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ORIGINAL ARTICLE

Predictive Value of Early Skin Rash in Cetuximab-Based Therapy of Advanced Biliary Tract Cancer

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Abstract Randomized trials in advanced biliary tract cancer (BTC) did not show benefit of cetuximab addition over chemotherapy. This is probably due to the lack of predictive biomarkers. The aim of this study was to explore possible predictive factors. Between 2009 and 2014, 57 patients were treated in 3-week cycles with cetuximab (250 mg/m^2/week, loading dose: 400 mg/m^2), gemcitabine (1000 mg/m^2 on day 1 and 8), and capecitabine (1300 mg/m^2/day on days 1–14). The objective response rate (ORR), progression-free (PFS) and overall survival (OS) and the adverse events (AEs) were evaluated. An exploratory analysis was performed to find possible predictive factors on clinicopathological characteristics, routine laboratory parameters and early AEs, which occurred within 2 months from the beginning of treatment. The ORR was 21%. The median PFS and OS were 34 (95% CI: 24–40) and 54 (43–67) weeks, respectively. The most frequent AEs were skin toxicities. In univariate analysis performance status, previous stent implantation, thrombocyte count at the start of therapy, early neutropenia and skin rash statistically significantly influenced the ORR, PFS and/or OS. In multivariate Cox regression analysis only normal thrombocyte count at treatment start and early acneiform rash were independent markers of longer survival. In patients showing early skin rash compared to the others the median PFS was 39 vs. 13 weeks and the median OS was 67 vs. 26 weeks, respectively. It is suggested that early skin rash can be used as a biomarker to select patients who would benefit from the treatment with cetuximab plus chemotherapy.

Keywords Acneiform rash · Predictive marker · Cetuximab · Chemotherapy · Cholangiocarcinoma

Introduction

Biliary tract cancer (BTC) is a rare disease with dismal prognosis [1]. Systemic therapy may improve survival when the tumor is not feasible for surgery or other locoregional interventions. In a randomized phase III trial with 402 patients the combination of gemcitabine and cisplatin significantly prolonged the overall survival (OS) over gemcitabine monotherapy (11.7 vs. 8.1 month, respectively) [2]. Based on these results the combination of gemcitabine and cisplatin have become the standard treatment in advanced BTC. The substitution of cisplatin with oxaliplatin in the combination therapy (GemOx) yielded similar efficacy with more favorable side effect profile, which makes GemOx a reasonable alternative [3, 4]. Fluoropyrimidines are also active in BTC with less toxicity then platinum compounds. In a meta-analysis of 83 trials it was concluded that chemotherapy combination containing gemcitabine resulted in significant longer survival, but the replacement of platinum with other drugs did not affect survival [5]. Epidermal growth factor receptor (EGFR) overexpression and mutations frequently occur in BTC, thus anti-

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EGFR treatments would be beneficial [3]. Three randomized trials using anti-EGFR agents (a phase 3 trial with erlotinib and two phase 2 trials with cetuximab) were published until now, all with GemOx as backbone chemotherapy [6–8]. The addition of anti-EGFR agents to GemOx resulted in higher response rates but did not improve OS in patients with advanced BTC. Neither EGFR expression nor *KRAS* mutational status proved to be predictive for efficacy in these trials; consequently, there is no established predictive factor for therapeutic effect of cetuximab to date.

In colorectal cancer (CRC) skin toxicity was reported to be in correlation with cetuximab efficacy [9]. In addition, there are reports that skin toxicity may predict longer survival with cetuximab therapy in BTC [8, 10]. On the other hand, previously it was reported that in a phase 2 trial cetuximab, gemcitabine, and capecitabine combination showed encouraging efficacy and acceptable toxicity (objective response rate (ORR) 17.6%, clinical benefit 76.5%, median progression-free survival (PFS) 34.3 weeks and median OS 62.8 weeks) [11]. In that analysis performance status and ORR had significant effect on survival. As this regime with advantageous toxicity profile had similar efficacy to the standard GemOx, the recruitment was continued in order to explore prognostic and/or predictive factors. The aim of this study was to find predictive markers of cetuximab + gemcitabine + capecitabine therapy in advanced BTC by analyzing clinicopathological parameters, circulating biomarkers and also early adverse events. However, the trial was designed for all BTC, it is well established that gall bladder cancer, intrahepatic and extrahepatic cholangiocellular carcinomas are different diseases [12]. Accordingly we performed subanalysis on different subtypes of BTC, as well.

