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Phase II study of 3-AP Triapine in patients with recurrent or metastatic head and neck squamous cell carcinoma

C. M. Nutting[1]*, C. M. L. van Herpen[2], A. B. Miah[1], S. A. Bhide[1], J.-P. Machiels[3], J. Buter[4], C. Kelly[5], D. de Raucourt[6] & K. J. Harrington[1]

[1]*Head and Neck Unit, Royal Marsden Hospital and Institute of Cancer Research, London, UK;* [2]*Department of Medical Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands;* [3]*Medical Oncology Unit, Université Catholique de Louvain, Cliniques Universitaires St-Luc, Brussels, Belgium;* [4]*Head and Neck Unit Vrije Universiteit Medical Center, Amsterdam The Netherlands;* [5]*Northern Centre for Cancer Treatment Newcastle General Hospital, Newcastle upon Tyne, UK and* [6]*'Centre de lutte contre le cancer', Head and Neck Unit, Centre François Baclesse, Caen, France*

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Background: Treatment options for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) are limited with response rates to cytotoxic chemotherapy of ~30% and median survival of 6 months.

Patients and methods: In a multicentre phase II study, 32 patients with recurrent or metastatic HNSCC received 3-AP Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone), an inhibitor of ribonucleotide reductase, 96 mg/m^2, daily for 4 days every 14 days (one cycle). Eligibility criteria required Eastern Cooperative Oncology Group performance status (ECOG PS) of zero to two with a life expectancy of >3 months; one prior chemotherapy regimen was allowed.

Results: Thirty patients were assessable for response and toxicity. Median age was 57 years (range 36–79) and median ECOG PS was one (range 0–2). Thirteen patients had previously been treated with chemotherapy. A total of 130 cycles were administered with a median number of cycles of 3.5 (range 1–8). Mild anaemia (40%), nausea (22%) and fatigue (22%) were commonly reported with G3 and G4 neutropenia documented in 22% and 22%, respectively. Overall response rate was 5.9% (95% confidence interval 0.2% to 28.7%). One patient achieved a partial response, eight had stable disease and 21 progressive disease. Median time to disease progression was 3.9 months.

Conclusions: 3-AP Triapine as a single agent, at this dose and schedule, is well tolerated but has only minor activity in the treatment of advanced HNSCC.

Key words: 3-AP Triapine, chemotherapy, head and neck cancer

introduction

The treatment options for recurrent or metastatic head and neck squamous cell carcinomas (HNSCCs) following primary surgery and/or radiotherapy are limited. Treatments using single-agent chemotherapy including methotrexate, bleomycin, cisplatin, paclitaxel, docetaxel, 5-fluorouracil (5-FU), gemcitabine, gefitinib and cetuximab have overall response rates ranging from 10% to 30% [1–7]. Combinations of cisplatin with 5-FU or paclitaxel produce higher response rates of ~30% but there is no increase in median or 1-year survival [8–10]. Recently, cetuximab combined with cisplatin and 5-FU has been shown to improve survival over chemotherapy alone [11].

3-AP Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone) is a potent inhibitor of ribonucleotide reductase (RR), an enzyme that mediates the conversion of ribonucleotides to deoxyribonucleotides, resulting in the arrest or slowing of DNA synthesis and cellular proliferation.

The antitumour activity and favourable therapeutic ratio demonstrated by 3-AP Triapine in murine models suggest that chronic intermittent inhibition of RR has greater effect on tumour cells compared with normal host tissues [12]. Phase I clinical studies have demonstrated the ability to administer 3-AP Triapine safely at a dose of 96 mg/m^2, by 2-h infusion daily for 4–5 days every 14 days. The schedule produces rapidly reversible haematological toxicity, suggesting that RR is effectively inhibited by this treatment regimen [13]. Finally, evidence of antitumour activity in refractory malignancies has been observed. In particular, a patient with progressing disease in the tonsillar region remained stable on 3-AP Triapine treatment for >10 months [14]. Therefore, we proposed to examine the activity of the novel RR inhibitor 3-AP Triapine in a phase II study in patients with recurrent or metastatic HNSCC.

