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Skin Reaction to Cetuximab as a Criterion for Treatment Selection in Head and Neck Cancer

PRIMOŽ STROJAN[1,2], BRANKO ZAKOTNIK[3], BARBARA ŽUMER[1], KATARINA KARNER[1], MARTA DREMELJ[1], BORIS JANČAR[1], SIMONA JEREB[4] and CVETKA GRAŠIČ-KUHAR[3]

[1]*Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia;*
[2]*Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia;*
[3]*Department of Medical Oncology, Institute of Oncology, Ljubljana, Slovenia;*
[4]*Department of Radiology, Institute of Oncology, Ljubljana, Slovenia*

Abstract. *Background/Aim: It can be hypothesized that in patients with locally advanced head and neck cancer and prominent cetuximab (CMb)-induced skin rash, immuno-radiotherapy would result in a survival advantage over chemoradiotherapy with cisplatin (CP). Patients and Methods: After a loading dose of CMb, one weekly cycle of CMb and CP concurrently with RT, patients who developed a grade ≥2 rash proceeded with immunoradiotherapy, and those with a grade 0-1 rash had chemoradiotherapy. Results: A grade 3-4 allergic reaction to CMb developed in 11/39 (28.2%) patients and further recruitment was stopped. These patients proceeded treatment with CP. In early assessment of skin rash 10/28 patients qualified for chemoradiotherapy and 18/28 patients for immunoradiotherapy. There was no difference in survival between the two groups. Conclusion: Rate of serious CMb-induced hypersensitivity reactions was unacceptably high. Even though immunoradiotherapy was administered only to the prognostically most favorable group of patients, it resulted in no advantage over chemoradiotherapy.*

In locally advanced squamous cell carcinoma of the head and neck (LASCCHN), the greatest overall survival (OS) benefit of combined treatment with radiotherapy (RT) and platinum-based chemotherapy *versus* RT alone was observed in concomitant use of both modalities. Recognized as the most effective were platinum-based mono-chemotherapy regimens where the hazard ratio (HR) of death was 0.74 (95% confidence interval [CI] 0.67-0.82) (1). On the other hand, in patients with LASCCHN, a concomitant administration of RT and cetuximab (CMb), an IgG1 monoclonal antibody with high affinity to the epidermal growth factor receptor, also resulted in a significant improvement of OS compared to RT alone (2). Furthermore, an update of the Bonner's pivotal study showed, for the patients treated with CMb and RT, that survival was significantly improved in those who experienced a prominent acneiform rash (grade 2-4) compared to the patients with no/mild rash (grade 0-1), giving the HR of death 0.49 (95%CI=0.34-0.72) (3). Indeed, those patients with no/mild skin reaction to CMb had a median survival similar to the RT-alone group (25.6 *vs.* 29.3 months): obviously, they exerted no OS benefit and should, therefore, better have been treated with the combination of RT and CP. The CMb-induced rash developed within 15 days of the initiating treatment in three quarters of patents, with a prominent rash recorded in 61% of them (3).

On the basis of these findings a hypothesis was made that early assessment of a CMb-induced skin rash could be used for treatment stratification in patients with LASCCHN. Thus, it was anticipated that in patients who would develop a prominent skin rash after CMb administration, bioradiotherapy should be more effective than the combination of RT and mono-chemotherapy with cisplatin (CP); whereas in those with no/mild rash induced by CMb administration, concomitant chemoradiotherapy with CP is expected to be more efficient than the RT-CMb combination. This study reports on the efficacy and toxicity results from the prospective study that tested the above hypothesis.

Patients and Methods

The trial was designed according to the Helsinki declaration and was approved by the National Medical Ethics Committee of the Republic of Slovenia (No. 149/06/11) and registered under the ClinicalTrials.gov with the following identifier: NCT01472653.

Patients. Patients with a newly diagnosed and histologically confirmed squamous cell carcinoma of the oral cavity, oropharynx,

Correspondence to: Primož Strojan, Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia. Tel: +386 15879110, Fax: +386 15879400, e-mail: pstrojan@onko-i.si

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hypopharynx, or larynx, UICC TNM stage III-IVB, entered the study. Other eligibility criteria were age ≥18 years; WHO performance status 0-2; adequate hematologic, renal, and liver function; no history of previous malignancy in the last 5 years (except for non-melanoma skin cancer or in situ carcinoma of the uterine cervix); and an expected survival of more than 6 months. Patients with any medical condition precluding safe administration of the planned therapy, including allergy, were deemed ineligible. A written informed consent was obtained from all the patients.

