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ORIGINAL ARTICLE

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Clinical trial with escalating doses of the antiepidermal growth factor receptor humanized monoclonal antibody EMD 72 000 in patients with advanced squamous cell carcinoma of the larynx and hypopharynx

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Abstract In this open uncontrolled phase I study, nine patients with stage III and IV squamous cell carcinoma of the head and neck (SCCHN) were treated with five administrations of the humanized antiepidermal growth factor receptor monoclonal antibody EMD 72 000 in three consecutive ascending dose groups. Loading doses of 100 mg (group I), 200 mg (group II), and 400 mg (group III) were followed by four weekly maintenance doses of half the loading doses, i.e. 50, 100, and 200 mg, respectively. Two EMD 72 000 administrations were scheduled before and three after surgery. The objectives of this trial were (a) to investigate the safety and toxicity of multiple EMD 72 000 doses, (b) to determine the cumulative maximum tolerated dose of EMD 72 000 at dosages between 300 mg and 1200 mg, and (c) to determine the serum pharmacokinetics of EMD 72 000. In total, 102 adverse events (AEs) were reported: five of toxicity grade 3, 18 of toxicity grade 2, 66 of toxicity grade 1, and 38 of toxicity grade 0. All AEs of toxicity grade 3 were considered to be not or remotely related to EMD 72 000. The most frequent study drug-related AEs were fever and a transient elevation of liver enzymes. In all patients, the time to reach peak serum concentrations (t_{max}) was within 1–3 h of the start of each EMD 72 000 infusion. Average peak serum concentrations (C_{max}) after correction for dosage appeared to be dose-independent, whereas the half-life ($t_{1/2}$) showed dose dependency. In conclusion, EMD 72 000 was very well tolerated in patients with advanced stage SCCHN. The pharmacokinetic data from this trial suggest the feasibility of conducting future studies with weekly doses of 200 mg EMD 72 000.

Keywords Phase I study · Head and neck cancer · Monoclonal antibody · EGF receptor

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Introduction

The majority of patients with squamous cell carcinoma of the head and neck (SCCHN) suffer from advanced disease with large primary lesions and regional lymph node metastasis. Although considerable progress has been achieved in the refinement of the standard treatment modalities, surgery and radiotherapy, and despite the promising introduction of simultaneous radiochemotherapy, the rate of cure of these patients continues to be poor. Therefore, recent research has increasingly focused on the exploration of novel treatment strategies, including immunotherapy [23]. The development of both hybridoma technology and molecular biology has led to the generation of a great variety of biologically and genetically engineered monoclonal antibodies (mAbs) initiating a new phase in the passive immunotherapy of malignancies. In particular, the production of chimeric and humanized mAbs is an important prerequisite to avoid the clinical problems of strong and potentially neutralizing human anti-mouse antibody responses in patients treated with murine mAbs.

Epidermal growth factor receptor (EGFR) has been found to be strongly expressed in a number of different cancers, including SCCHN [5, 6, 18, 21]. Because of the frequency and intensity of receptor expression, and its

supposed significance for the manifestation of the malignant phenotype [8, 9], EGFR is considered to be an interesting target for antitumor therapy in SCCHN [2, 26]. Accordingly, the localization of the receptor in the cell-surface membrane makes mAbs directed against the extracellular EGFR domain likely candidates for the exploration of this approach [13, 14]. Preclinical in vitro and in vivo studies using either murine EMD 55 900 or its humanized analog EMD 72 000, and also other anti-EGFR mAbs, have shown four major effects in SCCHN: induction of differentiation, antiproliferative activity, additive and synergistic intensification of antineoplastic chemotherapy, and induction of antibody-dependent cell-mediated cytotoxicity [4, 10, 11, 12, 15, 25]. These effects have been attributed to interference with ligand-receptor interactions, and to the coating of tumor cells with the mAb.

In a clinical trial in patients with advanced laryngeal and hypopharyngeal squamous cell carcinoma, single-dose administration of 100, 200, and 400 mg EMD 55 900 has been shown to be very well tolerated, and good (100 mg) to excellent (400 mg) homogeneous binding of the mAb to EGFR was detected in the resected tumor specimens by immunohistochemistry [3]. Employing the humanized mAb EMD 72 000, the objects of the present investigation were (a) to assess the safety and toxicity of multiple administrations, (b) to determine the cumulative maximum tolerated dose between 300 and 1200 mg, and (c) to monitor pharmacokinetic parameters. Ultimately, the results of this trial should help to establish a regimen for the clinical application of EMD 72 000 so that combined treatment protocols in patients with advanced SSCHN can be developed. This may include additive mAb administration before and/or after standard treatment, and combinations of immuno-, chemo- and/or radiotherapy.