patients and methods

patients

This was an international, multicentre, open-label, nonrandomised phase II study of patients with histologically or cytologically verified HNSCC with

**Correspondence to:* Dr C. Nutting, Head and Neck Unit, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK. Tel: +44-0207 8-082586; Fax: +44-02078-082235; E-mail: chris.nutting@rmh.nhs.uk

recurrent or metastatic disease and objective evidence of progressive disease (PD). Patients were required to be over 18 years of age and have at least one measurable lesion; Eastern Cooperative Oncology Group performance status (ECOG PS) of zero to two; life expectancy of >3 months; adequate nutritional status and no haematological, liver or renal function abnormalities. Prior chemotherapy was allowed. Any radiotherapy had to have been completed at least 4 weeks before trial entry.

treatment schedule

All patients received 3-AP Triapine by 2-h i.v. infusion, daily for 4 days every 14 days, at a dose of 96 mg/m^2/day. The administration of 3-AP Triapine for 4 days followed by 10 days rest was considered one cycle of treatment. Depending on toxic effects, the dose could be increased to 120 mg/m^2/day or reduced to 72 and 48 mg/m^2/day.

treatment evaluation

Full staging including computed tomography scans (head, neck and chest) and physical examination was carried out every four cycles. Toxicity assessments including blood count and serum biochemistry were carried out at every cycle. Patients were eligible to receive additional cycles if they had stable disease (SD), partial response (PR) at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD or complete response (CR) disappearance of all target lesions. Patients with PR or SD could continue treatment for up to 1 year. Stable or responding patients were followed for up to 1 year after completion of treatment of progression-free survival. Full staging was to be carried out every 2–3 months during the latter follow-up period.

outcome evaluation

Standard RECIST were used to assess response [15]. To be assigned a status of PR or CR, changes in tumour measurements had to be confirmed by repeat assessments that were carried out no <4 weeks after the criteria for response was first met. In the case of SD, follow-up measurements had to meet the SD criteria at least once after study entry at a minimum interval of 8 weeks. The National Cancer Institute of Canada—Common Toxicity Criteria version 2.0 (http://ctep.cancer.gov/reporting/ctc.html) were employed to grade toxicity.

Time to progression was measured from the date of first 3-AP Triapine therapy to the date of appearance of new lesions or objective tumour progression. The duration of overall response was measured from the time measurement criteria were first met for CR/PR until the first date that PD at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions was documented. SD neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started was measured from the start of the treatment until the criteria for progression were met. In addition to the standard PRs and CRs, for the purpose of this trial, a patient who had SD >6 months was considered as a 'response' for the purpose of statistical analysis. Survival time was defined from the first date of treatment to the date of death.

statistical methods

The trial was designed to determine a response rate of 5%–20% and hence justify its further investigation. Primary end point was to determine the response rate. Secondary end points were the duration of response, toxic effects to 3-AP Triapine, median survival and 1-year survival rate. The initial trial design allowed 13 patients to be recruited. If one objective response was observed among the first 13 patients, then an additional 14 patients were enrolled. A Simon two-stage phase 2 minimax design was used for analyses of the clinical results. The target response rate of interest was 20% with the lower activity level set at 5%. Type I and type II error rates were set at 0.05 and 0.20, respectively. Treatment results were expressed as response rates with 95% confidence intervals (CIs). A standard Kaplan–Meier curve was constructed for the overall survival (OS). An intention-to-treat analysis was carried out.

results

patient characteristics

Thirty-two patients were included in the trial from September 2002 to July 2003. Patients were recruited from six centres. The median age was 57 years (range 36–79). Ten were female. The median ECOG PS was one (range 0–2). Previous treatments are described in Table 1.

study treatment

Of the 34 patients entered into the study, 32 received 3-AP Triapine. Two patients did not start: one patient deteriorated with rapid weight loss shortly before the start of study treatment and the other died unexpectedly from a haemorrhage. They were excluded from the analysis.

Thirty of 32 patients who received 3-AP Triapine were assessed for response and toxicity, as two died before their first evaluation. Thus, 30 were assessable for response, but 32 for toxicity. In total, 130 cycles were administered [median 3.5 (range 1–8)]. Sixteen patients received less than four cycles (see Table 2). Twenty patients discontinued due to PD (Table 3).

