Anti-Cancer Drugs, 3, pp. 347–349

Hydroxyurea modulates 5-fluorouracil antineoplastic activity in advanced head and neck carcinoma pretreated with chemotherapy

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After informed consent 21 patients with advanced head and neck cancer resistant to folinic acid/5-fluorouracil (FA/5FU + cisplatin) were treated with weekly FA/5FU plus low dose hydroxyurea (HU) to evaluate if HU could further modulate 5FU antineoplastic activity. Five patients achieved a partial response (23.8%) which was short-lived (mean duration 6.5 months). Three patients (14%) had stable disease and 13 (62%) progressed. Among responders, four patients had epidermoidal carcinoma and one had clear cell carcinoma. Treatment was well tolerated and 5FU-related toxicity was not apparently worsened by the addition of HU. The most frequent toxicities were nausea/vomiting (81%), diarrhea (52%) and leukopenia (57%). Grade 3 nausea/vomiting and leukopenia were recorded in only 19 and 9% of cases, respectively. One patient had grade 1 cutaneous toxicity and a second patient showed a hand–foot syndrome. These results suggest that HU may further positively modulate 5FU antineoplastic activity.

Key words: 5-Fluorouracil, folinic acid, head and neck cancer, hydroxyurea.

Introduction

In the last decade 5-fluorouracil (5FU) has been widely employed in association with cisplatin in both palliative and induction therapy of advanced head and neck cancer (HNC).[1,2] Several attempts have been made recently to enhance 5FU antineoplastic activity and therapeutic selectivity through the modulation of its biochemical metabolism.[3–5]

The 5FU active metabolite FdUMP interacts with thymidylate synthethase in the presence of 5,10-methylene-tetrahydrofolate leading to the formation of a stable covalent ternary complex.[6,7] This ternary complex is devoid of enzymatic activity and dissociates slowly.[6,7] Folinic acid (FA) has been shown to increase 5FU cytotoxic efficacy in both preclinical and clinical studies.[8,9] In fact, phase III studies of FA plus 5FU versus 5FU alone in advanced colorectal cancer have generally shown the superiority of the combination over single agent 5FU, at least in terms of objective response rate.[9] Recently, encouraging results have been obtained in phase II studies on advanced HNC employing FA modulation of 5FU in association with other drugs, such as cisplatin.[10,11]

Preclinical data reported by Moran *et al.*[12,13] have suggested a possible further modulation of 5FU antineoplastic activity by hydroxyurea (HU). HU, a ribonucleotide reductase inhibitor, may deplete the intracellular pool of dUMP and thus decrease the competition with FdUMP for thymidylate synthethase and increasing 5FU antineoplastic activity.

In this paper we report the use of HU + 5FU in a group of patients with advanced HNC pretreated with FA and 5FU to assess if HU may further modulate 5FU activity.

Materials and methods

After informed consent 21 patients with advanced HNC were enrolled in the study. All patients had recurrent and or metastatic disease pretreated with FA and 5FU. Entry criteria were: histologically confirmed HNC; life expectancy >2 months; performance status (PS) according to Karnofsky

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Index ≥50; measurable disease; adequate bone marrow function (WBC ≥4000/mm^3; PLT ≥120 000/mm^3); 4 weeks or longer since last chemotherapeutic treatment; no major concomitant cardiological, metabolic, pulmonary and neurologic diseases. The main clinical characteristics of enrolled patients are given in Table 1. There were 17 males (81%) and four females (19%) with a mean age of 61 years (range 50–80) and a mean PS of 70 (range 50–90). Eight patients had laryngeal carcinoma, four patients had oropharyngeal carcinoma, four had rhinopharyn-geal carcinoma, three had maxillary sinus carcinoma, one had salivary gland carcinoma and one had pharyngolaryngeal carcinoma. Previous treatments were surgery in 52% of patients and radiotherapy in 57% of cases. All patients were pretreated with FA + 5FU/cisplatin on a weekly schedule and showed progressive disease. Fifteen patients had previously responded to chemotherapy, while six had not responded to previous chemotherapeutic treatment. Histologically there were 15 squamous cell carcinomas (71%), four undifferentiated carcinomas (19%), one clear cell carcinoma and one adenoid-cystic carcinoma. Sites of diseases were locoregional (14), node (11), lung (4), bone (1) and liver (1). Patients were treated as follows: levo-FA 100 mg/m^2 in 500 cm^3 of normal saline over 1 h on day 1; 5FU 450 mg/m^2 i.v. push 30 min after FA infusion started on day 1; HU 1000 mg/m^2 p.o. divided in three doses starting 6 h after FA infusion was completed. This schedule was repeated weekly for six consecutive weeks. All patients received a standard antiemetic treatment with levosulpiride 50 mg i.v. before 5FU. Patients were monitored weekly for toxicity. Toxicity and objective responses were recorded according to WHO criteria.[14] Survival was analyzed accordingly to tumor response using the Mantel–Byar method.