Patients and Methods

In this explorative single-center study patients with histologically confirmed unresectable BTC have been recruited from July 2009 to March 2014. The protocol has been approved by the Medical Research Council of the Ethics Committee for Clinical Pharmacology, the National Institute of Pharmacy, and the Local Ethics Committee and registered at the EMEA (clinicaltrialsregister.eu, 2006–004981-14). Signed informed consent was obtained from each patient. Ampullary carcinoma was not allowed. The inclusion and exclusion criteria and pathological methods have been described in details previously (including EGFR expression and KRAS mutation analysis) [11].

Study Design

In this phase 2a, open-label, investigator-initiated, single-center trial patients received gemcitabine 1000 mg/m^2 i.v. on day 1 and 8 over 60–90 min, capecitabine 1300 mg/m^2 every day on days 1–14 in 21-day cycles. Capecitabine daily dose was rounded down to a dose maintainable with 500 mg tablets and the daily dose was divided into two and given in 12-h intervals. Cetuximab was administered with a dose of 250 mg/m^2 weekly after a loading dose of 400 mg/m^2. Patients were monitored for toxicity weekly and laboratory tests were performed before every chemotherapy administration. Both dose modification and/or temporary or permanent discontinuation of any drug was at the physician's discretion. It was recommended that in case of grade 3/4 hematological or grade 3 non-hematological side effects the dose should be reduced by 25% as a first step and by 50% as the second step. In cases where grade 4 non-hematological side effects were observed the study treatment was permanently discontinued. If the administration of one compound from the drug combination was modified (dose reduction or discontinuation), the dose modification of the other compounds remained at the physician's discretion. The treatment was planned to be continued until radiological progression according to RECIST 1.0 criteria or unacceptable toxicity. Radiological assessment with helical CT was carried out within 28 days before the first cycle of therapy and then every eight to 12 weeks. No confirmatory evaluation was planned.

Statistical Analysis

An exploratory analysis was performed for potential predictive factors of response, PFS and OS. The ORR assessed according to RECIST 1.0 criteria was evaluated by CT. Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), ORR (CR + PR), and clinical benefit rate (CBR = CR + PR + SD) were specified. The PFS was calculated starting from the beginning of therapy until radiological or clinical progression, whichever occurred first. The OS was obtained with a starting date of the beginning of therapy until the date of death of any case. Exploratory survival estimates were performed in intrahepatic, extrahepatic cholangiocellular and gall bladder carcinomas separately. Factors involved in this analysis were all parameters listed in Table 1. and the early AEs: nausea, diarrhea, anemia, neutropenia, thrombocytopenia, HFS and skin rash. The cut-off level for laboratory parameters was the upper normal limit, except hemoglobin where the lower normal limit was chosen. PFS and OS were analyzed with Kaplan-Meier method and log-rank test was performed. Multivariate Cox regression analysis was also performed and only variables, which proved to be statistically significantly influenced the efficacy in the univariate analysis were included. Estimates were considered statistically significant if $p < 0.05$ and since the analyses were exploratory, the results were not corrected for multiple comparisons. The toxic effects were evaluated according to Common Terminology Criteria for Adverse Events v3.0. Only those AEs were considered in the search for predictive markers, which were previously described as drug-related AEs (acneiform rash, hand-foot syndrome, neutropenia,

Table 1 Clinicopathological characteristics of patients with biliary tract cancer treated with cetuximab-based chemotherapy