The pre-treatment staging evaluation included a clinical examination, standard laboratory tests, an upper aerodigestive tract endoscopy, contrast-enhanced head and neck CT scan or MRI, chest radiography/CT, and an abdominal ultrasound/CT. Other tests were performed if clinically indicated (bone scan, PET-CT). Patients with >5% weight loss were referred for gastrostomy feeding tube placement.

Study protocol (Figure 1). Induction chemotherapy was given only to patients with inoperable tumors and seriously impaired swallowing function that would soon necessitated a feeding-tube insertion. Criteria for technical inoperability were used as defined by Fu *et al*. (4). They received docetaxel 75 mg/m^2 (day 2), CP 75 mg/m^2 (day 2), and 5-fluorouracil 750 mg/m^2/day (continuous infusion, days 1-4), repeated every 21 days for 3 cycles. The dosing recommendations implemented in the case of toxicity were as described elsewhere (5).

One week before the first fraction of RT, all patients received a loading dose of CMb (400 mg/m^2, over 120 min) and during the first week of RT, a combination of CMb (250 mg/m^2) and CP (30 mg/m^2) was concurrently administered *via* separate lines in 1 h infusions. Prior to CMb infusions, patients were pre-treated with the antihistamine clemastine 2 mg and methylprednisolone 125 mg IV. Magnesium and potassium were supplemented as indicated by the results of weekly biochemical analyses. If the creatinine clearance was reduced to <60 ml/min and/or peripheral polyneuropathy grade >1 recorded, CP was replaced by carboplatin AUC 1.5 weekly.

Concomitant boost IMRT using 6 MV photon beam and 35 fractions (1 fraction/day, 5 days/week) was delivered in all patients (6). The definition of clinical target volumes (CTV) took into consideration the natural barriers to tumor spread: the CTV70 included primary and nodal gross tumor volumes (GTV) and in CTV56 areas considered at risk for harboring microscopic disease were included. Areas around larger nodes and non-palpable but radiologically suspicious nodes in the neck (intermediate-risk volumes) were treated to 63 Gy (CTV63). The planning target volumes (PTVs) were created by adding a 5 mm isotropic margin around corresponding CTVs. The delineation of nodal levels followed the outlining guidelines. Delineated organs at risk (OAR) were the spinal cord, brainstem, parotid glands, and the mandible, whereas oral cavity, larynx, pharyngeal constrictor muscles, and the submandibular glands were marked as appropriate (7). Position verification was performed according to the eNAL protocol (8).

At the end of the first week of RT, assessment of skin rash was done according to the criteria of the National Cancer Institute CTCAE, version 3.0 (CTCAE v3.0). The patients with no/mild reaction (grade ≤1) proceeded with concomitant chemoradiotherapy with CP (30 mg/m^2/week, CP group), whereas the patients with a prominent skin rash (grade ≥2) proceeded with bioradiotherapy with CMb (250 mg/m^2/week, CMb group).

Response evaluation and follow-up. During therapy, acute toxicity was evaluated weekly according to the CTCAE v3.0 criteria. After the end of treatment, patients were seen at 2-3 months intervals for the first two years end every 6 months thereafter, to record toxicity and tumor response. A radiological assessment of response was done after the completion of the induction chemotherapy (if any) and 12-14 weeks post-concomitant therapy by using the RECIST 1.1 response criteria (9). Patients with residual tumor considered operable were referred for surgery. The scoring criteria of the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group were used for the evaluation of late treatment-related morbidity.

Detection of human papillomavirus DNA. To determine the association between human papillomavirus (HPV) and oropharyngeal tumors, extraction of DNA from primary tumor tissue sections and HPV E6/E7 mRNA transcripts detection were performed as described elsewhere (10).

Compliance with Ethical Standards. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical analysis. The primary objective of the study was radiological complete response rate at 12-14 weeks post-therapy, according to the RECIST 1.1 criteria (9). The secondary objectives were LRC (event: local and/or regional recurrence and death from any cause other than distant metastases), progression-free survival (PFS, event: any recurrence, new primary cancer, or death from any cause) and OS (event: death from any cause) at 2 years after therapy, acute and late toxicities. The survival times were calculated from the first day of therapy by using the Kaplan-Meier method, and the differences between the curves were tested by the log-rank test. For categorical variables, the chi-squared test or chi-squared test for trends were used. Statistical analyses were performed by the SPSS v16 software package and the differences at $p<0.05$ were considered statistically significant.