Table 1. Characteristics of patients

No. of enrolled patients	21
Age mean (range)	61 years (50–80)
Sex	
male	17 (81%)
female	4 (19%)
Histology	
epidermoidal carcinoma	15 (71%)
undifferentiated carcinoma	4 (19%)
clear cell carcinoma	1 (5%)
adenoid-cystic carcinoma	1 (5%)
Site of primary	
larynx	8
oropharynx	4
rhinopharynx	4
maxillary sinus	3
salivary glands	1
pharyngolaryngeal	1
Previous treatments	
surgery	11 (52%)
radiotherapy	12 (57%)
chemotherapy	21 (100%)
Site of disease	
locoregional	14
node	11
bone	1
lung	1
liver	1

Results

Out of 21 evaluable patients, five patients (23.8%) obtained a partial response (PR) with a mean duration of 6.5 months (range 5.6–7.8). No complete response was recorded. Three patients (14%) had a stabilization of disease with a mean duration of 3.1 months (range 3.0–3.3) and 13 (62%) progressed. Four out of five patients who enjoyed a PR had locoregional recurrency of HNC (two oral cavity carcinomas, one maxillary sinus carcinoma and one rhinopharyngeal carcinoma), and one patient had lung and nodal metastases from oropharyngeal carcinoma. Among responders, four patients had epidermoidal carcinoma and one had clear cell carcinoma. All patients who showed PR after FA + 5FU + HU had responded to previous chemotherapeutic treatment (FA + 5FU/cisplatin).

The mean survival of responders was 8.9 months (range 6.2–12.0), while that of patients who had stable or progressive disease was 4.5 and 4.3 months, respectively. The difference in survival between patients who responded (PR) and non-responders (NC + PD) was statistically significant ($p < 0.05$, Mantel–Byar Test).

Table 2. Toxicity

Type of toxicity	Grade of toxicity [no. of patients (%)]			
	Total	grade 1	grade 2	grade 3
Gastrointestinal	17 (81%)			
nausea/vomiting	17 (81%)	16 (76%)	12 (57%)	4 (19%)
diarrhea	11 (52%)	6 (28%)	3 (14%)	2 (9%)
stomatisis	6 (28%)	4 (19%)	2 (9%)	0
Hematological	12 (57%)			
leukopenia	12 (57%)	9 (43%)	3 (14%)	0
thrombocytopenia	5 (24%)	5 (24%)	0	0
Cutaneous	1 (5%)	1 (5%)		
Neurological	2 (9%)			
Hand–foot syndrome	1 (5%)			

Treatment was generally well tolerated (Table 2). The most frequent toxicities were nausea/vomiting (81%), diarrhoea (52%) and leukopenia (57%). Grade 3 nausea/vomiting and leukopenia were recorded in only 19 and 9% of cases, respectively. One patient had grade 1 cutaneous toxicity and a second patient showed a hand-foot syndrome.

Discussion

In preclinical studies the S phase-specific agent HU has been shown to act synergistically with 5FU against murine L1210 lymphocytic leukemia and Erlich ascites tumor.[12,15] The biochemical mechanism of this synergism may be represented by the depletion of intracellular dUMP induced by HU, which allows FdUMP to compete more effectively for binding sites on thymidylate synthethase.

