 28% receiving between 9 and 12 cycles; and 1% in each arm receiving > 12 cycles of therapy. Treatment duration was 133.5 days with FLOT and 120.5 days with FLO. Median cumulative 5-FU and oxaliplatin dose per patient was similar in the two treatment arms (FLOT, 20,686 mg/m² and 547 mg/m², respectively; FLO, 18,218 mg/m² and 595 mg/m², respectively). Numbers of cycles and treatment durations according to treatment arm were also comparable when analysed in the patient subgroup aged ≥ 70 years (n = 74). Dose modifications due to toxicity were performed in 32 of 72 (44.4%) patients in the FLOT arm and 16 of 70 patients in the FLO arm (22.9%; p = .008).

Reasons for treatment discontinuation were comparable in the FLOT and FLO arms, and were disease progression (21.1% versus 26.0%), death (9.8% versus 8.6%, all but one due to disease progression), toxicity or patient’s request (23.8 versus 20.1%) and other reasons (11.2% versus 11.5%).

However, in the subgroup of patients aged ≥70 years, more patients discontinued treatment for toxicity in the FLOT arm (FLOT, 20.6%; FLO, 7.5%).

3.3. Safety

Significantly more patients had treatment-related NCI-CTC grade 3/4 adverse events in the FLOT arm (FLOT, 81.9%; FLO, 38.6%; P < .001). FLOT was associated with significantly more NCI-CTC grade 3 or 4 neutropenia (P < .001), leukopenia (P < .001) and nausea (P = .029; Table 2). FLOT was also associated with significantly more any grade alopecia (P < .001) and diarrhoea (P = .006). There was no difference in complicated neutropenia (febrile neutropenia or neutropenic infection) between treatment arms (FLOT, 1.4%; FLO, 0). Similar rates of serious adverse events (SAE)
were observed among patients in both treatment arms (FLOT, 55.6%; FLO, 49.3%). One toxic death with suspected relation to study treatment was observed with FLO (intestinal mucositis). Similar distributions of toxic effects according to treatment arm were observed when analysed in the subgroups based on age (<70 versus P ≥ 70 years; data not shown).

3.4. Quality of life

The proportions of patients with assessable QoL questionnaires at baseline, 8, 16 and 24 weeks were 123/143 (87%), 91/122 (75%), 51/76 (67%) and 21/31 (68%), respectively, and were similar in both arms. QoL global health status scores (means ± standard deviation) at these time points were 56.5 ± 24.4, 53.6 ± 19.9, 56.8 ± 19.5 and 53.7 ± 22.8 for FLOT and 49.4 ± 24.7, 58.2 ± 19.8, 53.3 ± 21.0 and 55.5 ± 16.9 for FLO, with no significant differences between arms.

However, a moderate to large (> 10 points) deterioration of QoL global health status scores during the first eight weeks of treatment occurred in 19 of 40 (47.5%) evaluable patients with FLOT compared to 9 of 44 (20.5%) evaluable patients with FLO (p = .011). The proportions of patients with a > 10 point improvement of QoL global health status scores were 10 (25%) with FLOT and 12 (27.3%) with FLO. No change was observed in 11 (27.5%) and 23 (52.3%) patients with FLOT and FLO, respectively.

3.5. Efficacy outcomes

In the ITT population, there was a statistically significant improvement in RR in favour of FLOT (48.6%; 95% CI: 36.65–60.69%) versus FLO (28.17%, 95% CI: 18.13–40.1%; 2-sided P = .016). In the FLOT arm, four patients (5.6%) had a CR and 31 patients (43%) had a PR. In the FLO arm, no patients had a CR and 20 patients (28.17%) had PR. Stable disease was achieved in 27 (37.5%) and 36 patients (50.7%), respectively, and progressive disease in 6 patients in each arm (8.5% and 8.3%, respectively). Four (5.6%) and nine (12.7%) patients were not evaluable for response in the FLOT and FLO arms, respectively.

In the subgroup analyses, FLOT was associated with improved RR in patients aged <70 years (FLOT, 63.2%, 95% CI: 45.99–78.19%; FLO, 23.3%, 95% CI: 9.93–42.28%; p = .001) or patients with locally advanced disease (FLOT, 59.1%, 95% CI: 36.35–79.29%; FLO, 18.2%, 95% CI: 5.19–40.28%; p = .012), while no difference regarding RR between arms was found in patients aged ≥ 70 years (FLOT, 32.4%; FLO, 31.7; p = 1.0) or patients with metastatic disease (FLOT, 44%; FLO, 32.7%; p = .303).

Patients treated with FLOT showed a trend towards longer median PFS (9.0 months, 95% CI 7.3 to 11.8) compared to patients in the FLO group (7.1 months, 95% CI: 5.2–10.1; P = .079) (Fig. 2a), and there was no significant difference in median OS between the two groups (FLOT, 17.3 months; 95% CI, 12.7 to undetermined; FLO, 14.5 months; 95% CI, 11.7–21.1 months; P = .39; Fig. 2b). Similar to the RR, FLOT was associated with longer median PFS in patients with locally advanced disease (p = .019; Fig. 2c) and in patients aged < 70 years (p = .05; Fig. 2e), while group differences in PFS were observed in patients with metastatic disease (p = .43; Fig. 2d) or in patients aged ≥ 70 years (p = .65; Fig. 2f).