For study sample calculation, the HRs of death as calculated by Pignon *et al*. (for patients treated with platinum-based mono-chemotherapy *vs*. RT alone, 0.74) and by Bonner *et al*. (for patients treated with CMb and RT who experienced grade 2-4 *vs*. grade 0-1 acneiform rash, 0.49) were used (1, 3). Accordingly, the risk of death was reduced by an additional 25% in those who developed a prominent skin rash after CMb administration compared to patients treated with concomitant chemoradiotherapy with CP. Anticipating that variation of 25% between the two treatments reflects the difference in locoregional control (LRC) at 12-14 weeks post-therapy, and taking into account the 3% expected rate of grade 3/4 allergic reactions to CMb and development of prominent rash in 60% of patients, a total of 120 patients would be included (α=0.05, β=0.8): 50 of them allocated to CP group and 70 to the CMb group (11). The planned recruitment period was 3 years.

Results

Between December 2011 and July 2013, 39 patients entered the study. In this group, 11 allergic reactions of grade 3 (9 patients) and grade 4 (2 patients) were observed during the

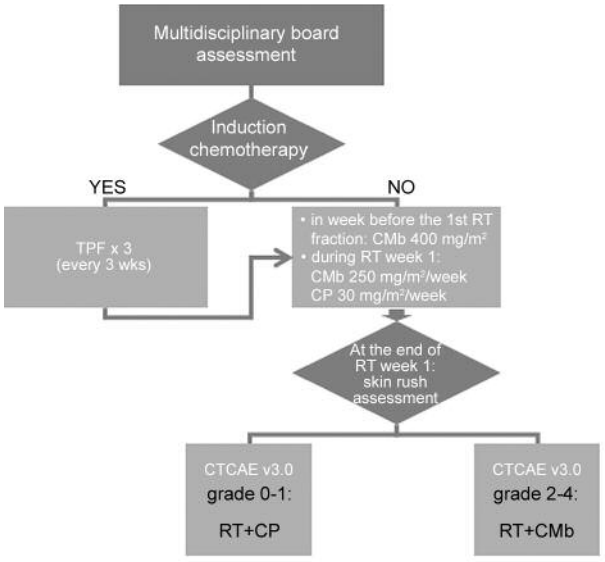

Figure 1. *Treatment protocol. TPF: Docetaxel/cisplatin/5-fluorouracil. RT: radiotherapy; CP: cisplatin; CMb: cetuximab.*

loading CMb infusion. This observation was reported to the National Medical Ethics Committee of the Republic of Slovenia which decided to prematurely stop the trial and further recruitment was terminated (No. 154/08/13).

There were 4 females and 35 males of a median age 57 years (range=42-75 years). The majority were active smokers (30, 76.9%), had an oropharyngeal primary tumor (30, 76.9%), and disease of UICC TNM stage IV (35, 89.7%) (Table I).

Compliance to treatment and response. Five (12.8%) patients had induction chemotherapy and all received the planned doses of chemotherapeutics. After the third chemotherapy cycle, partial response locally and/or regionally was recorded radiologically in all of them. A full RT dose was delivered as per protocol in all 39 patients over 47-60 days (median, 51).

During application of CMb loading dose, a grade 3-4 allergic reaction developed in 11 patients (28.2%) who proceeded with RT and the concomitant administration of CP (4-8 cycles, median 6). For assessment of CMb-induced skin rash at the end of the first week of RT, 28 patients were available. A grade 0-1 skin rash was recorded in 10 of these patients (35.7%) who continued treatment with RT and CP (6-8 cycles, median 7). In further analyses, the patients who received RT and concomitant CP, either due to an CMb-induced allergic reaction or the absence of a prominent skin rash, were analyzed together (CP group, N=21). Altogether, CP was replaced by weekly carboplatin due to renal toxicity in 6 patients (28.6%) and all planned cycles of CP/carboplatin were administered in 10 patients (47.6%). Of the patients who received CMb and experienced no serious allergic reaction, 18 developed a skin rash of grade ≥2 (CMb group, N=18) and proceeded with RT and CMb (4-9 cycles, median 8; 16 patients received all planed cycles, 88.9%).

