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A dose-finding and efficacy confirmation trial of the superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for locally advanced maxillary sinus cancer (JCOG1212): dose-finding phase

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ABSTRACT

BACKGROUND: We are currently undertaking a multi-institutional prospective trial of the superselective intra-arterial infusion of high-dose cisplatin with concomitant radiotherapy for patients with T4aN0M0 or T4bN0M0 locally advanced maxillary sinus squamous cell carcinomas (MS-SCC). We herein report the results of the dose-finding phase.

METHODS: The dose-finding phase sought to evaluate the incidence of dose-limiting toxicities (DLTs) and determine the recommended number of cycles (RC) of the intra-arterial infusion of cisplatin. In this phase, 100 mg/m² of cisplatin was administered intra-arterially weekly for 7 weeks with concomitant radiotherapy (70 Gy).

RESULTS: All 18 patients received a full dose of radiotherapy. The number of cycles of cisplatin was 7 in 13 patients and 6 in 5 patients. DLT was observed in 5 patients.

CONCLUSIONS: These results indicated that this therapy is safe and well-tolerated at 7 cycles of cisplatin, which was determined to be the RC for locally advanced MS-SCC.

Introduction

Locally advanced and resectable maxillary sinus cancers (T3-4a) require radical surgery with or without a complete resection of the orbital contents as a standard treatment. This often results in significant disfigurement and impairment of function in patients with T4a tumors, but this is seldom the case in those with T3 tumors [1]. A significant number of patients with T4a tumors refuse radical surgery through fear of disfigurement and functional impairment. Therefore, the development of a new, less invasive therapy that is as effective as radical surgery is critical. Concurrent intravenous chemotherapy and radiotherapy (IV-CRT) is a promising treatment option for locally advanced laryngeal and pharyngeal squamous cell carcinoma. However, IV-CRT does not necessarily lead to satisfactory treatment outcomes in cases of maxillary sinus cancer [2, 3]. In addition, induction chemotherapy has not shown particularly promising results in cases of maxillary sinus cancer either [4, 5]. On the other hand, radical surgery is not indicated for unresectable, locally advanced tumors (T4b), and IV-CRT is regarded as a community standard treatment in daily practice. However, the three-year overall survival for 7 patients with T4bN0M0 in our retrospective study was 14.3% [6]. This indicates that more effective therapies are necessary for patients with T4a who refuse surgery as well as for those with T4b.

Intra-arterial chemotherapy has been used to treat localized malignant neoplasms in patients with head and neck cancer for over 50 years based on the fact that the head and neck region is particularly well-suited to regional chemotherapy as the blood supply to these tumors is primarily

derived from branches of the external carotid artery. Intra-arterial chemotherapy was introduced in the 1960s through to the early 1980s in Japan, mainly for the treatment of maxillary sinus cancer, as maxillary sinus cancer accounted for approximately 30% of the cancers arising in the upper aerodigestive tract at that time. However, retrograde intra-arterial infusion via the superficial temporal artery, which was the standard method for intra-arterial chemotherapy at that time, resulted in inadequate selectivity in some patients in whom the cancer was supplied by multiple arteries. The drug was, therefore, not delivered to the cancer adequately in such patients. As a result, some patients appeared to show excellent outcomes, while others did not. In reality, the 5-yr overall survival (OS) was 60-80% in patients with T3 maxillary sinus cancer, which is usually supplied by one artery, whereas it was around 40% in those with T4 cancer, which is usually fed by more than one artery [7, 8]. Thereafter, advances in vascular interventional radiology techniques in the 1980s enabled superselective intra-arterial infusion to the head and neck structures. “Superselective” has been defined as the procedure in which a catheter is inserted into a branch of the external carotid artery [9]. Robbins et al. developed a specific concomitant chemotherapy protocol for head and neck cancer that employed the pharmacologic principles of intra-arterial cisplatin while capitalizing on the cisplatin-neutralizing activity of sodium thiosulfate [10]. The intra-arterial infusion procedure involves the angiographic introduction of a transfemoral microcatheter to the branch of the external carotid artery supplying the tumor. Cisplatin is then infused through the microcatheter to the dominant blood supply of the targeted tumor. At the same time, sodium thiosulfate is infused intravenously to neutralize the cisplatin. A phase I study demonstrated that cisplatin could be safely

administered to patients with advanced and recurrent head and neck cancer at a dose intensity of 150 mg/m² per week. As the next step, concomitant radiotherapy was added to the high-dose cisplatin infusion strategy [11]. The regimen, referred to as RADPLAT, was mainly indicated for patients with locally advanced head and neck cancers other than sinonasal cancer in Western countries. However, RADPLAT has also been used for patients with locally advanced sinonasal cancer in several institutions in Japan as the long-term use of the intra-arterial infusion procedure for sinonasal cancer made it readily accepted by physicians. Its use has been reported to result in favorable survival rates [12-14].