4. Discussion

We report the results of a randomised phase II trial specifically assessing the tolerability, feasibility and QoL of the addition of docetaxel to the duplet-drug combination 5-FU/leucovorin and oxaliplatin (FLO) in older adult patients with gastric cancer.

The addition of docetaxel to 5-FU/leucovorin and oxaliplatin (FLO) resulted in significant increases in individual toxicities such as neutropenia, leukopenia, diarrhoea and nausea. The rates and types of adverse events observed were consistent with those expected from the single drugs and previously reported in younger patients receiving FLOT.9 No differences were
observed in treatment duration and discontinuation due to toxicity, cumulative doses or toxic death between arms. The toxicity profile of FLOT also compared favourably with other docetaxel based triple-drug combinations such as DCF (grade 3 or 4 neutropenia, 82%; grade 3 or 4 leukopenia, 65%; complicated neutropenia, 29%).4 Nevertheless, the increase in side-effects in the triple-drug arm has to be considered as clinically relevant. Overall NCI-CTC grade 3 or 4 adverse events were approximately twice as high with FLOT as they were with FLO (FLOT, 81.9%; FLO, 38.6%; \( P < .001 \)), as were the rates of dose modifications due to toxicity (FLOT 44.4%; FLO, 22.9%; \( p = .008 \)), and the proportions of patients who experienced a \( \geq 10 \)-point deterioration of QoL global health scores after eight weeks of treatment (FLOT, 47.5%; FLO 20.5%; \( p = .011 \)). Since FLOT was associated with higher response rates and a rate of primary (at eight weeks) disease progression of 8.5% only, the deterioration of the QoL scores is likely attributed to the toxicity of the triple-drug combination.

The present study confirmed the role of doublet-drug combination FLO as a tolerable and active treatment option for older adult patients with metastatic gastric cancer. In a previous exploratory subset analysis of a phase III trial of metastatic gastric cancer, median PFS and OS with FLO were 6.0 and 13.9 months, respectively.8 In the current study, median PFS and OS in the metastatic subset are similar (6.0 and 11.7 months, respectively). The addition of docetaxel (FLOT) resulted in a significant improvement in ORR (FLOT, 48.6%; FLO 28.17%, \( P = .016 \)) and a trend towards an improvement in PFS (FLOT, 9 months; FLO, 7.1 months; \( P = .079 \)) in the total population. However, when the analysis was limited to patients having metastatic disease, no relevant differences in ORR and PFS were detected. Both end-points were significantly improved with FLOT in the locally advanced group, but this should be interpreted with caution because the subgroup of patients with locally advanced disease is small and can be extremely heterogeneous. A recent report of 46 patients with resectable

### Table 2
Main toxicities according to the National Cancer Institute Common Toxicity Criteria Version 3.0.4

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<th>Grade 3 or 4</th>
<th>( P )-valueb</th>
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<td>FLOT (n = 72)</td>
<td>FLO (n = 70)</td>
<td>FLOT (n = 72)</td>
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<tr>
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**Abbreviations:** FLOT, 5-FU, leucovorin, oxaliplatin, docetaxel; FLO, 5-FU, leucovorin, oxaliplatin; NA, not applicable; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST aspartate aminotransferase.

\( a \) Data for events (maximum grade per patient) with suspected relation to the study drugs.

\( b \) Fisher’s exact test was used. With the exception of alopecia, \( p \)-values are related to the groupings grade 0–2 versus grade 3–4 for FLOT versus FLO.

\( c \) \( P \)-value for the comparison of all grade diarrhoea with FLOT versus FLO is \( P = .006 \).
oesophagogastric cancer, in whom FLOT achieved high rates (17.4%) of pathological complete remission, was promising, but randomised trials in this setting are needed. The Arbeitsgemeinschaft Internistische Onkologie (AIO) has initiated a randomised clinical phase II trial in patients with oesophagogastric cancer comparing FLOT with ECF in the perioperative setting of potentially operable stages (ClinicalTrials.gov identifier: NCT01216644).

There is a worldwide debate about the most appropriate definition of ‘elderly’ patients. In clinical trials, the definition of elderly patients varied from 65 years of age or older to 70 years of age or older, although many experts favour a more functional definition of elderly patients, which is based on the patient’s functional health status or co-morbidities that may interfere with treatment decision-making. In the present trial, we chose the 65 years of age or older definition, mainly because this definition had been used by our group in the previous phase III study mentioned above.

This trial shows that fit elderly patients with advanced gastric cancer can tolerate an intensive triplet and, similar to younger patients, are likely to be compliant with therapy. This is in line with two retrospective pooled analyses that have shown that elderly patients with metastatic oesophagogastric cancer benefit from chemotherapy in a similar degree as younger patients. However, FLOT was associated with a substantial increase in toxicity and negatively impacted QoL, while the increment in efficacy with FLOT did not seem to be as substantial, particularly in patients over 70, or in those with metastatic disease, but this should be further studied in future trials.

Contributors

the results. S.E.A. and C.P. analysed data. S.E.A. and C.P. wrote the report. All authors reviewed, amended and approved the report.

Conflict of interest statement

S.E.A. has received research grants and honoraria for advisory role from Sanofi Aventis. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2012.09.025.

References