Thirty patients received 3-AP Triapine at a dose of 96 mg/m^2/day of which 15 continued at this level throughout the study. For 12 patients (38%), the dose was increased after the first cycle (120 mg/m^2/day). Three of these patients (9%) needed a dose reduction later in the study. Five patients (16%) following their first cycle required a dose reduction to 48–72 mg/m^2/day.

tumour response

Initial tumour evaluation showed 1 of 13 responses; so an additional 19 patients were recruited. When all 32 patients were assessed, one achieved a PR, eight had SD over a period of 2–6 months, 21 had PD and two patients died before their first evaluation. Overall response rate was 5.9%

Table 1. Prior treatments

	Number of patients
Prior surgery/biopsy	32
Prior radiotherapy (chemoradiation)	30 (13)
Prior palliative chemotherapy	
First-line chemotherapy	
Platinum and 5-fluorouracil	9
Docetaxel, platinum and 5-fluorouracil	1
Platinum alone	2
Methotrexate	1
Second-line chemotherapy	
Methotrexate	2

(95% CI 0.2% to 28.7%). The duration of the PR was 12.8 months. SD was evaluated for eight patients. Median duration of SD was 3.8 months (range 1.9–4.5). Median survival for all patients was 5.6 months (range 0.5–33.9). The 1-year survival was 25%. A standard Kaplan–Meier curve is presented in Figure 1.

Further subset analysis confirmed eight patients achieved SD of which three demonstrated minor regression of 4.8%, 16% and 33%. The duration of response was 2 months.

Thirteen patients in this study had received prior chemotherapy. The median survival in this group was 13.0 months (range 3.6–33.9). Nineteen patients had not received any previous chemotherapy. The median survival in this group was 4.1 months (range 0.5–32.4).

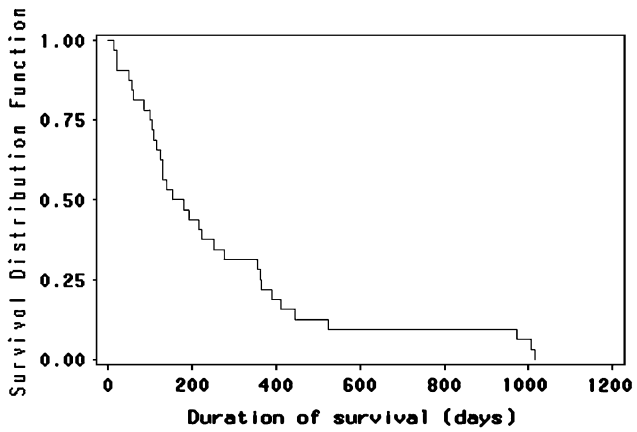
Table 2. Summary of Triapine administration

	n
Median number of cycles	3.5
Patients with four or less cycles	16
Patients with four cycles	7
Patients with five to six cycles	2
Patients with seven to eight cycles	7

Table 3. Summary of reasons for end of treatment

Reason for end of treatment	*n*
Progressive disease	20
Clinical deterioration (without tumour evaluation carried out)	5
Adverse event (arterial rupture, unrelated to 3-AP Triapine)	1
Death	2
Patient refusal	2
Other (fatigue)	2

3-AP Triapine, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.



Survival	0	200 days	400 days	600 days	800 days	1000 days
No of patients	32	14	6	3	3	2

Figure 1. Kaplan–Meier curve of overall survival.

toxicity

3-AP Triapine was well tolerated by patients at the dose and schedule in this clinical study. In no case were patients prematurely discontinued because of drug-related toxicity. G3 and G4 toxic effects reported were neutropenia (22% and 22%, respectively) and leucopenia (38% and 6%, respectively). Common G2 toxic effects included fatigue (22%), anaemia (40%) and nausea (19%) (Table 4).

discussion

3-AP Triapine as a single agent achieved an overall response rate of 5.9%. It is the only phase II study of this agent to be undertaken in the treatment of HNSCC. In comparison to the published literature, the response rate and OS are similar or marginally inferior to other single-agent studies in the treatment of recurrent or metastatic HNSCC [16, 17]. Toxic effects recorded were minimal and similar to those reported in the phase I studies.

