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ORIGINAL ARTICLE

Phase II clinical trial of h-R3 combined with radiotherapy in locally advanced nasopharyngeal carcinoma

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Summary

Purpose: *The purpose of this study was to evaluate the short- and long-term efficacy and toxicity of the humanized anti-epidermal growth factor receptor (EGFR) monoclonal antibody h-R3 when combined with radiotherapy for the treatment of locally advanced nasopharyngeal carcinoma (NPC)..*

Methods: *35 patients with stage III-IVb NPC with moderate- or strong-intensity EGFR expression were randomly divided into either a radiotherapy alone group or a group receiving radiotherapy combined with h-R3.*

Results: *The complete remission (CR) rates of the combination group at three time points were significantly higher ($p<0.05$) than those of the radiotherapy alone group. Overall survival, 3-year local control rate, and no distant metastasis rate did not differ between the two groups. No severe toxicity was noticed.*

Conclusion: *h-R3 is an agent with good safety profile which could help enhance the radiation antitumor effect in locally advanced NPC, but it did not seem to exhibit significant long-term efficacy.*

Key words: *epidermal growth factor receptor, h-R3, immunotherapy, monoclonal antibody, nasopharyngeal carcinoma, radiotherapy*

Introduction

In recent years, the breakthrough of molecular targeted therapies for tumors has provided a new method for fighting cancers. Overexpression of EGFR is linked to many types of tumors [1], and its signal transduction pathway is connected with tumor cell proliferation, metastasis and radiation sensitivity [2]. Therefore, blocking the EGFR signaling pathway of tumor cells could help enhance the effects of radiotherapy. Currently, there are several EGFR antagonists used clinically, including monoclonal antibodies (Cetuximab, Panitumumab and Matuzumab) and small molecule tyrosine kinase inhibitors (Iressa and Tarceva) [3-5]. Although these drugs have shown encouraging clinical results, their side-effects (such as acne-like rash) often lead to treatment interruption [5-7]. Therefore, it is necessary to further develop a new generation of anti-EGFR drug. One such drug is h-R3, a humanized monoclonal antibody developed specifically to target epithelial tumors via single-cell cloning and gene recombination technologies. Different from other anti-EGFR drugs, the degree of humanization is more than 90%, which could greatly reduce the human anti-mouse antibody response [8,9]. Initial clinical trials confirmed that h-R3 had very low toxicity, and its combination with radiotherapy in head and neck squamous cell carcinoma (SCC) could achieve better survival rates [10].

In June 2002, the Cancer Hospital of the Chinese Academy of Medical Sciences performed a phase I clinical trial in which patients with advanced NPC were treated with a combination of radiotherapy and h-R3. The results showed that the adverse reactions to h-R3 were mild, leading to a multi-center phase II clinical trial with the aim to observe the short- and long-term efficacy and toxicity of h-R3.

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Methods

Inclusion/exclusion criteria

Included were patients with newly diagnosed stage III-IVb (UICC 1997) nasopharyngeal squamous cell carcinomas and with moderate to strong immunohistochemically positive expression of EGFR (moderate: 25-50% positive per 1,000 tumor cells; >50% positive cells per 1,000-tumor cells. Patient age should be 18-70 years with Karnofsky score >70 and expected survival >6 months. Patients should have normal liver, kidney, and serum biochemistry results. Exclusion criteria included severe heart and lung diseases.

This study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of Jiangxi Provincial Ganzhou People's Hospital. Written informed consent was obtained from all participants.

The patients who met the inclusion criteria were divided via computer randomization into either the radiotherapy alone group or the combination of radiotherapy and h-R3 group.

