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Paclitaxel in the Neoadjuvant Treatment for Adenocarcinoma of the Distal Esophagus (AEG I). A Comparison of Two Phase II Trials with Long-Term Follow-Up

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Key Words
Paclitaxel · Adenocarcinoma of the esophagus · Neoadjuvant chemotherapy

Summary
Introduction: We report a comparative analysis of 2 sequential, prospective phase II trials on the efficacy of platinum/leucovorin/5-fluorouracil (PLF) +/– paclitaxel (T-PLF) in the neoadjuvant treatment of adenocarcinoma of the esophagus (AEG I). **Patients and Methods:** Inclusion criteria were histologically proven, locally advanced AEG I stage uT3/4 anyN cM0/M1a. 67 patients were treated with either PLF (n = 32) or T-PLF (n = 35). Paclitaxel (80 mg/m^2) was added to PLF on days 1, 15, and 29. Primary endpoint was the response. Additionally, 5-year survival was analyzed. **Results:** The study population was well balanced, apart from an imbalance in clinical cM1a (33.3% PLF vs. 8.6% T-PLF; p = 0.01). Histopathological response rates (23.3% PLF vs. 25.0% T-PLF) showed no significant difference. Clinical response rates were improved for T-PLF (21.9 vs. 45.7%; p = 0.04). Median overall survival for clinical and histopathological responders was significantly improved for T-PLF (p = 0.005, p = 0.01), but not for PLF (p = 0.08, p = 0.25). Median overall survival was better with T-PLF without reaching statistical significance (18.9 months PLF vs. 43.1 months T-PLF; p = 0.27). Toxicity was slightly increased by paclitaxel. No treatment-related deaths occurred. **Conclusion:** Our data failed to demonstrate statistically significant superiority of the T-PLF regimen except for clinical response. However, there was a trend towards improved survival.

*These authors contributed equally to this work and should be recognized as first authors.

Schlüsselwörter
Paclitaxel · Adenokarzinom des Ösophagus · Neoadjuvante Chemotherapie

Zusammenfassung
Einleitung: Die vorliegende Untersuchung vergleicht die Wirksamkeit zweier sequentieller Phase-II-Studien mit Cisplatin/Leukovorin/5-Fluorouracil (PLF) +/– Paclitaxel (T-PLF) in der neoadjuvanten Therapie von Adenokarzinomen des distalen Ösophagus (AEG I). **Patienten und Methoden:** Eingeschlossen wurden lokal fortgeschrittene AEG I der Stadien uT3/4, N±, cM0/M1a. 67 Patienten wurden mit PLF (n = 32) bzw. T-PLF (n = 35) neoadjuvant therapiert. Paclitaxel (80 mg/m^2) wurde an den Tagen 1, 15 und 29 zusätzlich zu PLF infundiert. Primärer Endpunkt war das Ansprechen. Zusätzlich wurde das 5-Jahres-Überleben analysiert. **Ergebnisse:** Das Studienkollektiv war bis auf die cM1a-Kategorie (33,3% PLF vs. 8,6% T-PLF; (p = 0,01) homogen. Das histopathologische Ansprechen zeigte keine signifikanten Unterschiede (23,3% PLF vs. 25,0% T-PLF). Das klinische Ansprechen war für T-PLF verbessert (21.9% vs. 45.7%) (p = 0,04). Das mediane Überleben für klinische und histhopathologische Responder war für T-PLF (p = 0,005; p = 0,01), nicht aber für PLF (p = 0,08; p = 0,25) verbessert. Das mediane Gesamtüberleben war tendenziell für das T-PLF-Regime (18,9 Monate PLF vs. 43,1 Monate TPLF; p = 0,27) besser, ohne statistische Signifikanz zu erreichen. Die Toxizität war in der T-PLF-Gruppe leicht erhöht. Es traten keine therapiebedingten Todesfälle auf. **Schlussfolgerung:** Es konnte keine statistisch signifikante Überlegenheit des T-PLF-Regimes gegenüber PLF gezeigt werden. Tendenziell zeigte sich jedoch verbessertes Überleben für die Dreifachkombination T-PLF.