Other RR inhibitors such as hydroxyurea and gemcitabine have demonstrated higher objective response rates in several solid tumours. Preclinical studies have suggested that 3-AP Triapine has a similar mode of action but a higher level of RR inhibition compared with hydroxyurea [12, 13]. Walder et al. have demonstrated in their phase I study evidence of antitumour effects. Of interest, one patient with HNSCC of the tonsillar area who had progressed through regimens of cisplatin with cetuximab, local radiotherapy and paclitaxel with gemcitabine commenced 3-AP Triapine at a dose of 80 mg/m^2/day. The patient received 26 cycles over 13 months with the majority of doses ranging 100–132 mg/m^2/day. The patient remained progression free for an additional 10 months [14]. Our responding patient also presented with squamous cell carcinoma of the right tonsil with metastases and had received prior chemotherapy and radiotherapy. He completed eight cycles of 3-AP Triapine and achieved a PR and remained progression free for an additional 13 months.

Other trials of single-agent RR inhibitors have demonstrated low response rates in recurrent or metastatic HNSCC or very poor responses in those heavily pretreated. This may suggest a mechanism of primary or acquired resistance. However, in our study, 13 patients who had received platinum, 5-FU combination or methotrexate demonstrated a better survival advantage when compared with chemotherapy-naive group, 13 versus 4.1 months, respectively. This may represent minor activity of 3-AP Triapine in platinum-refractory disease. Alternatively, this could be explained by acquired resistance overcome by more potent RR inhibition with Triapine when compared with other RR inhibitors. Also, our chemotherapy-naive group may represent biologically more aggressive disease.

In combination schedules, 3-AP Triapine has also been administered with gemcitabine in patients with metastatic non-small-cell lung cancer previously exposed to gemcitabine in a phase II trial. Twelve patients were treated with a median of two cycles without objective response [18]. In refractory myeloid malignancies, 3-AP Triapine followed by fludarabine has demonstrated a CR rate of 17% in a phase I study [19] compared with no response with 3-AP Triapine or fludarabine

Table 4. Adverse events by worst grade per patient, possibly/probably/definitely related to Triapine ($n = 32$)

System	Adverse event	Worst grade				Total abnormal (%)
		1	2	3	4	
Haematological	Anaemia	2	13	–	–	15 (47)
	Leucopenia	–	7	12	2	21 (66)
	Neutropenia	2	5	7	7	21 (66)
	Thrombocytopenia	1	3	–	–	4 (13)
Gastrointestinal disorders	Nausea	12	6	–	–	18 (56)
	Vomiting	8	4	–	–	12 (38)
General	Anorexia	2	2	–	–	4 (13)
	Asthenia	4	2	1	–	7 (22)
	Fatigue	5	7	2	–	14 (44)
	Pyrexia	6	1	1	–	8 (25)
	Rigours	2	1	–	–	3 (9)
Infections	Bacterial infection	–	1	–	–	1 (3)
	Gastrointestinal infection	–	1	–	–	1 (3)
	Infection-unspecified	–	–	1	–	1 (3)
	Infection in an immunocompromised host	–	1	–	–	1 (3)
	Respiratory tract infection	–	–	1	–	1 (3)
	Upper respiratory tract infection	–	1	–	–	1 (3)

alone [20, 21]. This sequential regimen may provide an effective treatment of refractory haematological malignancies.

To date RR inhibitors have confirmed limited benefit as radiosensitisers. A systematic review of eight clinical studies established little or no benefit of RR inhibitors used with radiotherapy [22]. However, 3-AP Triapine is a more potent inhibitor of RR compared with hydroxyurea and gemcitabine. *In vitro* and *in vivo* studies have demonstrated that 3-AP Triapine enhances tumour cell radiosensitivity [23]. Perhaps, this exhibits the potential to evaluate 3-AP Triapine concurrently with radiotherapy.

From this study, it can be concluded that 3-AP Triapine as a single agent, at this dose and schedule, is well tolerated, but has minor activity in the treatment of platinum-refractory advanced HNSCC.

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