Parameter	N (%)
Age (years) mean (range)	59.7 (28–78)
≤ 60 years	28 (49)
> 60 years	29 (51)
Sex	
male	22 (39)
female	35 (61)
Body mass index	
< 25	23 (40)
≥ 25	34 (60)
ECOG performance status	
0	31 (54)
1	20 (35)
2	6 (11)
Site of origin	
intrahepatic bile duct	28 (49)
extrahepatic bile duct	11 (19)
gallbladder	18 (32)
Stage	
2-4a (locoregional)	17 (30)
4b (distant metastatic)	40 (70)
Previous stent implantation	
yes	12 (21)
no	45 (79)
Previous surgery	
yes	18 (32)
no	39 (68)
Previous chemotherapy[a]	
yes	9 (16)
no	48 (84)
White blood cell count (G/l)[b]	
> 10	20 (35)
≤ 10	36 (63)
not available	1 (2)
Neutrophil count (%)[b]	
> 70	22 (39)
≤ 70	33 (58)
not available	2 (3)
Thrombocyte count (G/l)[b]	
> 350	18 (32)
≤ 350	38 (67)
not available	1 (2)
Hemoglobin level (g/dl)[b]	
> lower normal limit	32 (56)
≤ lower normal limit	23 (40)
not available	2 (3)
Alanine aminotransferase (U/l)[b]	
> 45	24 (42)
≤ 45	30 (53)
not available	3 (5)
Aspartate aminotransferase (U/l)[b]	
> 50	15 (26)
≤ 50	39 (68)
not available	3 (5)
Alkaline phosphatase (U/l)[b]	
> 290	41 (72)
≤ 290	14 (25)
not available	2 (3)
Lactate dehydrogenase (U/l)[b]	
> 450	14 (25)
≤ 450	31 (54)
not available	12 (21)
Bilirubin level (μmol/l)[b]	
> 21	9 (16)
≤ 21	44 (77)
not available	4 (7)

[a] fluorouracil + adriamycin + mitomycin

[b] laboratory results at the start of treatment

thrombocytopenia, anemia, diarrhea, nausea/vomiting) and occurred within two months from the beginning of treatment. All statistical tests were performed with NCSS software (Hintze, J. 2001. NCSS and PASS. Number Cruncher Statistical System, Kaysville, UT, www.ncss.com).

Results

All together 57 patients were recruited in this study. The clinicopathological characteristics of patients are shown in Table 1. Predominance (~60%) of females and overweight patients was observed. Most of the patients (89%) had a good performance status (ECOG 0 or 1) at the start of the treatment. The majority of patients (70%) presented with metastatic disease, while the others had locally advanced disease. Prior to the study entry 9 patients received first-line chemotherapy (fluorouracil + epiadriamicin + mitomycin combination i.v. (n = 3) or transarterial intrahepatic chemoembolization (n = 5); gemcitabine + cisplatin i.v. (n = 1)). The relatively high frequency of laboratory abnormalities at screening reflected the clinical manifestation of this malignancy.

The best clinical response was evaluable for all patients. Nearly one quarter of patients reached CR (n = 3) or PR (n = 9), while two third of patients presented clinical benefit (n = 38). The treatment was discontinued due to progression (n = 45), physician's decision (n = 4), patient's decision (n = 2) and toxicity (n = 2). Four patients (7%) were still in the study without evidence of progression at the end of the follow-up.

Second line treatment (fluorouracil + adriamycin + mitomycin) was applied for 7 (12%) patients. Despite of the relatively good response rates the majority of patients (46, 81%) died during the median follow-up of 202 (95% CI 155–207) weeks. The median progression-free survival (PFS) and OS were 34 (95% CI: 24—40) and 54 (95% CI, 43—67) weeks, respectively.

The AEs during the cetuximab-based therapy of patients are presented in Table 2. The most frequent AEs were skin toxicities (acneiform rash and hand-foot syndrome (HFS)); while the most frequent AEs of grade 3/4 were neutropenia, bilirubinemia, and skin toxicities.

As only those AEs can be clinically useful markers, which occur early during the therapy we have introduced the early AEs as new parameters in the exploratory analysis. The mean time (2 months) for the occurrence of any AE was considered as the threshold for early onset. Parameters, which statistically significantly influenced response and/or survival of patients were presented in Table 3. Only the early acneiform rash influenced significantly all three outcomes: ORR, PFS, and OS, while the other parameters have impact only on survivals.