Patients and methods

Patients

This uncontrolled two-center phase I trial included ten patients (eight males, two females, mean age 55.4 years) with histologically confirmed stage III and IV (T3/4, any N+) squamous cell carcinoma of the larynx or hypopharynx amenable to surgical resection with curative intent (Table 1). EGFR expression of the tumors was not determined prior to patient inclusion. The exclusion criteria are listed in Table 2. The study protocol was approved by the ethics committees of the Heinrich-Heine-University Düsseldorf and the Johann-Wolfgang-Goethe-University Frankfurt, and all patients gave written informed consent prior to enrollment. The number of patients per dosage group was established without test power considerations.

Study medication

The murine IgG2a mAb 425 (EMD 55 900; Merck, Darmstadt, Germany) was raised against the human epidermoid cancer cell line A431 and binds specifically to a protein epitope on the external domain of the human EGFR [17, 19, 20]. EMD 72 000 (Merck) is the reshaped IgG1 antibody produced without preservatives under GMP conditions and tested for sterility, pyrogenicity, and virus contamination.

Table 1 Patient characteristics and cumulative EMD 72 000 dose. Patient no. 5 decided not to continue the study after the first mAb infusion. TNM classification according UICC 1997

Patient no.	Age (years)	Sex	Tumor site	TNM stage	mAb dose (mg)
1	69	Male	Hypopharynx	T4N2M0	300
2	49	Male	Hypopharynx	T4N2M0	300
3	57	Male	Larynx	T3N3M0	300
4	51	Female	Hypopharynx	T3N0M0	600
5	48	Male	Hypopharynx	T2N2M0	200
6	64	Male	Larynx	T3N2M0	600
7	48	Male	Larynx	T1N1M0	1200
8	52	Male	Larynx	T4N0M0	1200
9	53	Male	Larynx	T2N1M0	1200
10	63	Female	Hypopharynx	T4N1M0	600

Table 2 Exclusion criteria. The presence of one of the criteria listed below was sufficient to exclude a patient from the study

Age under 18 or over 85 years
Karnofsky performance status less than 70%
History of psychiatric illness or drug abuse
Limited legal capacity
Pregnancy or lactation
Distant metastasis
Severe infection
Concurrent immunosuppressive therapy
Immunotherapy within the last 3 months
Participation in a clinical trial within the last month
Hemoglobin < 11 g/100 ml
Leukocytes $< 3000/mm^3$
Platelets $< 100{,}000/mm^3$
Liver transaminases exceeding twice the upper normal value
Serum creatinine > 1.3 mg/100 ml
Blood in urine (Dipstick analysis)

Trial design

EMD 72 000 was administered as a 1-h infusion in three consecutive ascending dose groups of three patients each. Patients received five mAb infusions at weekly intervals (days 0, 7, 14, 21, 28), two before and three after surgery. Two considerations led to the agreement on this perioperative schedule: onset of standard therapy in malignant disease must not be delayed, and proper assessment of study parameters during inpatient treatment is better guaranteed. Accordingly, the patients received only one or two mAb infusions as outpatients.

One-third of the total dose of EMD 72 000 was given as a loading dose with the first infusion followed by four maintenance administrations of one-sixth of the total dose, i.e. the loading/maintenance doses in the three groups were: group I 100/50 mg, group II 200/100 mg, and group III 400/200 mg. Accordingly, the respective total doses were 300, 600, and 1200 mg. The intermediate results of the trial did not require the application of pre-established dose modelling procedures.

Toxicity

Side effects of the EMD 72 000 treatment were monitored in terms of clinical parameters (physical examination, blood pressure, heart rate, and body temperature) and laboratory tests (hemoglobin, hematocrit, blood count, prothrombin and partial thromboplastin

times, serum electrolytes, creatinine, blood urea nitrogen, total serum protein, albumin, total bilirubin, liver enzymes, and urinalysis). The definitions of adverse events (AEs) and serious adverse events (SAEs) applied as well as the criteria for the assessment of the degree of causal relationship are summarized in Table 3. AEs were classified according the ECOG (grade 0 to 4) toxicity criteria.