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Introduction

After the publication of 3 randomized controlled trials, neoadjuvant chemotherapy (CTx) has become an accepted choice for the treatment of locally advanced adenocarcinoma of the esophagus and the esophagogastric junction (AEG I) [1–3]. However, the use of neoadjuvant chemotherapy without the addition of radiotherapy is not generally accepted for AEG I. In many institutions, additional or sequential radiotherapy is delivered [4–7], but a recent meta-analysis gives justification for both the neoadjuvant chemotherapy and chemoradiotherapy approach in the treatment of resectable adenocarcinomas of the esophagus [8]. However, there is some evidence that the addition of radiation therapy might increase the risk of postoperative morbidity and mortality, which may be due to stronger immunosuppression in comparison to preoperative chemotherapy alone [9, 10]. Due to these facts, neoadjuvant chemotherapy was the treatment of choice for locally advanced esophageal adenocarcinomas in our institution.

Previous studies defined a role for taxanes in patients with advanced esophagogastric cancer, who are able to tolerate a 3-drug regimen [11–14]. In preclinical studies, paclitaxel has been shown to act synergistically with cisplatin [4, 15, 16]. Therefore, we defined the clinical and histopathological response rates as the primary endpoints in these 2 prospective, non-randomized phase II studies, performed in patients with locally advanced AEG I treated either with cisplatin, leucovorin, and 5-fluorouracil (5-FU) (PLF), or with the addition of paclitaxel (T-PLF). Additionally, an analysis of survival based on long-term follow-up was included.

Table 1. Pre-therapeutic patient characteristics

Characteristics	Patients, n		p value
	PLF	T-PLF	
Median age, years (range)	56.4 (38.8–72.2)	51.6 (25–67.4)	0.02
Gender, n			
Male	29	33	n.s.
Female	3	2	
Karnofsky index			
100%	16	18	n.s.
90%	11	13	
80%	3	1	
70%	2	3	
Histological type			
Adenocarcinoma	30	33	n.s.
Anaplastic	2	2	
Grading			
G1/G2	8	15	0.20
G3/G4	24	20	
Lauren classification			
Intestinal	20	26	n.s.
Non-intestinal	12	9	
Barrett esophagus	15/32	20/35	n.s.
cT category			
cT_3	26	33	n.s.
cT_4	6	2	
cN category			
cN_0	2	0	n.s.
cN+	30	35	
cM category			
cM_0	21	32	0.01
cM_{1a}	11	3	
CTx			
< 50%	1	4	n.s.
> 50%	31	31	
100%	25	23	

PLF = Platinum/leucovorin/5-fluorouracil; T-PLF = PLF + paclitaxel; n.s. = not significant.

Material and Methods

Eligibility

Patients (aged 18–75 years) with locally advanced (uT3 and uT4, anyN, M0/M1a), histologically confirmed AEG I were enrolled. Patients were required to have a Karnofsky index of ≥ 70%, and must not have received previous chemo- and/or radiotherapy. Laboratory criteria included adequate bone marrow function, adequate renal function, and normal liver function. Women of childbearing potential were required to have a negative pregnancy test. Patients were considered ineligible if they had a history of concomitant or previous malignancy. All patients signed an informed consent form that was approved by the local ethics committee of the Technische Universität Munich.

Pre-Treatment Diagnostics and Staging

The pre-treatment evaluation included a detailed physical examination. Diagnostic tests comprised chest radiography, upper gastrointestinal endoscopy with biopsies, endoluminal ultrasound, barium esophagogram, and computed tomography (CT) scans of the chest, abdomen, and pelvis. To evaluate medical operability, every patient was assessed according to a detailed risk evaluation [17, 18].