Definitions

Prior to treatment, all patients underwent nasopharyngeal and neck MRI, chest X-ray, abdominal ultrasound, single photon emission computed tomography (SPECT) bone scanning to determine clinical stage and treatment planning. Cross-products of maximum diameter and the vertical diameter of the maximum diameter of the primary tumor and cervical lymph node metastases were measured from MRI cross-section to establish the baseline size of the tumor. The tests were repeated after 40 Gy, at the end of treatment, 5 weeks after the conclusion of treatment, and 17 weeks after the conclusion of treatment. Baseline measurements were compared with each of the four repeated measurements. World Health Organization categories for evaluation of short-term efficacy followed: complete remission (CR): complete tumor disappearance, partial remission (PR): reduction >50% of the cross product of the tumor two maximum diameters; stable disease (SD): condition not fitting neither with PR nor with PD; progressive disease (PD): increase of the cross product of the tumor two maximum diameters >25%, or appearance of new lesions.

Radiotherapy and h-R3 administration

Radiotherapy was identical in both groups. A linear accelerator with 6 MV X-ray radiation and CT simulation positioning were used. The dosage was 2 Gy per fraction (once daily, 5 days per week) for a total dose of 70 Gy to the nasopharynx. During radiotherapy, patients in the combination group received 100mg of h-R3 in 250ml normal saline iv guttae on the first day of treatment and weekly thereafter, with a final dose on the last day of radiotherapy.

Toxicity monitoring

Blood pressure, temperature, pulse and breathing in the combination group patients were recorded at multiple time points on the drug administration days (before medication, and 1, 4 and 24 hrs after medication) to monitor adverse reactions; serum of both groups were examined before therapy and in the middle of therapy. Additional testing at the end of therapy and 17 weeks after therapy was performed in the combination group patients. Toxicity evaluation was based on the CTC 2.0 standards. Radiation toxicity was evaluated daily according to RTOG scoring, and blood was monitored weekly during treatment.

Follow-up

Short-term follow-up was concluded 17 weeks after therapy. Long-term follow-up included physical examination and nasopharyngeal endoscopy performed ever 3-4 months, whereas nasopharyngeal MRI or CT, chest X-ray, abdominal ultrasound, SPECT bone scanning and serum biochemistry were performed at least once a year.

Statistics

Both intention-to-treat (ITT) and per-protocol (PP) data analysis were carried out [11]. Statistical analysis was performed with SPSS 12.0 software and data were evaluated by Student's t- test. Comparison of the data was done uning Fisher's exact test, with bilateral side α=0.05. Survival was calculated from the date of enrollment to either the date of death or the last follow-up. Non-local-regional control rate, no-distant metastasis rate and overall survival rate were calculated using the Kaplan-Meier method with log-rank test.

Results

General information

Biopsied tumor specimens from 61 patients with stage III-IVb NPC were examined for EGFR expression prior to therapy from March 2003 to June 2004. Of these, there were 48 positive cases (78.7%), among which 35 cases (57.4%) showed moderate or strong EGFR expression. These 35 patients were randomly divided into the radiotherapy alone group (17 cases) or the combination group (18 cases). One patient in the combination group dropped out of study in the 5th week, leaving a total of 34 patients that completed the trial. Therefore, the number of cases for ITT and PP analysis were 35 and 34, respectively. Because there was only 1 patient failing, the short-term efficacy indicators were analyzed with ITT and PP, while other indicators were analyzed with ITT. Except for mean age, there were no statistically

significant differences between groups, including gender, height, weight, pathological type, EGFR expression, clinical stage and radiation dose (Table 1).

Short-term efficacy

ITT analysis showed that the rates of completion in the combination group were significantly higher than in the radiotherapy alone group ($p<0.05$) at the middle of therapy, at 5 weeks after therapy and at 17 weeks after therapy. Similarly, the CR rates of the primary tumor at 5 and 17 weeks after therapy were significantly higher in the combination group than in the radiation alone group ($p<0.05$). At the conclusion of therapy, the CR rate of cervical lymph nodes was higher in the combination treatment group than in the radiation alone group ($p=0.05$) (Table 2). No patient died during the study period.

Long-term efficacy

Three patients could not be located 6 months after treatment, resulting in a follow-up rate of 91.4% (32/35). The median follow-up time was 31.9 months (range 4.2-40.7). No deaths occurred in the 32 patients remaining in the study 6 months post-treatment.

