Eur J Cancer Clin Oncol, Vol. 22, No. 3, pp. 241–243, 1986.
Printed in Great Britain.

0277-5379/86$3.00+0.00

Phase II Study of a Combination of Hydroxyurea, Fluorouracil and Mitomycin in Previously Treated Squamous Cell Carcinoma of the Head and Neck*†

PIERRE DODION,§‡ FRANSCESCO COGNETTI,‖ MARC VAN RYMENANT,‡ OTTILIA DALESIO,¶ ANNE KIRKPATRICK¶ and MARCEL ROZENCWEIG‡** For the EORTC Head and Neck Cooperative Group

‡*Institut Jules Bordet, Brussels, Belgium,* ‖*Institute Regina Elena, Roma, Italy and* ¶*EORTC Data Center, Brussels, Belgium.*

Abstract—*Thirty-six evaluable patients with locoregionally recurrent or metastatic squamous cell carcinoma of the head and neck were treated with a combination of mitomycin* (10 mg/m^2 i.v. day 1), *fluorouracil* (500 mg/m^2 i.v. *days* 1 + 8) *and hydroxyurea* (1 g/m^2 *orally days* 2–14). *Thirty-three patients had received prior radiation therapy and* 34 *prior chemotherapy. Only two patients exhibited a partial response. Hematological toxicity was substantial, with three patients experiencing leukopenia below* 1000/mm^3 *and seven patients experiencing thrombocytopenia below* 25,000/mm^3. *There were four cases of treatment-related bleeding and one infection. Other side-effects were mild to moderate. Low antitumor activity and substantial toxicity preclude further evaluation of this regimen in head and neck cancer.*

INTRODUCTION

MITOMYCIN, fluorouracil and hydroxyurea are three drugs with some activity in head and neck cancer [1–7]. The largest experience with mitomycin in head and neck cancer was reported by Moore *et al.* [2]. A response rate of 18% was reported among 49 patients. Fluorouracil was found to be active by several investigators [3–5]. In a phase II study reported by Moore *et al.*, there were five responders among a total of 36 patients [3]. More recently, Amer *et al.* reported a response rate of 31% with a variety of schedules [4]. Experience with hydroxyurea is more limited [5–7]. A response rate of 39% has been observed among 18 patients [5]. These three drugs have been often incorporated in combination chemotherapy of head and neck cancer [8]. The contribution of hydroxyurea and mitomycin to these regimens is unclear [9–12] but the combination of cisplatin and fluorouracil has been reported as highly effective [13, 14].

The activity of a combination of fluorouracil, mitomycin and hydroxyurea has not yet been investigated. In a pilot study conducted at the Institut Jules Bordet, patients with recurrent or metastatic head and neck cancer received a combination of mitomycin (10 mg/m^2 i.v. on day 1), fluorouracil (500 mg/m^2 i.v. on days 1 and 8) and hydroxyurea (1 g/m^2 orally on days 2–14). Although no antitumor activity was documented in this heavily pretreated population, this combination could be administered easily on an outpatient basis and proved to induce an acceptable toxicity, mainly myelosuppression. On these grounds, the EORTC Head and Neck Cooperative Group investigated the antitumor activity and the toxicity of a combination of these three drugs. This trial was specifically designed for patients progressing under first-line chemotherapy with a combination of cisplatin, methotrexate, bleomycin and vincristine [15].

MATERIALS AND METHODS

Patients were considered eligible for this trial if they had squamous cell carcinoma of the head and neck previously treated with chemotherapy. Measurable, non-ulcerated lesions and a performance status (ECOG) of 0–2 were required. A minimum delay of 4 weeks after prior therapy and

Accepted 26 July 1985.
*This work was supported in part by the Fonds de la Recherche Scientifique Médicale (FRSM No. 3.4521.83), a grant from the National Cancer Institute (NCI–NIH NO1/CM53840) and a grant from the Fondation pour la Chimiothérapie Anticancéreuse (FOCA).
†The following institutions also participated in the study: Centre Léon Bérard (M. Clavel, Lyon, France), Clinique Louis Caty (E. Longeval, Baudour, Belgium), Medizinische Klinik (U. Bruntsch, Nürnberg, F.R.G.) and Akademisch Ziekenhuis (C. Vendrik, Utrecht, The Netherlands).
§To whom correspondence and requests for reprints should be addressed at: Institut Jules Bordet, 1, Rue Héger–Bordet, 1000 Brussels, Belgium.
**Present address: Bristol-Myers Company, Syracuse, New York.