Neoadjuvant Chemotherapy

The neoadjuvant T-PLF chemotherapy regimen consisted of paclitaxel 80 mg/m^2, administrated as a 3-h intravenous (i.v.) infusion on days 1, 15, and 29. A total of 50 mg/m^2 cisplatin was administrated as a 1-h i.v. infusion on days 2, 16, and 30. In addition, 500 mg/m^2 leucovorin were applied i.v. over 2 h on days 2, 9, 16, 23, 30, and 37, followed by a 2,000 mg/m^2 i.v. infusion of 5-FU over 24 h. The second cycle started on day 50. Toxicity was classified according to the Common Toxicity Criteria (CTC), National Cancer Institute (NCI). In the PLF regimen, the schedule was identical, except that no paclitaxel was delivered.

Clinical and Histopathological Response Evaluation

Endoscopy with endoluminal ultrasound and CT scans were used after the first and second cycle as recently described [19–21]. Response evaluation was performed by the interdisciplinary tumor board of the Technische Universität Munich. Clinical response was defined as an at least 50% reduction in size of the primary tumor, as measured by endoscopy and imaging studies. When there was a minor reduction in tumor size (≤ 50%), or when new metastatic lesions were detected, the tumor was classified as non-responding. The same criteria for response have been used in our study as well as in other previous studies, and have been shown to be of prognostic relevance [19–23]. All histopathological analyses of the resected specimens were performed by an experienced pathologist (K.B.). Tumor regression was assessed semi-quantitatively according to a recently published scoring system [24]. For the purpose of this study, all

Table 2. Post-therapeutic patient characteristics

Characteristics	Patients, n		p value
	PLF	T-PLF	
Clinical response			
Responder	7 (21.9)	16 (45.7)	0.04
Non-responder	25 (78.1)	19 (54.3)	
Histopathological response			
Responder	7 (23.3)	8 (25.0)	n.s.
Non-responder	23 (76.7)	24 (75.0)	
Operation			
Yes	30	32	n.s.
No	2	3	
Type of resection			
Transhiatal EE	25	18	n.s.
Transthoracic EE	4	11	
Esophagogastrectomy	0	1	
Transhiatal EG	1	2	
Type of reconstruction			
GT posterior mediastinum	25	24	n.s.
GT anterior mediastinum	3	5	
Colonic interposition	1	1	
Esophagojejunostomy	1	2	
Location of anastomosis			
Cervical	27	21	0.07
Intrathoracic	2	9	
Esophagojejunostomy	1	2	
ypT category			
ypT_0	2	3	n.s.
ypT_1	0	4	
ypT_2	9	5	
ypT_3	18	20	
ypT_4	1	0	
ypN category			
ypN_0	11	11	n.s.
ypN+	19	21	
ypM category			
ypM_0	25	28	n.s.
ypM_{1a}	5	4	
Lymphangiosis			
Yes	20	16	n.s.
No	10	16	
Lauren classification			
Intestinal	16	24	n.s.
Non-intestinal	12	7	
R category			
R0	20 (66.7)	22 (68.8)	n.s.
R1	10 (33.3)	7 (21.9)	
R2	0	3 (9.3)	
Postoperative complications			
Yes	21 (70.0)	20 (62.5)	n.s.
No	9 (30.0)	12 (37.5)	

PLF = Platinum/leucovorin/5-fluorouracil; T-PLF = PLF + paclitaxel; n.s. = not significant; EE = esophagectomy; EG = extended gastrectomy; GT = gastric tube.

patients with less than 10% residual tumor cells (score 1a: complete response, score 1b: subtotal response) were classified as histopathological responders. All other patients were classified as histopathological non-responders.

Surgery

Patients underwent either a transhiatal or a transthoracic esophagectomy 3–4 weeks after completion of chemotherapy. Reconstruction was performed with a small gastric tube in the posterior mediastinum with intrathoracic or cervical anastomosis (table 1). In all cases with esophagectomy, a 2-field lymphadenectomy including the lymph nodes of the celiac trunk was performed. In patients with transhiatal extended gastrectomy, a D2 lymphadenectomy was performed.