After therapy, a complete response was achieved locoregionally in 14 patients (66.7%, 95% CI=52.1-81.3) from the CP group and 10 patients (55.6%, 95%CI=34.4-76.7) from the CMb group ($p>0.05$). There were no statistically significant differences in the clinical characteristics between the two groups, except that more patients treated with CP had advanced nodal disease (N2b-3, $p=0.07$) and received induction chemotherapy ($p=0.05$) (Table I).

Table I. *Patient and tumor characteristics.*

Characteristics	All (N=39)	RT+CP (N=21)	RT+CMb (N=18)	*p*-Value[3]
Patients				
Males	34 (87.2%)	20 (95.2%)	14 (77.8%)	n.s.
Age[1]	57 (42-75)	57 (42-75)	58 (45-63)	n.s.
Active smokers	30 (76.9%)	17 (80.9%)	13 (72.2%)	n.s.
Primary tumor site				
Oral cavity	2 (5.1%)	1 (4.8%)	1 (5.6%)	n.s.
Oropharynx	30 (76.9%)	17 (80.9%)	13 (72.2%)	
Hypopharynx	5 (12.8%)	2 (9.5%)	3 (16.7%)	
Larynx	2 (5.1%)	1 (4.8%)	1 (5.6%)	
HPV status[2]				
Positive	8 (26.7%)	4 (23.5%)	4 (30.8%)	n.s.
Negative	18 (60%)	10 (58.8%)	8 (61.5%)	
Unknown	4 (13.3%)	3 (17.6%)	1 (7.7%)	
T-stage				
T1	1 (2.6%)	1 (4.8%)	0	n.s.
T2	4 (10.3%)	1 (4.8%)	3 (16.7%)	
T3	13 (33.3%)	8 (38.1%)	5 (27.8%)	
T4	21 (53.8%)	11 (52.4%)	10 (55.6%)	
N-stage				
N0	5 (12.8%)	1 (4.8%)	4 (22.2%)	0.034[4]
N1	4 (10.3%)	0	4 (22.2%)	0.072[5]
N2A	2 (5.1%)	2 (9.5%)	0	
N2B	12 (30.8%)	8 (38.1%)	4 (22.2%)	
N2C	10 (25.6%)	6 (28.6%)	4 (22.2%)	
N3	6 (15.4%)	4 (19.0%)	2 (11.1%)	
Overall UICC TNM stage				
Stage III	3 (7.7%)	0	3 (16.7%)	0.059[4]
Stage IVA	26 (66.7%)	14 (66.7%)	12 (66.7%)	
Stage IVB	10 (25.6%)	7 (33.3%)	3 (16.7%)	
Induction chemotherapy				
Yes	5 (12.8%)	5 (23.8%)	0	0.027
No	34 (87.2%)	16 (76.2%)	18 (100.0%)	

[1]Median (range), in years; [2]Oropharyngeal primary tumors, N=30; [3]RT+CP *vs.* RT+CMb; [4]Chi-square for trends; [5]Chi-square test, stages N0-2A *vs.* N2B-3. N: Number of patients; RT: radiotherapy; CP: cisplatin; CMb: cetuximab; HPV: human papilloma virus; n.s.: not significant.

Survival. On the close out date on 31 December 2016, the median follow-up time of patients alive at the last follow-up examination was 3.9 years (range=3.6-5.0 years). Three patients from the CMb group had salvage surgery at primary tumor site 6, 8 and 14 months after treatment completion; all died due to a further local progression of the disease. Salvage neck dissection was successfully performed in 3 patients, all from the CP group, 5.5, 8, and 12 months post-therapy. During follow-up, distant metastases were diagnosed in 6 patients (CP group 5, CMb group 1) and secondary primary tumor in 5 patients (CP group 4, CMb group 1; lung 2, larynx, prostate, testis). On the close-out date, 13 patients were alive (12 with no evidence of disease) and 26 patients died: 21 due to tumor progression and 5 due to other causes, unrelated to the treated malignant disease.

The actuarial survival rates at 2 years in patients from the CP group and the CMb group are shown in Table II. No statistically significant differences were found between the two groups in respect to any of the studied survival objectives (Figure 2). Also, when only 28 patients were considered, who were grouped in respect to the grade of CMb-induced skin rash (excluding patients with a grade 3/4 allergic reaction to CMb), no difference in outcome was observed (Table II).