In the radiotherapy alone group, there were 6 cases with residual primary tumors after treatment. One was associated with cervical nodal residual disease, 2 were lost to follow-up. One case with right fossa residual nodal disease developed a tumor at the same site 6 months after radiotherapy; 1 case with residual primary tumor was controlled through three repeats of intracavitary after-loading therapy (15Gy), and the other 2 cases did not undergo any further treatment and no tumor relapse was detected in the subsequent follow-up. In 2 cases with residualcervical nodal disease the tumor totally disappeared in the 7th to 10th months of follow-up after therapy; 2 additional cases in the combination group developed solitary lung metastasis 8 and 11 months after therapy, but after local radiotherapy the tumor completely disappeared.

The 3-year locoregional control rate of the radiotherapy alone and the combination group were

Table 1. Comparison of general characteristics between the 2 groups

Characteristics	*RT alone (N=17)* *N (%)*	*RT plus h-R3 (N=18)* *N (%)*	*p-value*
Sex			
Male	12 (70.59)	13 (72.22)	0.915
Female	5 (29.41)	5 (27.78)	
Age, years, median (range)	47 (32-63)	36 (26-57)	0.006
Height (cm), median (range)	165 (153-175)	165 (152-175)	0.463
Weight (kg), median (range)	55 (41-80)	62 (41-72)	0.878
WHO grade			
2	2 (11.76)	3 (16.67)	1.000
3	15 (88.24)	15 (83.33)	
EGFR expression			
Moderate	12 (70.59)	14 (77.78)	0.711
Strong	5 (29.41)	4 (22.22)	
T stage			
T1	3 (17.65)	0 (0)	0.308
T2	2 (11.76)	2 (11.11)	
T3	8 (47.06)	10 (55.56)	
T4	4 (23.53)	6 (33.33)	
N stage			
N0	4 (23.53)	4 (22.22)	0.564
N1	5 (29.19)	5 (22.78)	
N2	8 (47.06)	7 (38.89)	
N3	0 (0)	2 (11.11)	
TN stage			
III	13 (76.47)	11 (61.11)	0.324
IV_a	4 (23.53)	5 (27.78)	
IV_b	0 (0)	2 (11.11)	
Total dose to the NP (Gy; range)	70 (60-74)	70 (70-72)	0.346
Total dose to the neck (Gy; range)	60 (50-70)	66 (50-74)	0.917

RT: radiotherapy, EGFR: epidermal growth factor receptor, NP: nasopharynx

Table 2. Comparison of treatment responses for primary tumors and cervical lymph nodes between the two groups

Observation point	*RT alone group (N=17)*			*RT plus h-R3 (N=18)*			
	CR N (%)	*PR N (%)*	*SD N (%)*	*CR N (%)*	*PR N (%)*	*SD N (%)*	*p*[a]
RT to 40 Gy							
Primary tumor	3 (17.6)	13 (76.5)	1 (5.9)	4 (22.2)	12 (66.7)	2 (11.1)	1.000
Lymph node[b]	6 (40.0)	8 (53.3)	1 (6.7)	6 (42.9)	7 (50.0)	1 (7.1)	1.000
Overall evaluation	2 (11.8)	14 (82.4)	1 (5.9)	3 (16.7)	13 (72.2)	2 (11.1)	1.000
End of treament							
Primary tumor	8 (47.1)	9 (52.9)	0	13 (72.2)	5 (27.8)	0	0.176
Lymph node[b]	7 (46.7)	7 (46.7)	1 (6.7)	12 (85.7)	2 (14.3)	0	0.050
Overall evaluation	6 (35.3)	11 (64.7)	0	13 (72.2)	5 (27.8)	0	0.044
Five weeks after treatment							
Primary tumor	9 (52.9)	8 (47.1)	0	16 (88.9)	2 (11.1)	0	0.027
Lymph node[b]	11 (73.3)	4 (26.7)	0	12 (85.7)	2 (14.3)	0	0.651
Overall evaluation	7 (41.2)	10 (58.8)	0	15 (83.3)	3 (16.7)	0	0.015
Seventeen weeks after treatment							
Primary tumor	11 (64.7)	6 (35.3)	0	17 (94.4)	1 (5.6)	0	0.041
Lymph node[b]	11 (73.3)	4 (26.7)	0	12 (85.7)	2 (14.3)	0	0.651
Overall evaluation	8 (47.1)	9 (52.9)	0	15 (83.3)	3 (16.7)	0	0.035