Follow-Up

Follow-up was performed on an outpatient basis. During the first year after surgical resection, patients were observed at 3-monthly intervals by CT scan of the chest and abdomen and an endoscopy, followed by 6-monthly intervals in the second and third year, and then 12-monthly intervals. No patient was lost to follow-up.

Statistical Analysis

All quantitative data are expressed as mean ± one standard deviation. Differences in patients' proportion were analyzed by Fischer's exact test or χ^2 test. Inter- and intra-individual comparisons of quantitative data were made by using a Mann-Whitney-U and a Wilcoxon signed rank test. Survival rates were estimated according to Kaplan-Meier. Statistical comparisons between different patient groups were performed with a log-rank test. All tests were two-sided, and were performed at the 5% level of significance by using SPSS 14 (SPSS Inc., Chicago, IL, USA).

Results

A total of 67 patients were included in the 2 sequential phase II studies. 32 patients treated with PLF were enrolled from December 8th 1993 to August 27th 1996, 35 patients treated with T-PLF from September 25th 1996 to May 2nd 2000. The median follow-up for the 9 surviving patients in the PLF group was 109.3 months (84.2–134.4); the median follow-up for the 13 surviving patients in the T-PLF group was 78.3 months (68.1–94.9). The 2 study groups were well balanced, only the number of cM1a-staged patients was significantly higher in the group treated with PLF alone (11 vs. 3; p = 0.01) (table 1). All patients classified as cM1a had suspicious lymph nodes at the celiac trunk so that all suspicious lymph nodes were analyzed histopathologically. Moreover, patients were older at the time of diagnosis in the PLF group (median 56.4 years) compared to the T-PLF group (median 51.6 years) (p = 0.02).

Toxicity

No chemotherapy-related deaths occurred in both groups. 31 patients in each group completed at least 1 cycle, while 5 patients stopped chemotherapy after the first cycle in both groups. Of these 26 patients starting the second cycle in both groups, 25 patients (78.1%) within the PLF group completed the entire chemotherapy compared to 23 patients (65.7%) within the T-PLF group. Chemotherapy-related hospitalization in the PLF group was necessary in 6 patients during the first cycle and in 5 patients during the second cycle. In the T-PLF group, 5 and 6 patients were hospitalized during the first and the second cycle. Toxicity was increased in the T-PLF group, but manageable. Statistically significant differences be-

Table 3. Overall toxicity of the PLF and T-PLF group according to the Common Toxicity Criteria (CTC), National Cancer Institute (NCI)

	Patients, n (%)				p value
	CTC grade 1 and 2		CTC grade 3 and 4		
	PLF	T-PLF	PLF	T-PLF	
White blood cells	26 (81.3)	33 (77.7)	4 (12.6)	5 (14.7)	n.s.
Neutropenia	19 (59.4)	12 (37.6)	9 (28.1)	8 (23.5)	0.06
Platelets	8 (25.0)	1 (2.9)	–	–	0.026
Hemoglobin	27 (84.4)	27(79.4)	4 (12.6)	–	0.07
Emesis	10 (31.3)	12 (36.4)	2	1 (2.9)	n.s.
Nausea	17 (53.2)	27 (79.4)	4 (12.6)	1 (2.9)	n.s.
Mucositis	15 (46.9)	17 (50.0)	–	1 (2.9)	n.s.
Diarrhea	6 (18.8)	14 (41.1)	3	8 (23.5)	0.04
Alopecia	3 (9.4)	27 (79.4)	–	6 (17.6)	0.001
Dysphagia	23 (71.9)	19 (55.9)	4 (12.6)	10 (29.4)	n.s.
Anorexia	8 (25.0)	15 (44.1)	4 (12.6)	–	0.04
Infections	5 (15.6)	5 (14.7)	–	–	n.s.
Constipation	9 (28.1)	21 (61.8)	–	–	0.01
Central nervous system	4 (12.6)	–	–	–	n.s.
Fatigue	11 (34.4)	15 (44.1)	1 (3.1)	–	n.s.

PLF = Platinum/leucovorin/5-fluorouracil; T-PLF = PLF + paclitaxel; n.s. = not significant.