recovery from major toxic effects were required. All patients had normal hematologic (WBC > 4000/mm^3 and platelet count > 100,000/mm^3), renal (serum creatinine < 1.5 mg/dl), and hepatic (bilirubin < 1.5 mg/dl) functions. Patients were excluded from the trial if they were older than 75 yr or if they had previously received mitomycin, fluorouracil or hydroxyurea. Patients with major intercurrent diseases including other malignancies, uncontrolled infections, marked psychosis or senility were excluded from this trial. Informed consent was obtained according to individual local regulations.

Treatment consisted of mitomycin (10 mg/m^2 i.v. bolus on day 1), fluorouracil (500 mg/m^2 i.v. bolus days 1 and 8) and hydroxyurea (1 g/m^2 per day orally on days 2–14). The dose of fluorouracil on day 8 and that of hydroxyurea on days 8–14 were reduced according to myelosuppression on day 8: 50% for WBC between 3000 and 4000/mm^3 or platelet counts between 75,000 and 100,000/mm^3 and 75% for WBC between 2000 and 3000/mm^3 or platelet counts between 50,000 and 75,000/mm^3; no treatment was given for lower hematological values. Courses were repeated every 4 weeks or at hematological recovery, whichever occurred last. At retreatment the dose of all drugs was reduced by 50% if WBC < 1000/mm^3 or platelet count < 50,000/mm^3 had been observed during the previous course.

Standard criteria for responses were used [16]. Patients were to be treated until disease progression. Adequate treatment consisted of at least two courses of therapy, unless there was evidence of clear progression after one course.

RESULTS

Thirty-seven eligible patients were entered between June 1981 and November 1983 by seven institutions. Two additional patients who had not received prior chemotherapy are also included in this analysis. Thirty-six patients were evaluable for response; three patients did not receive two courses of therapy because of death (one patient) or loss to follow-up (2 patients). None of these patients had any sign of progressive disease or toxicity. The characteristics of the 36 evaluable patients are indicated in Table 1.

Twenty-three patients received one or two courses of therapy and 11 patients received three or more courses of treatment. Only two partial responses were observed, for an overall response rate of 6% (95% confidence interval: 0–13%). Both responders had locoregional recurrence and prior treatment with radio- and chemotherapy consisting of intra-arterial bleomycin and a combination of cisplatin, bleomycin, methotrexate and vincristine, respectively. Response durations were 11 and 15 weeks, respectively. The two patients who did not receive prior chemotherapy had no response.

Table 1. *Patient characteristics*

	No. of patients (n = 36)	
Male/female	35/1	
Median age (range)	58	(43–75)
Median PS (ECOG)	1	(0–2)
Prior therapy	36	
Surgery		2
Radiotherapy		2
Surgery + radiotherapy		31
Chemotherapy (with cisplatin and/or methotrexate)		34 (32)
Primary sites		
Oral cavity		11
Larynx		10
Tongue		6
Oropharynx		5
Others		4

Blood cell counts were obtained weekly. Leukopenia was encountered in 30 patients (three patients with WHO grade IV leukopenia); 27 patients developed thrombocytopenia; seven patients had platelet counts below 25,000/mm^3. Four patients had minor bleeding during episodes of thrombocytopenia. There was one treatment-related infection. Other toxic effects were mild to moderate and consisted mainly of nausea and vomiting (five patients), alopecia (six patients), diarrhea (five patients) and stomatitis (four patients). Therapy possibly contributed to otherwise unexplained fever (three patients), dyspnea and cough (two patients), and confusion (one patient).