Acute and late toxicity. No treatment-related death was recorded in our patients. Locoregional treatment induced grade ≥3 acute toxic events in 85.7% patients from the CP group and in all patients from the CMb group ($p>0.05$) (Table III). During treatment, a nasogastric or a percutaneous endoscopic gastroscopy tube was inserted in 3 patients from each group ($p>0.05$), and total parenteral nutrition was required in 10 CP-group patients and in 5 CMb-group patients ($p>0.05$) with a median duration of 11.5 days (range=5-46 days) and 11 days (range=8-32 days) ($p>0.05$), respectively. The median change in weight from baseline ranged from –16.8% to 0% (median, –10.1%) in the CP group and from –18.3% to +6.7% (median, –9.1%) in the CMb group ($p>0.05$). Significantly higher proportion of grade 3 radiomucositis ($p=0.05$) and in field radiodermatitis ($p<0.01$) developed when RT was combined with CMb (Table III).

Late toxicity was assessed in 16 patients who survived more than 6 months after treatment completion and had no residual or recurrent disease above the clavicles (median observation time 3.7 years, range=1.3-4.9 years). No grade 3 or higher late therapy-related toxicity was seen in these patients. Altogether, 15 adverse events of grade 2 were recorded in 6 patients (66.7%) from CP the group, whereas in the CMb group 6 adverse events occurred in 3 patients (42.9%) ($p>0.05$). None of the patients remained dependent on tube feeding at 3 months post-therapy and there was no difference in the occurrence of any grade 2 late toxicity between the two study groups (Table IV).

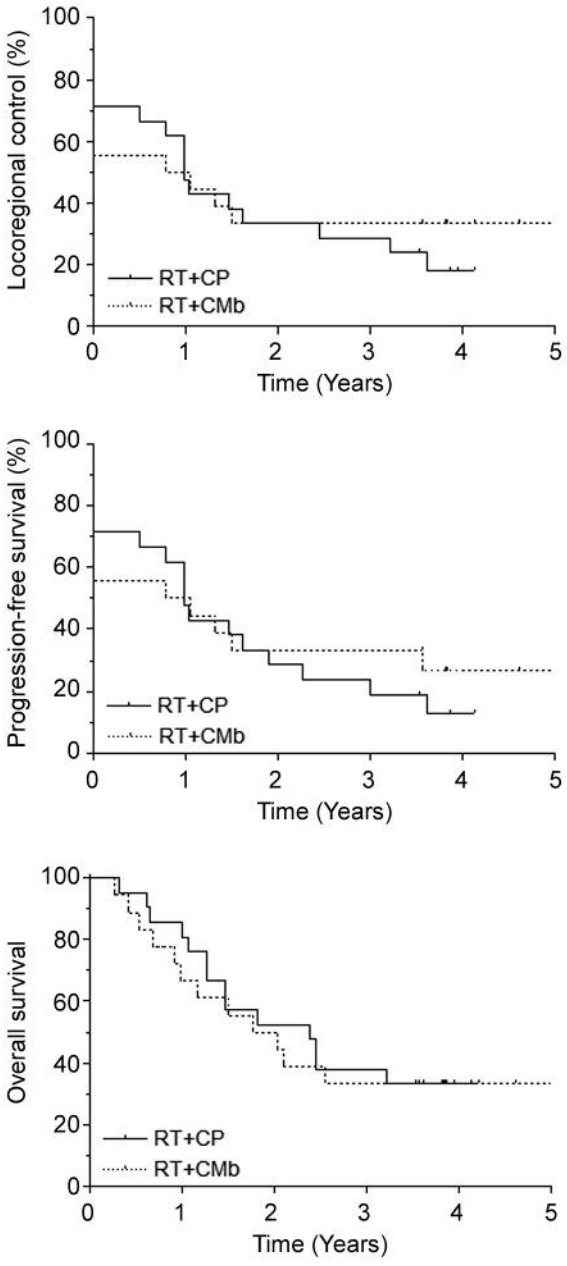

Figure 2. *Survival of patients according to treatment group. RT: Radiotherapy; CP: cisplatin; CMb: cetuximab.*

Discussion

In the present study, an early assessment of CMb induced-skin rash in patients with LASCCHN was used to select between the treatments with RT and concomitant weekly CP or CMb. Due to the high rate (28.2%) of grade 3/4 allergic reactions to CMb, the study was prematurely terminated, and the planned number of patients was not reached. Even in the

Table II. *Therapy response and survival*.