Table 4. Postoperative complications

	Patients, n (%)	
	PLF	T-PLF
Bleeding	1 (3.3)	0
Chylothorax	1 (3.3)	0
Cervical insufficiency	15 (50.0)	11 (34.4)
Intrathoracic insufficiency	1 (3.3)	1 (3.1)
Wound infection	1 (3.3)	0
Necrosis of the gastric tube	0	1 (3.1)
Sepsis	1 (3.3)	1 (3.1)
Recurrent nerve paralysis	0	1 (3.1)
Facialis nerve paralysis	1 (3.3)	0
Pneumonia	0	2 (6.3)
Tachyarrhythmia	0	1 (3.1)

PLF = Platinum/leucovorin/5-fluorouracil; T-PLF = PLF + paclitaxel.

tween the 2 treatment groups were found for thrombocytopenia (p = 0.026), diarrhea (p = 0.04), alopecia (p = 0.001), anorexia (p = 0.04), and constipation (p = 0.001) (table 2).

Response to Chemotherapy – Clinical Response of the Primary Tumor

A total of 7 patients (21.9%) in the PLF group and 16 patients (45.7%) in the T-PLF group were classified as clinical responders (p = 0.04) (table 3). In the T-PLF group, 3 patients were not transferred to surgery due to metastatic disease that developed during neoadjuvant chemotherapy. In the PLF group, 2 patients were not resected. A significant association between clinical response and prognosis could be shown. The median survival for clinical responders was not yet reached for the PLF and T-PLF group, and was 15.9 months (PLF) and 18.0 months (T-PLF) for clinical non-responders (p = 0.01).

Response to Chemotherapy – Histopathological Response of the Primary Tumor

Histopathological response could be evaluated for 30 resected patients in the PLF study, and 32 in the T-PLF study. A total of 7 patients (23.3%) within the PLF group and 8 patients (25.0%) within the T-PLF group were classified as histopathological responders, but there was no significant difference between the 2 study groups (p = 0.86) (table 3). Complete histopathological response (regression score 1a) was achieved in 2 patients (6.7%) treated with PLF compared to 3 patients (9.4%) treated with T-PLF. In 2 out of 3 patients in the T-PLF group with complete histopathological response of the primary tumor, locoregional lymph node metastases were found.

Surgery

Resection procedures are shown in table 3. For reconstruction, a gastric tube was used in 57 patients, a colonic interposition in 2 patients, and an esophagojejunostomy in 3 patients. The second colonic interposition was necessary due to 1 necrosis of the gastric tube in the T-PLF group (table 4). No significant differences were found between the 2 analyzed groups regarding surgical techniques (table 3). In both groups, no intraoperative complications occurred; the 30- and 90-day mortality was 0%. The duration of stay in the intensive care unit was a median 8 days (2–14; PLF) and 7 days (4–22; T-PLF) (p = 0.74).

Complications

Postoperative complications occurred in 70% of the patients in the PLF study and in 62.5% of the patients in the T-PLF study (p = 0.60). There were no significant differences between the type of complications within the 2 groups (p = 0.60) (table 4).

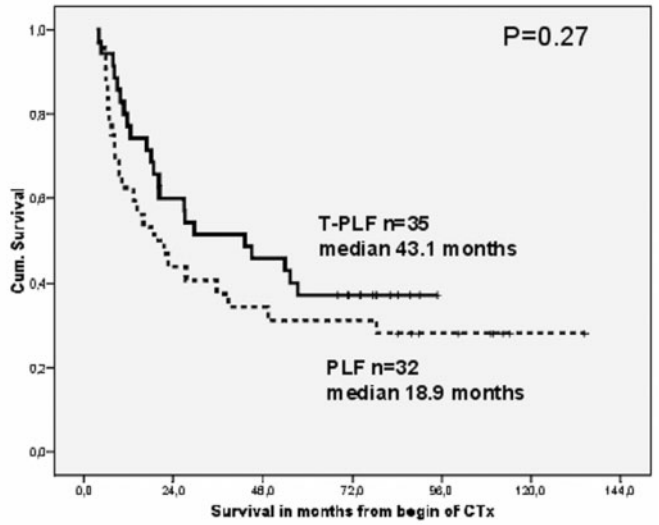

Fig. 1. Overall survival of the PLF and T-PLF group (p = 0.27).