This procedure was introduced in Japan with a reduced dose of 100 mg/m² per cycle administered once a week as there were some initial concerns over the potential for adverse events. Based on the favorable results obtained, this procedure is now used in Japan with 100 mg/m² generally administered once a week per cycle, although the number of cycles of cisplatin infusion varies (4-7 cycles) by institution. On the other hand, in the original report by Robbins et al., 150 mg/m² was administered once a week for only 4 cycles [10, 11]. Theoretically, a greater number of cisplatin infusions while patients are receiving radiotherapy are more effective as such a regimen increases the radiosensitizing effect of cisplatin. However, the number of cycles of cisplatin at a dosage of 100 mg/m² has not been optimized, and the recommended number of cisplatin cycles (RC) should be determined for patients with locally advanced maxillary sinus cancer.

Based on the above, we, the Head and Neck Cancer Study Group of Japan Clinical Oncology Group, are now engaged in a multi-institutional dose-finding and efficacy confirmation trial of the superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus squamous cell carcinoma (MS-SCC) (JCOG1212, Fig.1) [1]. This study was planned to confirm whether RADPLAT contributes to organ preservation in patients with resectable disease and to afford survival benefits in those with unresectable disease. We herein report the results of the dose-finding phase.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in February 2014 and the study was activated in April 2014. Approval was obtained from the Institutional Review Board prior to starting patient accrual at each institution. This trial was registered at the UMIN Clinical Trials Registry under Trial No. UMIN000013706 (<http://www.umin.ac.jp/ctr/>).

Materials and methods

Patients

For inclusion in this study, patients had to fulfill the following criteria: primary lesion located at the maxillary sinus, histologically proven squamous cell carcinoma, clinical stage T4aN0M0 or T4bN0M0, no severe carotid stenosis as evaluated by ultrasonography, aged between 20 and 75

years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, no prior therapy for maxillary sinus cancer, no prior radiotherapy to the head and neck or the brain, no prior chemotherapy for any other malignancies, sufficient organ function as shown by a peripheral blood white blood cell count of at least 4000 cells per μL and 12,000 cells per μL or less, hemoglobin concentration of at least 9.5 g/dL, platelet count of at least 100,000 cells per μL , serum total bilirubin concentration of 2.0 mg/dL or less, AST of 100 IU/L or less, ALT of 100 IU/L or less, serum creatinine concentration of 1.2 mg/dL or less, normal electrocardiogram, ability to reach the external carotid arteries from the femoral artery with a catheter, and satisfy normal tissue radiation dose constraints for the ipsilateral eyeball and optic nerve, spinal cord, brainstem and chiasma. Written informed consent was obtained from all patients prior to registration.

Patients were excluded if they had any of the following conditions: simultaneous or metachronous (within 5 years) double cancers other than in situ carcinoma or intramucosal tumors, active infection requiring systemic therapy, body temperature $\geq 38^{\circ}\text{C}$, women during pregnancy, breastfeeding or within 28 days after delivery, severe psychosis, need for systemic steroid medication or immunosuppressant medication, poorly controlled diabetes mellitus, poorly controlled hypertension, an angina pectoris attack within 3 weeks or myocardial infarction within 6 months, or were positive for serum HBs antigen.

Treatment methods

The protocol treatment consists of weekly superselective intra-arterial infusion of cisplatin with concomitant radiotherapy and salvage surgery where necessary.

Chemotherapy

In the dose-finding phase, 100 mg/m² of cisplatin was administered intra-arterially weekly for 7 weeks. At the same time, sodium thiosulfate was administered at a dose of 20 g/m² intravenously to neutralize the cisplatin. Digital subtraction angiography and/or an IVR-CT system, which combines angio and CT imaging with the patient remaining on the same table, was performed to accurately and carefully identify the arteries feeding the tumor and their perfusion. Tumors of the maxillary sinuses are usually fed by the internal maxillary artery, but for cases in which the facial artery, transverse facial artery, or so on fed the tumor, part of the dose was administered through these alternative arteries [12, 15]. The dose of cisplatin infused from each artery was determined as described in previous reports. The RC was determined in the dose-finding phase for application in the efficacy confirmation phase.