Pharmacokinetics

Serial blood samples were drawn from patients before, immediately after, and 1, 2, 4, 24, and 72 h after the infusion of EMD 72 000. Samples were immediately centrifuged for 10 min at 3500 *g*, and the resulting serum supernatants were stored in tubes (Cryo Tube, Nunc, Roskilde, Denmark) at –20°C. Serum concentrations of the mAb were determined using a validated enzyme-linked immunosorbent assay (Merck). Using standard noncompartmental and compartmental methods (Kinetica, Version 2.0, Innaphase, Champs sur Marne, France), various pharmacokinetic target variables were calculated. These included half-life ($t_{1/2}$), total body clearance of drug from the serum (CL), volume of distribution during the terminal phase (Vz), volume of distribution of the central compartment (Vc), area under the serum concentration time curve (AUC), average serum concentration (C_{avg}), minimum serum concentration (C_{min}), maximum serum concentration (C_{max}), and time to reach C_{max} (t_{max}). The analysis was based on all patients treated with at least a single dose of EMD 72 000, and the three dose groups were compared descriptively.

Results

The mAb treatment was completed in nine of the ten patients included in this trial. Patient no. 5 decided to withdraw after having experienced toxicity grade 1 AEs (sense of heat, dyspnea, tachycardia, and muscle tremor) during the first infusion. In patient no. 10 the fourth mAb administration was postponed by 11 days due to surgical complications. No other noteworthy protocol violations occurred.

Adverse events

In total, 102 AEs were observed in ten patients and each patient experienced at least one AE. The vast majority of AEs were of toxicity grade 0, 1, or 2 ($n = 97$). Three patients developed five toxicity grade 3 AEs, and no toxicity grade 4 AE occurred (Table 4). Since the patients underwent major head and neck surgery, peri- and intraoperative medications as well as blood loss and substitution of blood components required a special consideration of AEs in the postoperative phase. The monitoring of blood pressure and heart rate revealed no major alterations, whereas a transient increase in body temperature (maximum 39.6°C) was observed nine times in eight patients (toxicity grade 0, 1 and 2) shortly after mAb administration. Furthermore, two patients experienced exanthema (toxicity grade 1), and one patient experienced two episodes of headache (toxicity grade 1 and 2).

Abnormal laboratory values and the assessment of their relationship with either EMD 72 000 or surgery are summarized in Table 5. Elevated liver enzymes (14 AEs toxicity grade 0, 1, and 2; 2 AEs toxicity grade 3), in particular, appeared to be primarily drug-related. However, as many patients with SCCHN have a history of heavy alcohol intake and considering the hepatic stress during a long general anesthesia, the increase of γGT, SGPT or SGOT, at least in some cases, was likely to have been multifactorial. Episodes of increased bilirubin ($n = 1$) and blood urea ($n = 1$), leukocytosis ($n = 2$), leukopenia ($n = 1$), and decreased sodium ($n = 1$) and prothrombin time ($n = 1$) were classified as possibly related to the study medication (toxicity grade 0 and 1). As expected, surgery was associated with decreased amounts of serum protein, erythrocytes and hemoglobin.

Three of the five toxicity grade 3 AEs (Table 6) were judged to be remotely related to the test drug, and a single SAE – cervical fistula after jejunum interposition – was probably related to surgery.

Pharmacokinetics

Example mean serum EMD 72 000 concentration versus time curves are shown for group III (loading dose 400 mg, maintenance doses 4 × 200 mg) in Fig. 1. In all patients C_{max} was reached within 1–3 h (t_{max}) of the start of each EMD 72 000 infusion. The average C_{max} and the respective dose-corrected values are listed in Table 7. After correction for dosage, this parameter appeared not

Table 3 Definitions of AEs and SAEs, and the criteria for the assessment of the degree of causal relationship

Adverse events (AEs)
All unfavorable changes in general condition
All subjective or objective symptoms
All concomitant diseases or accidents
All clinically relevant changes of laboratory parameters
Serious adverse events (SAEs)
Result in death
Life-threatening
Require inpatient treatment
Result in persistent or significant disability
Determination of causal relationship
None: reasonable explanation must be given
Remote: not likely according to present knowledge
Possible: no alternative explanation or known from similar drugs
Probable: clear coincidence with exposure to test drug
Highly probable: rechallenge caused same symptoms
Not assessable: no information available for judgement

Table 4 AEs by toxicity grade and their relationship to the administration of EMD 72 000

Toxicity grade	None	Remote	Possible	Probable	Highly probable	Total
0 (none)	1	4	8	0	0	13
1 (mild)	17	23	12	7	7	66
2 (moderate)	3	10	2	1	2	18
3 (severe)	2	3	0	0	0	5
4 (fatal)	0	0	0	0	0	0
Total	23	40	22	8	9	102