At 2 years	RT+CP		RT+CMb		*p*-Value
	%	95%CI	%	95%CI	
All patients (N=39)					
Locoregional survival	33.3	13.2-53.5	33.3	11.6-55.1	n.s.
Progression-free survival	28.6	9.2-47.9	33.3	11.6-55.1	n.s.
Overall survival	52.4	31.0-73.7	50.0	26.9-73.1	n.s.
Patients with assessment of skih rush (N=28)					
Locoregional survival	50.0	19.0-81.0	33.3	11.6-55.1	n.s.
Progression-free survival	40.0	9.6-70.4	33.3	11.6-55.1	n.s.
Overall survival	50.0	19.0-81.0	50.0	26.9-73.1	n.s.

RT: Radiotherapy; CO: cisplatin, CMb: cetuximab; CI: confidence interval; N: number of patients; n.s.: not significant.

Table III. *Acute toxicities*.

Acute toxicity	RT + CP (N=21)				RT + CMb (N=18)			
	Grade 3	Grade 4	Total %	%	Grade 3	Grade 4	Total %	%
Neutropenia	3	0	3	14.3	0	0	0	0
Thrombocytopenia	1	0	1	4.8	0	0	0	0
Hypomagnesemia	1	0	1	4.8	1	0	1	5.6
Creatinine	1	0	1	4.8	0	0	0	0
Dysphagia	12	0	12	57.1	13	0	13	72.2
Weight loss	10	0	10	47.6	7	0	7	38.9
CMb-induced rash[1]	0	0	0	0	7	0	7	38.9
Mucositis[1]	11	0	11	52.4	15		15	83.3
(Radio)dermatitis, in-field[1]	1	0	1	4.8	11	1	12	61.1
Any AE (no. of patients)	18	0	18	85.7	18	1	18	100

[1]$p<0.05$. N: Number of patients; AE: adverse event.

Table IV. *Late toxicities*.

Late toxicity	RT + CP (N=9)				RT + CMb (N=7)			
	Grade 2	Grade 3	Total %	%	Grade 2	Grade 3	Total %	%
Xerostomia	3	0	3	33.3	0	0	0	0
Dysphagia	2	0	2	22.2	0	0	0	0
Alteration of taste	1	0	1	11.1	0	0	0	0
Laryngeal edema	0	0	0	0	0	0	0	0
Skin fibrosis	4	0	4	44.4	2	0	2	28.6
Altered skin pigmentation	1	0	1	11.1	1	0	1	14.3
Chronic neuropathy, sensory	1	0	1	11.1	0	0	0	0
Soft tissue necrosis	0	0	0	0	0	0	0	0
Thyroid dysfunction	3	0	3	33.3	3	0	0	42.9
Mandibular osteonecrosis	0	0	0	0	0	0	0	0
Any AE (no. of patients)	6	0	6	66.7	3	0	3	42.9

N: Number of patients; AE: adverse event.

potentially prognostically most favorable group of patients who developed a prominent skin rush to CMb that qualified them to enter the bioradiotherapy arm of the study, the combination of RT and CMb did not result in a survival advantage over chemoradiotherapy with CP. It only aggravated acute mucosal and in-field skin toxicity.

According to reports of pivotal trials employing CMb in cancer patients, the rate of grade 3-4 infusion related reactions associated with the first CMb administration was <5% (2, 12-14). In this respect, a premedication with histamine H1-receptor antagonist and corticosteroids was recommended as it appears beneficial in decreasing the occurrence of these reactions (15). Despite the rigorous use of anti-allergy premedication in our patients, grade 3-4 hypersensitivity reactions were observed in 28.2% of cases which resulted in the premature termination of the study. Indeed, a similar experience was obtained in our previous study employing CMb and CP concomitantly with RT, after TPF induction chemotherapy, and it was also reported from the Southeastern United States, *i.e.* 12.4-24.6% of severe hypersensititvity reactions (5, 16-20).