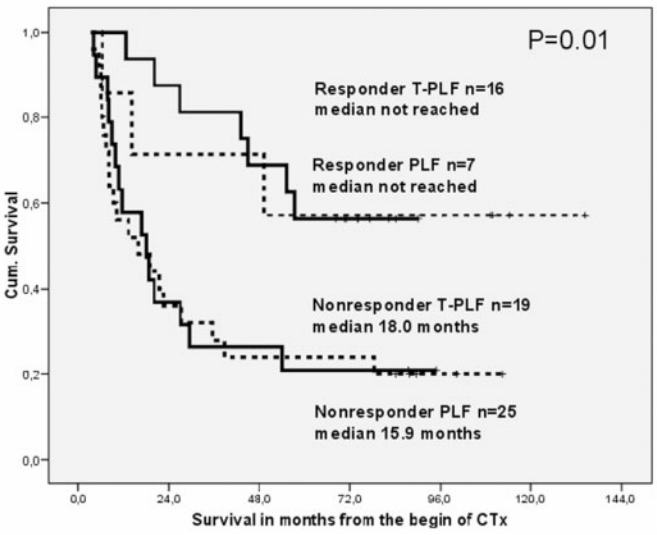

Fig. 2. Median survival with respect to clinical response and non-response for the PLF and T-PLF group (p = 0.01).

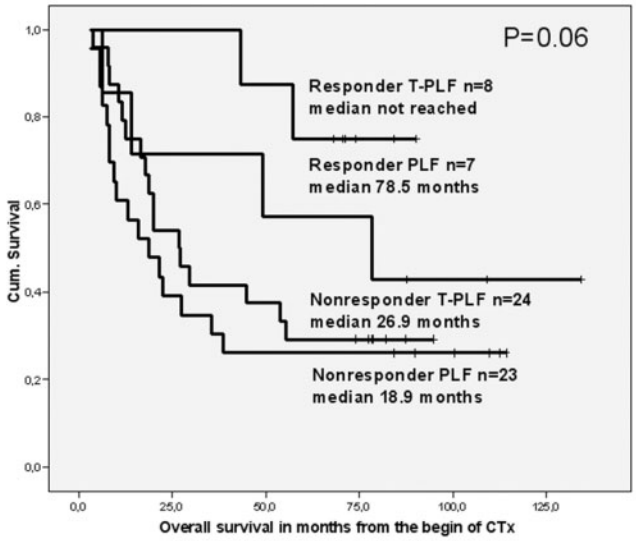

Fig. 3. Median survival with respect to histopathological response and non-response for the PLF and T-PLF group (p = 0.06).

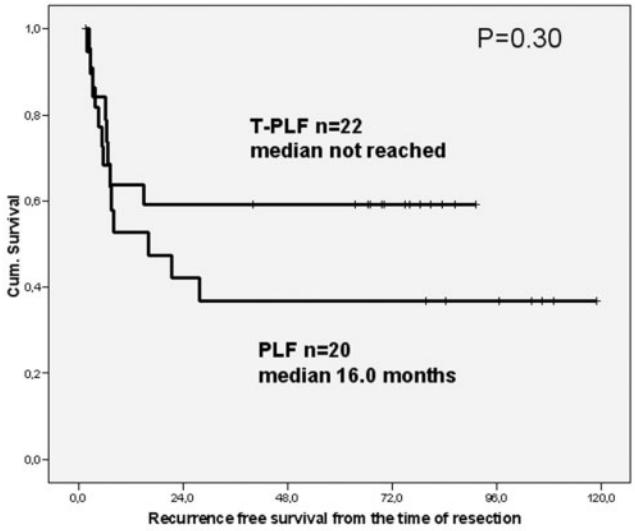

Fig. 4. Recurrence-free survival for the PLF and T-PLF group (p = 0.30).