Table 2 Adverse events during cetuximab-based therapy in patients with biliary tract cancer

Adverse event[a]	All grades N (%)	Grade 3–4 N (%)
Acneiform rash	41 (72)	8 (14)
Fever/infection	31 (54)	1 (2)
Hand-foot syndrome	29 (51)	7 (12)
Elevated liver enzyme level	25 (44)	4 (7)
Fatigue	21 (37)	5 (9)
Pain	20 (35)	1 (2)
Neutropenia	18 (32)	8 (14)
Nausea/vomiting	18 (32)	0
Anemia	17 (30)	0
Hyperbilirubinemia	16 (28)	8 (14)
Thrombocytopenia	14 (25)	1 (2)
Constipation	9 (16)	0
Loss of appetite	8 (14)	1 (2)
Diarrhea	8 (14)	0
Edema	8 (14)	0
Hypercalcemia	7 (12)	4 (7)
Abdominal distension	6 (11)	0
Epistaxis	5 (9)	1 (2)
Allergic reaction	4 (7)	4 (7)
Febrile neutropenia	3 (5)	3 (5)
Hyperglycemia	2 (4)	2 (4)
Dyspnoe	2 (4)	1 (2)

[a] occurred in at least 10% of patients or if grade 3–4 adverse event was present

Comparing Tables 2 and 3 it can be concluded that all cases of acneiform rash and 78% of neutropenia occurred within 2 months from the start of therapy. In contrast only 45% of HFS occurred in the first two months of the treatment (data not shown).

Kaplan-Meier estimates (according to the thrombocyte count at the start of therapy and early skin rash) performed separately for gall bladder cancer, intrahepatic and extrahepatic cholangiocellular carcinomas revealed the same results as for all patients. Even in case of non-significant survival differences the general trend reported for the whole cohort was present (Supplementary table and figures).

Multivariate Cox regression analyses revealed that thrombocyte count at the start of therapy and early acneiform rash were independent predictive markers of both PFS and OS (Table 4). Kaplan-Meier survival curves according to the independent predictive markers are presented in Fig. 1. An evident synergism between occurrence of early skin rash and presence of normal platelet count at treatment start could be observed (Fig. 2).

Discussion

The data of 57 patients with BTC were analyzed. The predominance of females reflects the gender distribution in the Hungarian epidemiology of BTC [1]. In other trials only patients with ECOG 0/1 performance status were recruited, in this study six patients had ECOG 2. Despite of this the presented efficacy data were similar with our previous results and other combination therapies in BTC [3].

In the exploratory analysis for prognostic and predictive factors we extended our research for all available and potentially important factors: patients' basic characteristics, laboratory results, tumor specific factors, and adverse events. In univariate analysis beyond overall response to therapy thrombocyte count at the start, previous stent implantation, ECOG performance status, early neutropenia and early skin rash affected survival. In multivariate analysis the initial thrombocyte count and early onset rash were independent predictors for survival. Thrombocyte count after surgery of patients with gallbladder cancer is a known prognostic factor [13], thus it is reasonable to exclude it as a predictive factor. Moreover, the thrombocytosis is a known adverse prognostic factor in gastrointestinal malignancies [14], but evidence for its significans in advanced BTC is scarce [15]. This result gives additional proof of thrombocyte count as prognostic factor.

Only early skin rash remains as a potential indicator of cetuximab-based treatment efficacy.

In omics era it is debated whether a clinical phenomenon like an adverse event or early sign of clinical efficacy can be used as a predictive factor. In a recently published editorial Helleday pondered that in a case of therapy without significant

Table 3 Parameters, which statistically significantly influenced the efficacy of treatment