Table 5 Abnormal laboratory values, their toxicity grade, and their relationship to the study medication and surgery (*grade of toxicity* 0 none, 1 mild, 2 moderate, 3 severe, 4 fatal; *relationships* 1 none, 2 remote, 3 possible, 4 probable, 5 highly probable)

Symptom	*n*	Grade of toxicity				Relationship to EMD 72 000					Relationship to surgery				
		0	1	2	3	1	2	3	4	5	1	2	3	4	5
Anemia	8	2	3	3			8								8
Serum protein decreased	5		4	1		2	3								5
Erythrocytes decreased	1		1			1									1
Hemoglobin decreased	3		1	1	1	2	1								3
Bilirubin increased	1	1						1				1			
γGT elevated	8	2	4	1	1		2	4	1	1	4			4	
SGPT increased	5	1	3		1		1	1	2	1	4		1		
SGOT increased	3		2	1			1			2	2		1		
Leukocytosis	2		2					2						2	
Leukopenia (decreased)	2	2					1	1			2				
Ca decreased	1		1				1								1
Na decreased	1	1						1					1		
Blood urea increased	1	1						1				1			
PTT increased	1		1			1					1				
PT decreased	1	1						1						1	

Table 6 Adverse events of severe toxicity grade

Patient no.	Dose (mg)	Adverse event	Toxicity grade	Relationship to EMD 72 000	Relationship to surgery
6	200	Hemoglobin decreased	3	None	Highly probable
10	200	γGT elevated	3	Remote	Probable
		Necrotic jejunal interponate	3	Remote	Probable
7	400	Swallowing disturbance	3	None	None
		SGPT increased	3	Remote	Possible

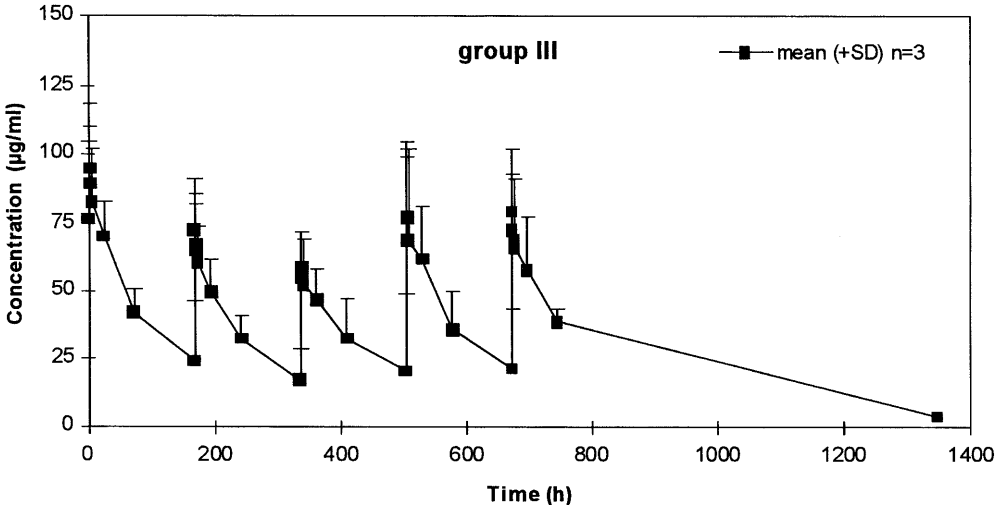

Fig. 1 Mean serum EMD 72 000 concentration versus time curves in group III (loading dose 400 mg, maintenance doses 4×200 mg)

to be dose dependent. Vz ranged between 2.5 and 5.6 l and was approximately constant in all dose groups.

Both noncompartmental and compartmental analysis was carried out for each subject, and the resulting parameters are listed in Table 8. All concentration-time profiles could best be described by a one-compartment model. With regard to the dose-dependent half-life, similar results were obtained in the noncompartmental ($t_{1/2}$) and compartmental ($t_{1/2\alpha}$) analyses (group I 22.3 vs 20.2 h, group II 57.5 vs 43.9 h, group III 85.8 vs 88.6 h). The trough level before each additional administration of EMD 72 000 was detectable for all patients in the high-dose group III: C_{min} values were between 7 and 38 µg/ml, and C_{avg} values ranged from 20 to 61 µg/ml. Concentration-time profiles during weeks 2–5 in group III (maintenance doses 200 mg) showed no differences

Table 7 Average values of C_{max} (μg/ml) in groups I, II, and III after each of the five EMD 72 000 administrations, and the respective values after dose correction (100 mg = 1)