Histopathological Work-Up

The complete resection rate (R0) was 66.7% (20/30 PLF) and 68.8% (22/32 T-PLF) (p = 1.0). Of the remaining 20 patients of both groups, 17 were found to have microscopically residual tumor (13: deep resection margin, 2: deep resection margin and aboral resection margin, 2: aboral resection margin). Three patients had macroscopically residual tumor (1: tumor bed, 1: aboral resection margin, 1: lung metastasis). The ypTNM categories are shown in table 3. A down-categorizing (< ypT3) of the primary tumor was found in 11 of 30 resected patients treated with PLF (36.7%) compared to 12 of 32 patients treated with T-PLF (37.5%) (p = 1.0). Lymphangiosis was found in 66.7% of patients within the PLF study, and in 50% within the T-PLF study (p = 0.21) (table 3).

Survival

The median survival of 43.1 months for patients treated with T-PLF vs. 18.9 months for patients treated with PLF failed to show statistical significance (p = 0.27) (fig. 1). The corresponding 1-, 2-, 3-, 4-, and 5-year survival rates were 62.5, 43.8, 37.5, 34.4, and 31.3% for the patients within the PLF study, and 77.1, 60.0, 51.4, 45.7, and 37.1% for the patients within the T-PLF study. Clinical and histopathological response predicted improved prognosis in the T-PLF study (p = 0.005, p =

0.01), but not in the PLF study (p = 0.08, p = 0.25) (figs. 2, 3). Down-categorizing (tumor category less than ypT3) of the primary tumor was associated with a significantly better prognosis in the T-PLF study (p < 0.001). In contrast, down-categorizing in the PLF study had no prognostic influence (p = 0.7). Generally accepted prognostic factors like R category (PFL: p = 0.02, T-PLF: p = 0.008), ypN category (PLF: p = 0.02, T-PLF: 0.04), and lymphangiosis (PLF: p = 0.01; T-PLF: p = 0.04) had a significant prognostic impact in both studies. To reduce an inclusion bias, a separate survival analysis for the initially cM0-staged patients was performed. The median overall survival for the T-PLF patients was 45.0 months, and the median survival for the PLF patients was 27.4 months (p = 0.36).

Patterns of Recurrence

Of the 42 completely resected patients, 21 had recurrences during the follow-up period. 41% of the patients treated with T-PLF had a recurrence, compared to 60% of the patients treated with PLF. Patterns of recurrence were not significantly different in the 2 groups (p = 0.27). Local recurrence occurred in 4 (18.2%) T-PLF patients and in 2 (10%) PLF patients. Distant metastases occurred in 5 (22.7%) T-PLF patients and in 9 (45.0%) PLF patients. In 1 (5%) patient treated with PLF, a pleural carcinomatosis was evident as first site of failure. The median recurrence-free survival for the T-PLF study is not yet reached compared to 16.0 months for the PLF study (p = 0.30) (fig. 4). The corresponding 1-, 2-, 3-, 4-, and 5-year recurrence-free survival rates are 52.6, 42.1, 36.8, 36.8, and 36.8% for the PLF study and 63.6, 59.1, 59.1, 59.1, and 59.1% for the T-PLF study.