Parameter	N (%)	ORR (%)	*P*	mPFS weeks	95% CI	*P*	mOS weeks	95% CI	*P*
Thrombocyte count (G/l) at the start of treatment									
≤ 350	39 (68)	10 (26)		41	34–61		81	50–124	
> 350	18 (32)	2 (11)	0.303	13	10–24	**<0.001**	26	23–46	**0.001**
Previous stent implantation									
no	45 (79)	12 (27)		38	25–44		67	46–93	
yes	12 (21)	0	0.053	18	7–30	**0.023**	43	22–53	**0.032**
Eastern Clinical Oncology Group performance status									
0	31 (54)	9 (29)		38	25–65		81	46–128	
1–2	26 (46)	3 (12)	0.107	24	13–39	0.070	45	23–58	**0.045**
Neutropenia within the first 2 months of therapy									
grade 0	43 (75)	7 (16)		25	15–34		46	36–58	
grade 1–3	14 (25)	5 (36)	0.121	49	39–143	**0.018**	81	54–192	**0.034**
Acneiform rash within the first 2 months of therapy									
grade 0	16 (28)	0		13	11–24		26	21–40	
grade 1–3	41 (72)	12 (21)	**0.013**	39	30–51	**<0.001**	67	50–120	**0.001**

side effects such approach should be discussed [16]. As regards the cetuximab in BTC when there is no skin toxicity cetuximab can be omitted and without significant side effect it does not cause harm to the patients. If acneiform rash develops the cetuximab is presumably beneficial and the therapy can be carried on. In this concept the clinical advantage compensates the burden of side effects.

It is a general observation that in targeted therapies treatment-related AEs influence survival. Thus hypertension may be a surrogate marker for bevacizumab activity in CRC [17] or of sunitinib activity in metastatic renal cell carcinoma [18, 19]. Although this correlation was not observed in tumors of other origins [20]. The accumulation of AEs and its beneficial impact on survival was also observed in renal cell cancer [18]. Furthermore, in the adjuvant BIG 1–98 trial of breast cancer arthralgia-myalgia-carpal tunnel syndromes affected disease outcomes independently from treatment arms (tamoxifen or letrozole) [21]. In a Canadian phase III trial with the combination of erlotinib and gemcitabine in patients with advanced pancreatic cancer a sub-analysis indicated that skin rash was associated with a higher likelihood of achieving disease control and better survival [22]. However, dose escalation of erlotinib to achieve higher frequency of skin rash resulted in no survival benefit in a phase II trial [23]. In CRC the RAS status is a well-established predictive biomarker for anti-EGFR antibodies, where mutation predicts no advantage of their application. According to a recent systemic review skin rash could also exhibit a predictive value on treatment efficacy and survival [9].

Table 4 Results of multivariate Cox regression analysis

Parameter	HR_{PFS}	95% CI	*P*	HR_{OS}	95% CI	*P*
Thrombocyte count (G/l) at the start of treatment						
≤ 350	1	reference		1	reference	
> 350	2.76	1.42–5.34	**0.003**	2.27	1.15–4.48	**0.018**
Previous stent implantation						
no	1	reference		1	reference	
yes	1.74	0.87–3.51	0.120	1.59	0.77–3.27	0.210
Eastern Clinical Oncology Group performance status						
0	1	reference		1	reference	
1–2	1.59	0.91–2.79	0.107	1.44	0.82–2.55	0.207
Neutropenia within the first 2 months of therapy						
grade 0	1	reference		1	reference	
grade 1–3	0.67	0.35–1.29	0.233	0.85	0.44–1.65	0.632
Acneiform rash within the first 2 months of therapy						
grade 0	1	reference		1	reference	
grade 1–3	0.39	0.20–0.78	**0.007**	0.38	0.20–0.76	**0.006**

In contrast to "targeted" agents for chemotherapy it is widely accepted that higher dose results in higher treatment efficacy [24, 25]. Investigations however suggested that altered schedules may lower side effects without affecting disease outcome [26, 27] and interventions preventing side effects are recommended which may contribute to maintain dose intensity [28, 29]. Interestingly, in a recent study reduced doses of cytotoxic drugs in combination with full dose of cetuximab (or bevacizumab) resulted in improved OS and quality of life for more than half of the patients with end-stage cholangiocarcinoma [30].