Group	C_{max1}		C_{max2}		C_{max3}		C_{max4}		C_{max5}	
	Average	Dose-corrected	Average	Dose-corrected	Average	Dose-corrected	Average	Dose-corrected	Average	Dose-corrected
I	30.5	30.5	17.4	34.8	11.6	23.2	12.4	24.9	13.2	26.3
II	71.6	35.8	55.0	51.3	40.5	34.7	49.6	37.3	59.2	44.5
III	95.8	24.0	71.8	35.9	60.3	30.2	79.0	39.5	79.1	39.6

Table 8 Pharmacokinetic parameters of EMD 72 000 in groups I, II, and III. Values are means ± SD ($t_{1/2}$ half-life, *CL* total body clearance of drug from serum, *Vz* volume of distribution during terminal phase, *AUC* area under the serum concentration time curve, *Vc* volume of distribution of the central compartment)

Parameter	Group I	Group II	Group III
Noncompartmental			
$t_{1/2}$ (h)	22.3 ± 5.7	57.7 ± 5.7	85.8 ± 24.0
CL (ml/h)	146 ± 75.7	31 ± 1	29 ± 19
Vz (ml)	4292 ± 1202	2598 ± 153	3185 ± 1198
Compartmental			
$AUC_{0-73\ h}$ (h·μg/ml)	378 ± 124	2908 ± 880	5559 ± 2315
$t_{1/2\alpha}$ (h)	20.2 ± 4.9	43.9 ± 11.5	88.6 ± 22.6
Vc (ml)	3942 ± 478	2915 ± 202	4813 ± 801

from those in group II after a loading dose of 200 mg EMD 72 000.

Discussion

In this open uncontrolled phase I study, nine of ten patients with advanced squamous cell carcinoma of the larynx or hypopharynx received five intravenous administrations of the humanized anti-EGFR mAb EMD 72 000 in three consecutively ascending dose groups. Loading doses of 100, 200, and 400 mg were followed by four maintenance doses of 50, 100, and 200 mg mAb in groups I, II, and III, respectively. In total, 102 AEs were reported: 5 of toxicity grade 3, 18 of toxicity grade 2, 66 of toxicity grade 1, and 13 of toxicity grade 0. The five grade 3 toxicities occurred in three patients, and they were considered to be not or remotely related to the study drug. Hence, repeated administrations of EMD 72 000 up to a total dose of 1200 mg caused only mild to moderate side effects, mostly transient elevations in body temperature and liver enzymes.

This favorable toxicity profile of EMD 72 000 corresponds to experiences that were gained with mainly single application protocols of its murine precursor in earlier clinical trials [3, 7, 22, 24], and similar results have been obtained with other EGFR mAbs of different source and isotype [1, 16]. In addition, the reported toxicities do not suggest an undesirable interference with side effects typically encountered in the course of chemotherapy or irradiation. Thus, the very good tolerability of EGFR mAbs underlines their potential role in combined adjuvant treatment strategies of EGFR-expressing cancers.

In order to establish a regimen for future clinical studies, the following results need particular consideration. For all patients, the time to reach the peak serum concentration, t_{max}, was 1 to 3 h after the start of EMD 72 000 infusions. The dose-corrected average maximum serum concentration, C_{max}, turned out to be dose-independent, whereas the half-life, $t_{1/2}$, showed dose-dependency. Accordingly, the $t_{1/2}$ in group III was over 85 h which is thought to have been responsible for the prolongation of t_{max} that was sometimes observed. For the high-dose group III, the average serum concentration, C_{avg}, ranged from 20 to 61 μg/ml, and the minimum serum concentration, C_{min}, just before the next EMD 72 000 infusion was between 7 and 38 μg/ml. Most importantly, these EMD 72 000 concentrations substantially exceeded 5 μg/ml that we have found to be effective in in vitro investigations, including antiproliferative activity, intensification of antineoplastic chemotherapy, and induction of antibody-dependent cell-mediated cytotoxicity [4, 10].

Therefore, we conclude from this clinical study that (a) weekly intravenous administrations of 200 mg EGFR mAb EMD 72 000 guarantee reasonable serum concentrations, (b) this regimen does not require the administration of a loading dose, (c) the observed toxicity profile indicates the potential of EMD 72 000 for use in novel treatment strategies in conjunction with chemo- and radiotherapy, and (d) the excellent tolerability of EMD 72 000 warrants the consideration of long-term protocols, e.g. repeated cycles as an adjuvant treatment after standard therapy.

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