Radiotherapy

Radiotherapy was administered with high-energy photons by 4–10 MV X-rays to a total dose of 70 Gy in 35 fractions five times weekly. The gross tumor volume (GTV) included the volume of the primary tumor. The clinical target volume (CTV) included the GTV with a 0.5 cm margin and the entire ipsilateral maxillary sinus, at least. The CTV did not include the area of potential lymph node

metastasis in the neck. The planning target volume (PTV) for the CTV was defined as a 0.5 cm margin around the CTV to compensate for set-up variations and internal organ motion. To protect normal vital structures, such as the contralateral eye ball and/or optic nerve, chiasma, spinal cord and brain, a partial reduction in the PTV margin of 0.1 cm from the initial 0.5 cm was allowed.

Dose-finding method

In the dose-finding phase, 100 mg/m² of cisplatin was administered weekly for 7 weeks with concomitant radiotherapy to 18 patients. The dose of cisplatin was not modified in the case of adverse events. The grade of toxicity was assessed according to the Common Terminology Criteria for Adverse Events v4.0. Cisplatin was skipped in the case of adverse events that met the skipping criteria defined in the protocol as follows: (1) leukopenia $\geq$ Grade 3, (2) neutropenia $\geq$ Grade 3, (3) thrombocytopenia $\geq$ Grade 2, (4) AST/ALT $\geq$ Grade 2, (5) total bilirubin $\geq$ 2.5 mg/dL, (6) estimated creatinine clearance (Ccr) <50 mL/min, (7) infection $\geq$ Grade 3 (8) febrile neutropenia $\geq$ Grade 3, (9) body temperature $\geq$ 38°C with infection, or (10) need for G-CSF administered the same day.

The RC was determined according to the distribution of the number of cycles of administered cisplatin and the incidence of dose-limiting toxicities (DLTs). RC was taken as the maximum number of cycles of administered cisplatin at which no more than one-third of the patients experienced DLTs. More specifically, the mode, the most frequent value, was considered to be the prime candidate for the RC, and the incidence of DLTs among patients who were administered the mode number of cisplatin cycles and that among those administered no more than the mode were

compared. If the mode was tolerable, the mode+1 cycle was evaluated in the same way. However, if the mode was not tolerable, the mode-1 cycle was evaluated. Where necessary, mode-2, mode-3, mode+2, and mode+3 were also evaluated. Continuation of the dose-finding phase with dose escalation to 120 mg/m² of cisplatin per cycle was set for consideration where 12 or more of the 18 patients (two-thirds of the patients) were administered 7 cycles of 100 mg/m² of cisplatin.

Definition of DLTs

The DLT observation period was defined as the period from the date of the beginning of treatment to 28 days after the last radiotherapy session. DLTs were defined using the following criteria: (1) Grade 3 febrile neutropenia, (2) Grade 4 thrombocytopenia, (3) estimated Ccr <40 mL/min, (4) Grade 3 or more severe non-hematologic toxicity, except for mucositis, dermatitis, electrolyte abnormalities and complications related to intervention, (5) radiation break of >14 days due to toxicity, (6) skipping chemotherapy administration for 3 or more consecutive cycles, and (7) treatment-related death.

Follow-up

All enrolled patients were to be followed for at least 5 years, while analysis of the primary endpoint of the efficacy confirmation phase was planned to be conducted 3 years after accrual completion. Efficacy and safety were to be evaluated at least every 3 months during the first year, at least every 4 months during the second year, and then every 6 months during the third to fifth year.

Quality control of intra-arterial chemotherapy

All participating interventional radiologists had to agree to the technical details for superselective intra-arterial chemotherapy pre-specified in the study protocol. To control the quality of the interventional technique, the central review of photographs and movies for arbitrarily selected patients was performed at semiannual investigators' meetings. All interventional procedures were performed or directly supervised by interventional radiologists certified by the study chair. The major criteria for certification in this study included (i) having experienced interventional radiology on ≥ 40 occasions with ≥ 10 occasions as the principal operator, (ii) having experience with two patients or more requiring intervention with superselective arterial infusion of cisplatin for head and neck cancer within 2 years and (iii) being board certified in societies related to interventional radiology.