In case of BTC there is no published data that would clearly prove the advantage of a "targeted" agent (not even in combination) over conventional chemotherapy. In a phase II trial cediranib improved response rate added to gemcitabine and cisplatin, but did not influenced survival [31]. Two phase II randomized trials of GemOx with or without cetuximab and one phase III trial of GemOx with or without erlotinib failed to show benefit in terms of survival compared to chemotherapy

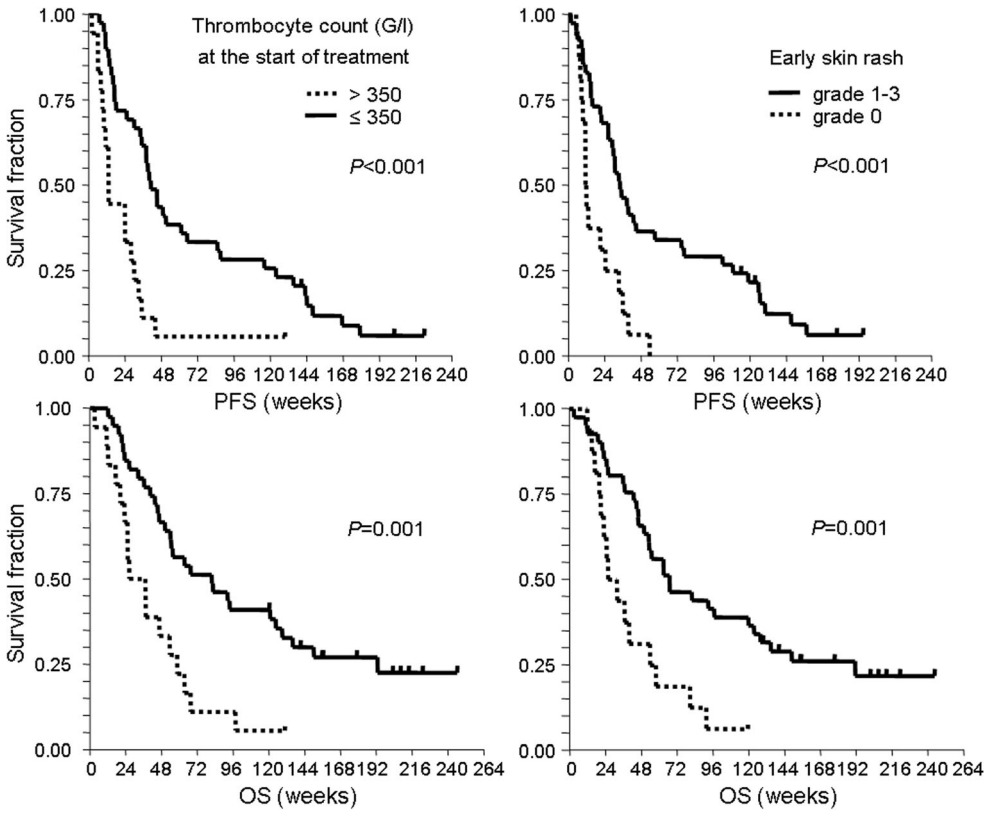

Fig. 1 Progression-free (PFS) (*upper figures*) and overall survival (OS) curves (*lower figures*) of patients with advanced biliary tract cancer according to the thrombocyte count at the start of cetuximab-based treatment (*left column*) and early skin rash, which occurred in the first two months of therapy (*right column*)

[6–8]. The authors did not report any biomarkers, which may predict treatment outcome; even *KRAS* status did not influence OS. In another phase II trial of gemcitabine and cetuximab similar efficacy data was reported as in our study, and skin toxicity ≥grade2 was associated with increased PFS and OS [8]. In randomized phase II trials skin rash, mucositis, neutropenia and allergic reaction happened significantly more often in the cetuximab containing arm suggesting connections with cetuximab treatment [7, 8]. In our study acneiform skin rash (even as an early adverse reaction), which is mainly a consequence of cetuximab therapy were observed to have independent effect on survival.