RT: radiotherapy, CR: complete remission, PR: partial remission, SD: stable disease. [a]Comparison of CR rates using Fisher's exact test. [b]Fifteen patients in the RT alone group and 14 in the RT plus h-R3 group had cervical lymph node metastases, Overall evaluation: CR, PR or SD for both primary tumor and cervical lymph node.

93.8 and 100%, respectively (p=0.303), and the short-term metastasis rates were 100 and 88.2%, respectively (p=0.177). If the patients lost during follow-up are considered as deaths, the 3-year overall survival rates of the 2 groups drop to 88.2 and 94.4%, respectively (p=0.518).

Toxicity

Throughout the monitoring period, no significant changes were observed in temperature, pulse, blood pressure, or breathing in the combined group. With the exception of one case of grade II vomiting, no drug-related adverse events such as nausea, dizziness, headache, tremor, muscle pain, drowsiness, disorientation, chills, hematuria, rash, skin flushing, serum creatinine or elevated transaminases occurred.

No grade IV radiation-related toxicity occurred in either group during therapy. The incidence of grade III toxicity in both groups was very low, and the difference was not statistically significant (p>0.05) (Table 3).

Discussion

According to the literature, the positive expression rate of EGFR in NPC is 68-89% [12-14], and closely related to the progression, radiosensitivity and prognosis of disease [15,16]. Wang et al. [13] reported that the EGFR-positive rate of stage III-IV NPC was 77.1%, which is significantly higher than in stage I-II (28.6%). The overall survival for the positive patients was significantly lower compared with negative patients, and the disease progression was much faster. Chua et al. [12] reported that the moderate or higher EGFR expression of the patients with advanced-stage NPC was 72%. Compared with the mildly positive patients, the 5-year disease-specific survival, disease-free survival and local non-recurrence survival were significantly reduced. The EGFR expression rate detected before therapy (78.7%) in this study was similar to the literature [12]. In order to better observe the anti-tumor effects of EGFR inhibitor h-R3 in advanced-stage carcinomas, patients with stage III-IVb NPC with moderate or strong expression of EGFR were enrolled as the research subjects.

Anti-EGFR targeted therapy has been an important aspect of cancer treatment progress in recent years. Preclinical studies have shown that blocking the EGFR signaling pathway could

Table 3. Comparison of adverse events between the two groups

Adverse event	*RT alone (N=17)*		*RT plus h-R3 (N=18)*	
	Grade 1-2 N (%)	*Grade 3 N (%)*	*Grade 1-2 N (%)*	*Grade 3 N (%)*
Dermatitis	16 (94.1)	1 (5.9)	17 (94.4)	1 (5.6)
Oral mucositis	16 (94.1)	1 (5.9)	16 (88.9)	2 (11.1)
Pharyngeal mucositis	100 (100)	0	17 (94.4)	1 (5.6)
Leukopenia	5 (29.4)	0	8 (44.5)	0
Anemia	1 (5.9)	0	1 (5.6)	0
Thrombocytopenia	1 (5.9)	0	0	0

p>0.05 comparison between two groups

block cell cycle progression, promote apoptosis, inhibit angiogenesis, suppress tumor invasion and metastasis, and enhance the sensitivity of radiotherapy and chemotherapy [6]. The humanized monoclonal antibody h-R3 (IgG1) could bind specifically with the EGFR extracellular ligand, thus inhibiting EGFR activation and signal transduction [17]. Phase I/II clinical trials have shown that patients with localized advanced head and neck SCC had good tolerance for radiation therapy combined with h-R3, without the occurrence of drug-related skin reactions or hypersensitivity reactions [10]. Compared with murine (m-R3) or human/mouse chimeric monoclonal antibodies (Cetuximab), h-R3 has the advantages of reduced immunogenic response and the prolonged *in vivo* clearance time [8,9,18].