The background mechanism is a type I anaphylactic reaction mediated by pre-existing IgE antibodies that cross-react with galactose-α-1,3-galactose, an oligosaccharide on the Fab portion of the CMb heavy chain (21). Exposure to the lonestar tick (*Amblyomma americanum*) of the ixodidae family, with its proven ability to induce the production of IgE antibodies, was suggested to mediate presensitization of individuals (19, 22). Slovenia is a region well known for ixodides (23). Male gender (20), current smokers (20), history of allergy (16, 19), and patients with head and neck cancer (18, 24) were found more likely to be associated with severe hypersensitivity reactions, whereas premedication with steroids may have a protective effect (19). However, a successful identification of patients at risk of severe CMb-induced hypersensitivity reactions is only possible by detection of pre-treatment elevated IgE levels with a specific enzyme-linked immunosorbent assay or by quantification of drug-specific IgE on basophils (25-27). Testing of Slovenian head and neck cancer patients and control subjects for specific pre-existing IgE is in progress.

Concomitant bioradiotherapy with CMb was introduced in routine clinical practice a decade ago, even though the results of a head-to-head comparison to concomitant chemoradiotherapy employing CP in patients with LASCCHN became available only recently (28). After an enrollment of 70 patients (53.8% of the planned number), the trial was discontinued due to slow accrual and, consequently the results are under-powered. However, they showed no difference in the efficacy outcomes and CMb concomitant to RT increased acute toxicity and lowered compliance. In a subgroup analysis limited to the patients with oropharyngeal and oral cavity tumors only, the outcome was superior in patients treated with CP (28). A similar conclusion favoring platinum-based concomitant chemoradiotherapy over the CMb and RT combination was made by Petrelli *et al.* in a meta-analysis of 15 published series (3 of them were prospective) with a total of 1,808 patients included (29).

In our study, CMb administration was limited only to the patients who developed a prominent skin rash after the initial doses of CMb. These patients were expected to have a death risk reduction of 25% compared to those treated with concomitant combination of RT and CP mono-therapy (1, 3). Beside Bonner's pivotal trial, a significant association between the appearance of CMb-induced skin a rash and survival in patients with LASCCHN was detected also by others and was reported for other cancer types, *i.e.* colorectal, pancreatic and non-small-cell lung cancer, but was not seen in patients with recurrent or metastatic SCCHN treated with a combination of CMb plus platinum-based chemotherapy (5, 12, 30-34). Furthermore, two thirds of the oropharyngeal primary tumors in our study were HPV negative: analyzing over 600 patients with LASCCHN from two randomized RTOG trials, Bar-Ad *et al.* found that a severe skin rash was associated with a favorable outcome only in p16 negative oropharyngeal tumors (but not in patients with p16 positive tumors) (31). However, regardless of such a favorable selection, no survival advantage was observed with CMb over CP-mono-therapy when combined with RT, despite a trend of more advanced nodal disease in the latter group and the fact that all planned doses of CP/carboplatin were administered to only 47.6% of these patients *vs.* 88.9% in the CMb group. In addition, CP in weekly doses of 30 mg/m^2 was used which adversely affected a cumulative CP dose and intensity of chemoradiation (35). Of note: the same survival outcome was found when the bioradiotherapy arm was compared with patients who experienced no/mild rash to CMb (N=10) or with all patients who received CP (patients with severe allergic reaction to CMb included, N=21).

As already reported, CMb adds significantly to the acute mucosal and in-field cutaneous toxicity compared to the CP plus RT combination (28, 36), although no difference in acute toxicities between the two regimens has also been described (37). The rates of these two adverse events in our CMb patients were in the higher range of those reported in other studies (38-40), but still the compliance to CMb treatment was high and all patients received a planned RT dose in the time frame not significantly different from the CP group. No other difference in acute or late adverse effects was observed between the two groups.

The above observations must be interpreted with caution. Because of an early termination of the study due to safety reasons, it has several weaknesses, above all the low patients' number and a relatively short observation time. The number of enrolled patients reached only one third of the planned one, thus the study was too underpowered to show any statistically

significant difference in efficacy outcomes. The reason for high proportion of CMb hypersensitivity reactions that remained unanswered and rather inhomogeneous study population (*i.e.* in respect to disease subsites, HPV status and treatment) are additional limitations of the study.

To conclude, the concomitant administration of CMb with RT resulted in unexpectedly and unacceptably high rate of serious hypersensitivity reactions in our patients with LASCCHN, which necessitated a premature termination of the study. Even though a full course CMb treatment was limited only to the potentially, prognostically most favorable group of patients who developed a prominent skin rash early, their survival outcome did not differ from that of patients treated with concomitant CP and RT. As the acute toxicity profile favored CP over CMb, a refinement of selection criteria for the use of CMb in combination with RT is needed.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

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