Study design and statistical analysis

This is a multi-institutional, single-arm, prospective trial of superselective intra-arterial infusion of high-dose cisplatin with concomitant radiotherapy for patients with T4aN0M0 or T4bN0M0 locally advanced maxillary sinus squamous cell carcinomas (Fig. 1). The trial consists of a dose-finding phase and an efficacy confirmation phase. The dose-finding phase was designed to determine the RC through the study of patients with either T4aN0M0 or T4bN0M0 tumors. The efficacy confirmation phase is being conducted separately for patients with T4aN0M0 and T4bN0M0 disease. The primary endpoint of the dose-finding phase was the incidence of DLTs. The secondary endpoint was the incidence of adverse events. Toxicities were analyzed at the end of the DLT observation period for

the last patient in the dose-finding phase, and the RC was determined. Based on our previous experience, all patients were expected to be able to tolerate 100 mg/m² of cisplatin administration at least 5 times. The planned sample size in the dose-finding phase was 18 patients in order to maintain almost the same precision for the mode number of cycles in a traditional 3 + 3 design when the actual number of cycles ranges from 5 to 7 times for the enrolled patients.

Patient demographics and clinical characteristics were summarized using descriptive statistics. For categorical variables, such as patient gender, disease stage, response, and toxicity at each grade level, frequency and percentage were determined. For numerical variables, such as age and dose of cisplatin administered, the median and range were calculated. All statistical analyses were carried out using SAS software version 9.2 (SAS Institute, Cary, NC, USA). This report is based on the data available as of May 24, 2016. The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) and the institutional review boards of the participating institutions approved the study protocol. This trial is registered at the UMIN Clinical Trials Registry under Trial No. UMIN000013706 (<http://www.umin.ac.jp/ctr/>).

Results

Eighteen patients from 7 institutions were registered in the dose-finding phase between April 2014 and September 2015. Of the 18 patients (14 male and 4 female), 16 were diagnosed as T4aN0M0

and 2 as T4bN0M0. Ages ranged from 40 to 75 years (median 64 years). Other characteristics are shown in Table 1.

All patients achieved a full dose of radiotherapy. The number of cycles of cisplatin administered was 7 in 13 patients and 6 in 5 patients. DLTs were observed in 5 patients, with Grade 3 liver dysfunction (1 patient), Grade 4 thrombocytopenia (1), estimated Ccr<40 mL/min (1), Grade 3 retinopathy (1), and Grade 3 retinal detachment (1) also observed (Table 2). Acute toxicities are shown in Table 3. No treatment-related deaths or neural complications were observed.

Dose escalation to 120 mg/m² of cisplatin per cycle was discussed among the members of the Head and Neck Cancer Study Group in the JCOG. The proportion of patients administered 7 cycles of cisplatin (13/18) was a little more than 2/3 of the study population and the proportion of patients experiencing DLTs (5/18) was a little less than 1/3. Therefore, dose escalation to 120 mg/m² of cisplatin per cycle was not performed and the RC was determined to be 7 cycles of 100 mg/m² cisplatin per cycle.

Discussion

Robbins et al., who originally developed RADPLAT, previously conducted a phase I study designed to determine the maximum-tolerated dose (MTD) of cisplatin for intra-arterial administration [10].

The number of cycles of cisplatin administered was fixed at 4 and the MTD was set at 150 mg/m²

once a week for the first 4 weeks. Next, they conducted a phase II study of a chemoradiation protocol based on intra-arterial cisplatin at 150 mg/m^2 every week for four doses with concomitant radiotherapy (1.8 to 2.0 Gy/day x 35 fractions) for 29 patients with untreated stage IV head and neck cancer [11]. As mentioned above in the introduction, repeated cisplatin infusion while patients receive radiotherapy is, theoretically, more effective as it increases the radiosensitizing effect of cisplatin. Therefore, there was a concern that the radiosensitization was limited because cisplatin was concurrently administered with radiotherapy for only the first 4 of the 7 weeks of radiotherapy in Robbins's regimen.