Currently, the standard chemotherapy is gemcitabine combined with a platinum agent. This combination is accompanied with significant toxicity. Probably the most bothersome side effect is peripheral neuropathy, which may develop as grade 3/4 in up to 24% of patients [7]. The use of fluoropyrimidine instead of platinum may be better tolerated but the

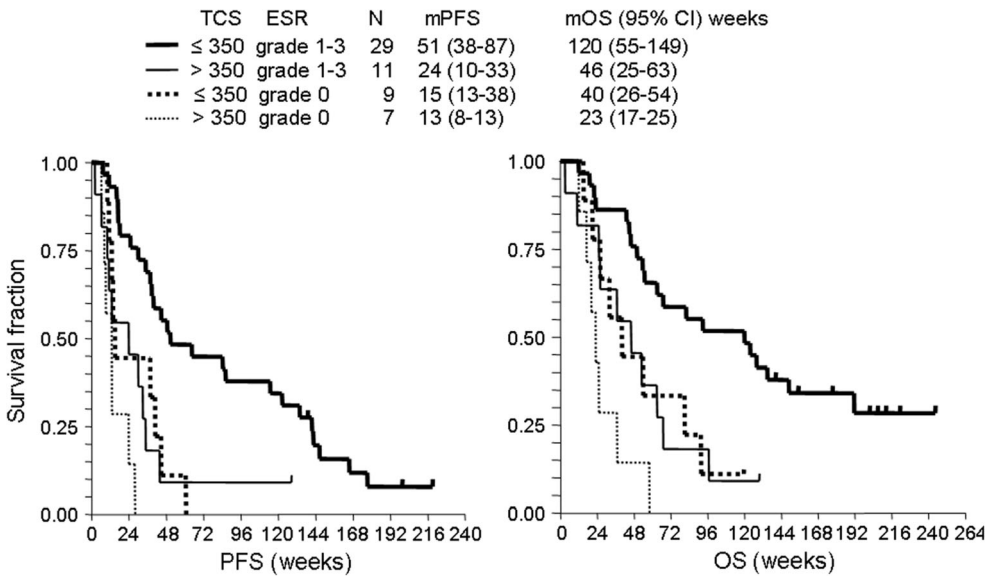

Fig. 2 Synergistic effect of thrombocyte count at the start of cetuximab-based treatment (TCS) and early skin rash (ESR), which occurred in the first two months of therapy on progression-free (PFS) and overall survival (OS) of patients with advanced biliary tract cancer. m – median; CI – confidence interval

demonstration of its equivalency is remaining to be proven [32]. The toxicity profile in our study was similar to those reported in previous trials on cetuximab-based chemotherapy, except neuropathy, which was understandably not observed in our trial. The role of EGFR expression was not investigated hence EGFR positivity was an inclusion criterion.

KRAS mutations were reported in 3–54% of BTC in different series with no significant association between its presence and treatment outcome [6–8]. In our study only three patients were detected with *KRAS* mutations (6.7% in available samples, all in gene 2 codon 12/13), which is most likely due to the low number of recruited patients.

This study has several limitations. It was a single institutional one-arm study recruiting a relatively limited number of patients. The analyses for prognostic and predictive factors were not planned outright in the original trial and the roles of side effects were investigated as a sub-analysis.

In patients with advanced BTC, chemotherapy can prolong survival at the expense of acceptable but significant toxicity. If the gemcitabine-fluoropyrimidine combination will be non-inferior to gemcitabine-platinum than the former one could serve as an attractive alternative treatment. Predictive biomarkers are ideally measured before starting the treatment and are generally obtained from the tumor itself. The observation that side effects occur with a different pattern when using the same dose of a certain drug is mostly explained by the differences in even hidden host characteristics.

In conclusion, lacking solid predictive factors we think that if the predictive value of certain early side effects, like early onset of acneiform skin rash, is confirmed in greater series, it can be used as "surrogate" predictive biomarker. Therefore, with these considerations in mind our data suggests that patients with advanced BTC who benefit from continuing cetuximab-based chemotherapy may be selected. It seems that for patients lacking the above described early events cetuximab is not favorable. For this purpose the classification of skin rash must be standardized and reproducible. This concept could be confirmed by similar retrospective analysis in greater series and also should be investigated in a prospective trial in which patients would be randomized to continue chemotherapy with or without cetuximab based on occurrence of skin rash within two month of cetuximab containing therapy.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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