DISCUSSION

The very low response rate observed in this trial could result from cross-resistance with conventional chemotherapy or from intrinsic ineffectiveness. Although antagonistic effects in combinations cannot be ruled out, lack of efficacy in this trial is more likely related to marginal agent activity, extensive prior therapy or both. The activity of cisplatin, bleomycin, methotrexate or combinations of these agents is probably not better than that reported in this trial for the kind of patients treated in this study [4, 17]. In any event, the low therapeutic index noted in this trial strongly suggests that our three-drug regimen is not suitable for second-line treatment or alternating chemotherapy programs that would include combinations incorporating cisplatin and methotrexate.

REFERENCES

1. Crooke ST, Bradner WT. Mitomycin C. A review. *Cancer Treat Rev* 1976, **3**, 131–139.
2. Moore GE, Bross IDJ, Ausman R *et al.* Effects of mitomycin C (NSC–26980) in 346 patients with advanced cancer. *Cancer Chemother Rep* (part 1) 1968, **52**, 675–684.
3. Moore GE, Bross IDJ, Ausman R, *et al.* Effects of 5–fluorouracil on patients with cancer. *Cancer Chemother Rep (Part 1)* 1968, **52**, 641–563.
4. Amer MH, Al-Sarraf M, Vaitkevicius VK. Factors that affect response to chemotherapy and survival of patients with advanced head and neck cancer. *Cancer* 1979, **43**, 2202–2206.
5. Livingston RB, Carter SK. *Single agents in cancer chemotherapy*. New York, IFI/Plenum, 1970.
6. Bloedow CE. Phase II studies of hydroxyurea (NSC–32065) in adults: miscellaneous tumors. *Cancer Chemother Rep* 1964, **40**, 39–41.
7. Lerner HJ, Beckloff GL, and Godwin MC. Hydroxyurea (NSC–32065) intermittent therapy in malignant disease. *Cancer Chemother Rep (Part 1)* 1969, **53**, 385–395.
8. Muggia FM, Rozencweig M, Louie AE. Role of chemotherapy in head and neck cancer: systemic use of single agents and combinations in advanced disease. *Head Neck Surg* 1980, **2**, 196–205.
9. Eisenberger MA, Denefrio J, Silverman M, Lessner HE. Combination chemotherapy with bleomycin and hydroxyurea in the treatment of advanced head and neck cancer. *Cancer Treat Rep* 1982, **66**, 1439–1440.
10. Medenica R, Alberto P, Lehmann W. Combined chemotherapy of head and neck squamous cell carcinoma with methotrexate, bleomycin, and hydroxyurea. *Cancer Chemother Pharmacol* 1981, **5**, 145–149.
11. Abele R, Honegger HP, Grossenbacher R, Kaplan E, Mermillod B, Cavalli F. Randomized trial of methotrexate, bleomycin, hydroxyurea with versus without cisplatin in advanced squamous cell carcinoma of the head and neck. *Proc ASCO* 1984, **3**, 186.
12. Vogl SE, Lerner H, Kaplan BH, Camacho F, Cinberg J, Schoenfeld D. Mitomycin-C, methotrexate, bleomycin and cis-diamminedichloroplatinum II in the chemotherapy of advanced squamous cancer of the head and neck. *Cancer* 1982, **50**, 6–9.
13. Rowland KM, Taylor SG, O'Donnell MR *et al.* Cisplatin/5-fluorouracil infusion chemotherapy in advanced recurrent cancer of the head and neck. *Proc ASCO* 1984, **3**, 184.
14. Kish JA, Weaver A, Jacobs J, Cummings G, Al-Sarraf M. Cisplatin and 5-fluorouracil infusion in patients with recurrent and disseminated epidermoid cancer of the head and neck. *Cancer* 1984, **53**, 1819–1824.
15. Rozencweig M, Dodion P, Bruntsch U *et al.* Combination chemotherapy with cisplatin, methotrexate, bleomycin and vincristine (CABO) in advanced squamous cell carcinoma of the head and neck. *Cancer* 1984, **54**, 1499–1503.
16. *WHO Handbook for Reporting Results of Cancer Treatment*. Geneva, WHO, 1979.
17. Mead GM, Jacobs C. Changing role of chemotherapy in treatment of head and neck cancer. *Am J Med* 1982, **73**, 582–595.