We further considered the dose per cycle and the number of cycles of cisplatin. As for the dose per cycle, we adopted a dose of 100 mg/m^2 of cisplatin, which is commonly used in Japan. One institution in Japan treated 19 patients with maxillary sinus cancer by RADPLAT [16]. Patients were intended to receive 7 cycles at a dose of 100 mg/m^2 of cisplatin. Eventually, 13 patients (68%) received 7 cycles, 3 (16%) received 6, 2 (11%) received 5, and 1 (5%) received 4. With regard to adverse events $\geq$ Grade 3, nausea/vomiting was observed in 7 patients and mucositis in 9 patients, which was considered to be acceptable. According to these results, 7 cycles at a dose of 100 mg/m^2 of cisplatin appears to be feasible, and we did not consider a dose escalation study to be necessary. Rather, we planned to confirm the feasibility of 7 cycles at a dose of 100 mg/m^2 of cisplatin in the multi-institutional setting. As for the number of cycles of cisplatin, we aimed at determining the RCs in our study, which we speculated might be more than 4 cycles. DLT for this study was defined as

any adverse event serious enough to prevent an increase in number of cycles of cisplatin administered such as Grade 3 febrile neutropenia and Grade 4 thrombocytopenia in terms of myelosuppression; estimated Ccr <40 mL/min, which is an important cisplatin-induced toxicity; and complications related to intervention, which is a form of toxicity specific to this treatment. As a result, all patients were found able to receive a full dose of radiotherapy, and 13 patients received 7 cycles of intra-arterial chemotherapy, with the remaining 5 patients receiving 6 cycles in the multi-institutional setting.

The median total dose of cisplatin administered was 700 mg/m², with a range from 600 to 700 mg/m². A phase II trial of RTOG9615 in the United States [17] and a randomized trial in the Netherlands [18] were conducted with a treatment regimen consisting of intra-arterial cisplatin at 150 mg/m² every week for four doses with concomitant radiotherapy (70 Gy, 2 Gy/fraction, daily for 5 days over 7 weeks), although these trials did not include patients with sinonasal malignancies. In the former study, intra-arterial cisplatin infusions were delivered as follows: four infusions in 45 patients (74%), three in 13 (21%), two in two (3%), and one in one (2%). Sixteen patients (26%) were administered less than 600 mg/m² of cisplatin. In the latter trial, compliance, which was defined as complete delivery of both radiation and chemotherapy within the treatment time, was 76% (90/118). Compared with these results, a schedule consisting of 100 mg/m² of cisplatin per cycle is thought likely to result in better compliance.

No treatment-related deaths or neural complications were observed in the dose-finding phase. As for Grade 3/4 toxicities, both hematological toxicities (3 patients, 16.7%) and mucositis (4, 22.2%) were observed. In RTOG9515, Grade 3/4 hematological toxicities and mucositis occurred in 51% and 58% of patients, respectively. However, RTOG9515 was conducted in the 1990s and, the radiation technique and supportive care employed are considered to differ markedly from those in this study [17]. The development of antiemetic and comprehensive management for mucositis and dermatitis, including pain reduction therapy and nutritional support, is believed to have helped to reduce toxicities during and after treatment. Moreover, the radiation field in this study did not include the oral cavity or pharynx to any great extent. These factors are thought to have contributed to the lower incidence of severe adverse events and higher total dose of cisplatin administered.

In addition, there were no catheter-related cerebrovascular accidents in the dose-finding phase, although the incidence of cerebrovascular accidents among patients treated by RADPLAT in other studies were variously reported to be 3.3% (Grade ≥ 3)[19], 6.8% (Grade ≥ 2)[18], and 8.2% (Grade ≥ 3)[17]. This difference is thought to be due to the fact that patients with severe carotid stenosis, as evaluated by ultrasonography, were excluded from this study, and all interventional procedures were performed or directly supervised by interventional radiologists certified by the study chair. In addition, the training workshops held irregularly before and during the study period together with the semiannual investigator meetings may also have contributed to the absence of any catheter-related cerebrovascular accidents to date. These workshops not only contributed to safe performance of the

treatment but also allowed more sophisticated interventional procedures to be performed in each institution.

The increase in the number of interventions resulted in an increase in the physicians' workload. However, it also resulted in more adept cisplatin infusion. For example, physicians sometimes found the ideal intra-arterial infusion to the targeted vessels in the first couple of interventions. Under such circumstances, the ideal intra-arterial chemotherapy can be achieved only once or twice in cases where only four cycles are administered. On the other hand, the ideal intra-arterial chemotherapy can be achieved more often if there are seven cycles. We expect the increase in the number of interventions to lead to better tumor control.