Discussion

In these 2 sequential phase II studies, we could not demonstrate a statistically significant higher histopathological response rate or improved survival for patients treated with paclitaxel in addition to cisplatin, 5-FU, and leucovorin. Only for the endpoint of clinical response, which may be more investigator-dependent than histopathological response, we were able to show a significantly higher activity for paclitaxel. However, clinical response was translated into significantly improved survival for patients who received paclitaxel. The tendency for improved overall survival and recurrence-free survival for patients treated with paclitaxel did not reach statistical significance. A higher frequency of distant relapses and lymphangiosis was found in the PLF study compared to the T-PLF study. The apparently higher systemic efficacy may explain the trend towards a better survival for the T-PLF patients observed in these 2 studies, because the local efficacy seems to be identical in both regimens. When it comes to chemotherapy in the preoperative setting, the patients' safety and the feasibility of a chemotherapy regimen is a concern. Comparing toxicity in these 2 sequential phase II studies, the number of side effects was increased in the T-PLF group. On the other hand, all toxicity-related side effects in the T-PLF group were manageable. Importantly, no therapy-related deaths occurred in either groups, and no increase in the rate of postoperative complications was observed. The non-hematological toxicity reported in this study was similar to that published by van Cutsem et al. [14] for the treatment of metastatic gastric cancer with the taxoid docetaxel plus cisplatin and 5-FU. The reported toxicity for the treatment with paclitaxel in the study by Ilson et al. [12] was higher, and required hospitalization in nearly 50%. A neoadjuvant 3-drug regimen might be better tolerated than a 3-drug regimen given in the metastatic setting. Since treatment with T-PLF resulted in increased toxicity, the need for vigilant patient selection, education, monitoring, and active management should be emphasized.

Most reported studies delivering taxanes in esophageal cancer investigated paclitaxel or docetaxel in combination with radiotherapy in a mixed patient population presenting with adenocarcinomas or squamous cell carcinomas [4, 6, 25]. Histopathological complete response rates after neoadjuvant chemoradiotherapy in combination with taxanes were reported to be between 17.5 and 38% [4, 6, 25]. In the metastatic situation, taxane-based chemotherapy was shown to be effective [12, 26]. Ilson et al. [12] reported a clinical response rate of 46% and a pathological complete response (pCR) rate of 3% for esophageal adenocarcinoma. Lorenzen et al. [26] showed an overall response rate of 47% in AEG and gastric cancer. The pCR rate was at the upper expected limit for a neoadjuvant chemotherapy without the addition of radiotherapy in the T-PLF group. Notably, 2 of the 3 patients treated with T-PLF having a pCR of the primary tumor presented with locoregional lymph node metastases. This adds information to the ongoing discussion of whether or not patients with a complete response of the primary tumor after neoadjuvant chemotherapy should be operated on. Because there is the possibility of a mixed response with regional lymph node metastases that contain residual viable tumor cells in patients achieving a pCR of the primary tumor, a resection of the tumor with a 2-field lymphadenectomy for a curative concept in AEG I – even after a pCR of the primary tumor – seems to be of paramount importance.

The reported survival data for T-PLF are promising for a single phase II study, but failed to show superiority compared with PLF. This could be owed to the small sample size. Furthermore, the imbalanced study population with regard to the significantly higher number of cM1a patients in the PLF group has to be scrutinized. To minimize an inclusion bias as a potential reason for that, we analyzed the 2 regimes without the cM1a patients in each group, and got essentially the same results. In addition, the histopathological work-up revealed nearly identical numbers of histopathological ypM1a for both groups. Due to these analyses, the gross imbalance between the 2 studies with respect to cM1a should not account for all the differences seen in the analysis, but might be related to an initial overstaging of the included patients.

General limitations of this study are its non-randomized design, the small sample size, and the above mentioned imbalance regarding cM1a patients. The studies were arranged as prospective clinical phase II studies, but the comparative analyses were not preplanned. The sample size certainly does not allow for a definitive demonstration of the superiority or inferiority of either one of the two neoadjuvant chemotherapy regimes. However, one strength of the study is the homogeneity of the study population.

Conclusion

The addition of paclitaxel to PLF failed to demonstrate significant improvement of histopathological response rates or survival, but could show superiority for clinical response. Toxicity for the T-PLF regimen was slightly higher compared to PLF, but manageable. No increased postoperative mortality or morbidity was generated by the addition of paclitaxel. Trends toward an improved survival and better clinical response rates suggest a role for taxanes in patients with locally advanced and potentially resectable AEG I, who are able to tolerate a 3-drug regimen after careful evaluation. To improve prognosis and response in the future, the addition of more novel targeted agents or the addition of radiotherapy to increase complete resections is warranted.

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