In this prospective study, h-R3 was combined with radiotherapy to evaluate the treatment benefits on advanced localized NPC. Short-term results indicated that at the end of therapy, and at 5 and 17 weeks after therapy, CR in the combination group was significant compared with the radiation alone group. The CR rates for metastatic cervical lymph nodes were also significantly higher in the combination group at the end of therapy (p=0.05). The total efficacy of the two groups at the above 3 assessment time points had statistically significant difference. These results suggested that h-R3 had a synergistic effect when combined with radiotherapy, which could promote the complete eradication of both primary tumor and cervical lymph node metastases or accelerate the tumor regression rate. These results are in concordance with other early-stage clinical studies in head and neck SCC. Dattatreya et al. [4] reported that Cetuximab combined with radiotherapy achieved 68.42% CR in the treatment of 19 cases of unresectable, locally advanced head and neck SCC. Crombet et al. [10] reported that of 12 patients with advanced head and neck SCC who were given radiotherapy combined with different doses of h-R3, 6 cases achieved CR. Of these, the CR rate (4/6) of the high-dose (200-400 mg/m^2) group was higher than in the low-dose (50-100 mg/m^2) group (2/6).

Although the results suggested that h-R3 could enhance the antitumor activity of radiotherapy, the long-term follow-up results failed to show a significant difference between h-R3+radiotherapy vs radiotherapy alone in the control rate of the primary tumor site, long-term metastasis rate and survival rate. The reasons might be related to the following: According to recent reports, the main reason that Cetuximab improved the 3-year survival rate of locally advanced head and neck SCC after radiotherapy was the improved local and regional tumor control [19]. Patients in our study received radiotherapy with improved technique used at our center, namely the CT simulation positioning was used to design the gradual-field-shrinking technique, which would give different doses of prescription towards different targets. Literature reports show that this radiotherapy technique has achieved good results in improving the local control rate [20]. Therefore, it could be inferred that the strength of h-R3 combined with radiotherapy in NPC was still largely due to the strengthening the local control of radiotherapy. Because this study used improved radiotherapy technology, the local control rate of NPC was improved, resulting in prolongation of the overall survival rate of the combination group, failing to show superiority to the radiotherapy alone group. Alternatively, the number of cases enrolled was small; differences in the efficacy in the 2 groups may not emerge with a small sample size. Another possibility is that the follow-up time was not long enough, and the long-term effects of h-R3 still needed further observation.

In terms of safety, compared with other EGFR inhibitors, h-R3 shows a greater advantage. The

toxicities of erlotinib are diarrhea and rash [5] and of cetuximab, includes acne-like skin rash, itching, fever, chills, nausea, and reactions at the injection site [19]. Because the humanized degree of h-R3 is over 90%, it could greatly reduce the human anti-mouse antibody and allergic reactions. A previous phase I clinical study showed that common toxicities of h-R3 (50-400 mg) were fever, hypotension and tremor, while there were no rash or hypersensitivity reactions [10]. A phase II clinical trial conducted by Huang et al. [21] also showed a small percent of increased temperature. The results of the present study also confirmed the h-R3 had mild toxicity with the exception of 1 patient with transient grade II vomiting; the rest of the patients had no fever, rash, hypotension and tremor, or other adverse reactions. This might be related to the low dose of h-R3 (100 mg). In addition, the results also showed that h-R3 combined with radiotherapy did not aggravate the acute radiation reactions, which were significantly reduced compared with the same period of RT alone.

These preliminary results indicate that h-R3 is an EGFR inhibitor with a good safety profile, that could enhance the antitumor effects of radiotherapy in localized advanced NPC. It may accelerate the regression rate of nasopharyngeal primary tumor and neck nodal metastases. However, no significant effect on long-term efficacy was demonstrated. Future studies with larger patient enrollment and longer follow-up are needed to confirm the early indications that h-R3 combined with radiotherapy increases the efficacy of treatment of NPC SCCs.

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