The limitation of this study was that the treatment might not be applied to patients with lymph node metastasis as patients with lymph node metastasis were excluded to ensure homogeneity of the population and allow more accurate evaluation of RADPLAT efficacy based on the fact that such patients were reported to have a poorer prognosis than those without lymph node metastasis [12, 20]. In addition, only 2 of the 18 patients enrolled in the dose-finding phase of this study were diagnosed with T4b disease. This might have been because normal tissue radiation dose constraints for the ipsilateral eyeball and optic nerve, and chiasma are not often satisfied by 3D-CRT in patients with T4b. Therefore, the protocol has been modified to use IMRT instead of 3D-CRT in hospitals certified by the JCOG Radiotherapy Committee. As a result, more T4b patients are expected to be enrolled in the efficacy confirmation phase.

In conclusion, RADPLAT appears to be safe and well-tolerated at 7 cycles of cisplatin at a dose of 100 mg/m² per cycle, which was determined to be the recommended number of cycles for locally advanced MS-SCC. The efficacy confirmation phase was begun in January 2016 and is now open for accrual. A total of 65 patients with T4aN0M0 and 62 patients with T4bN0M0 will be enrolled in the efficacy confirmation phase.

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Disclosure Statement

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Figure Legend

Fig. 1. Patient flow diagram of a dose-finding and efficacy confirmation trial of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer. MS-SCC, maxillary sinus squamous cell carcinoma; PS, performance status.

Untreated
T4aN0M0 or T4bN0M0
SCC-MS, PS 0-1

Total 127 pts

[65 T4a patients
62 T4b patients

Dose finding phase
(n=18)

.....

T4aN0

T4bN0

Efficacy confirmation
phase

.....

T4aN0

T4bN0

Table 1. Characteristics of patients with SCC-MS who participated in the dose-finding phase

Characteristic	
Age, years	
Median	64
Range	40-75
Gender	
Male	14
Female	4
Performance status	
0	16
1	2
T classification	
T4a	16
T4b	2

Table 2. Number of cisplatin administrations and DLTs for each patient with SCC-MS who participated in the dose-finding phase

Patient	Age	Gender	T classification	PS	Number of cisplatin administrations/Reason	DLT	Component
1	51	M	4a	0	7	No	
2	64	F	4a	0	6	liver dysfunction, scheduling problem	Yes
3	43	M	4a	0	6	general disorders, blood disorder	No
4	67	M	4a	0	7		No
5	66	M	4b	0	7		No
6	70	M	4a	0	6	infection, fatigue, scheduling problem	No
7	60	M	4a	0	7		Yes
8	64	M	4a	1	7		Yes
9	45	M	4b	0	7		No
10	40	M	4a	0	6	blood disorder	No
11	61	M	4a	0	7		No
12	74	M	4a	1	7		No
13	61	F	4a	0	7		No
14	46	M	4a	0	7		No
15	75	F	4a	0	6	fatigue	No
16	67	F	4a	0	7		Yes
17	66	M	4a	0	7		Yes
18	71	M	4a	0	7		No

Table 3. Overall toxicities in patients with SCC-MS who participated in the dose-finding phase from the start of treatment to 90 days after start of treatment (n=18)

Toxicity	No. of patients				Grade 3-4, %
	Grade 1	Grade 2	Grade 3	Grade 4	
Leucopenia	3	6	1	0	5.6%
Neutropenia	0	7	0	1	5.6%
Thrombocytopenia	2	3	0	0	0%
AST increased	2	0	1	0	5.6%
ALT increased	7	1	1	0	5.6%
Fever	4	1	0	0	0%
Creatinine	2	0	0	0	0%
Hypomagnesemia	1	0	0	0	0%
Hypermagnesemia	4	-	0	0	0%
Anemia	10	1	1	1	11.1%
Mucositis - oral cavity	1	13	4	0	22.2%
Mucositis - pharynx	3	2	1	0	5.6%
Radiation dermatitis	7	10	1	0	5.6%
Allergic reaction	1	0	0	0	0%
Hearing	1	1	1	0	5.6%
Tinnitus	2	0	0	-	0%
Dysgeusia	4	3	-	-	-
Fatigue	3	2	0	-	0%
Alopecia	1	2	-	-	-
Nausea	3	1	0	-	0%
Epistaxis	3	1	0	0	0%
Watering eyes	10	3	0	-	0%
Cataract	1	0	0	0	0%
Corneal ulcer	-	0	1	0	5.6%
Retinopathy	0	0	2	0	11.1%

Adverse events were graded according to Common Toxicity Criteria for Adverse Events version 4.0.