The association of HU and 5FU has been employed in metastatic colorectal cancer with discouraging results.[16] However, a recent randomized study of FA + 5FU with or without HU showed a statistically significant advantage of the HU arm in terms of ORR.[17]

Although high dose HU has been reported to be active in recurrent HNC,[18] Vogl *et al.*[19] reported for the Eastern Cooperative Oncology Group (ECOG) that HU may decrease cisplatin-related toxicity, but it does not improve clinical results of the methoprexate + bleomycin + cisplatin (MBP) regimen in advanced HNC. Encouraging results have recently been obtained by other authors employing the association of HU + 5FU and concomitant radiotherapy in poor-prognosis advanced HNC carcinoma.[20]

In this study we treated a group of patients resistant to FA + 5FU with low dose weekly HU + 5FU/FA to evaluate if HU could further modulate fluoropyrimidine antineoplastic activity. Short-lived partial responses were seen in 20% of patients. Expected toxicity related to 5FU did not seem to be worsened by the addition of HU.

In conclusion these data support the possibility that HU may modulate 5FU antineoplastic activity. However, further trials are needed to test this combination in untreated patients.

References

1. Al Sarraf M. Head and neck cancer: chemotherapy concepts. *Sem Oncol* 1988; **15**: 70–85.
2. Clarke JR, Dreyfuss AI. The role of cisplatin in the treatment regimens for squamous cell carcinoma of the head and neck. *Sem Oncol* 1991; **18**: 34–48.
3. Mckintosh JF, Coates AS, Tattersall MHN, *et al.* Chemotherapy of advanced head and neck cancer: updated results of a randomized trial of the order of administration of sequential methotrexate and 5-fluorouracil. *J Clin Oncol* 1989; **7**: 1234–9.
4. Kemeny N, Schneider A, Martrin DS, *et al.* Phase I trial of N-(phosphonacetyl)-l-aspartate, methotrexate, and 5-fluorouracil with leucovorin rescue in patients with advanced cancer. *Cancer Res* 1989; **49**: 4636–9.
5. Moran RG. Leucovorin enhancement of the effects of the fluoropyrimidines on thymidylate synthase. *Cancer* 1989; **63**: 1008–12.
6. Ullman B, Lee M, Martin DW, *et al.* Cytotoxicity of 5′-fluoro-2′-deoxyuridine: requirement for reduced folate cofactors and antagonism by methotrexate. *Proc Natl Acad Sci USA* 1978; **75**: 980–3.
7. Evans RM, Laskin JD, Hakala MT. Effect of excess folates and deoxyinosine on the activity and site of action of 5-fluorouracil. *Cancer Res* 1981; **41**: 3288–95.
8. Houghton JA, Maroda SJ, Phillips JO, *et al.* Biochemical determinants of responsiveness to 5-fluorouracil and its derivatives in xenografts of human colorectal adenocarcinoma in mice. *Cancer Res* 1981; **41**: 144–9.
9. Erlichman C. Fluorouracil and leucovorin for metastatic colorectal cancer. *J Chemother* 1990; **2** (suppl 1): 38–40.
10. Vokes EE, Choi KE, Schilsky RL, *et al.* Cisplatin, fluorouracil, and high dose leucovorin for recurrent or metastatic head and neck cancer. *J. Clin Oncol* 1988; **6**: 618–26.
11. Gebbia V, Russo A, Gebbia N, *et al.* High dose folinic acid and 5-fluorouracil plus cisplatin on a weekly schedule in the treatment of advanced cancer of the head and neck. *J Cancer Res Clin Oncol* 1992; in press.
12. Moran RG, Danenberg PV, Heidelberger C. Therapeutic response of leukemic mice treated with fluorinated pyrimidines and inhibitors of deoxyuridylate synthesis. *Biochem Pharmacol* 1982; **31**: 2929–35.
13. Moran RG, Keyomarsi K. Biochemical rationale for the synergism of 5FU and folinic acid. *Natl Cancer Inst Monogr* 1987; **5**: 159–63.
14. Miller AB, Hoogstraten B, Staquet M, *et al.* Reporting results of cancer treatment. *Cancer* 1981; **471**: 207–14.
15. Frankfurt OS. Enhancement of antitumor activity of 5-fluorouracil by drug combinations. *Cancer Res* 1973; **33**: 1043–7.
16. Lokich J, Pitmasn SW, Skarin AJ. Combined 5-fluorouracil hydroxyurea therapy for gastrointestinal cancer. *Oncology* 1975; **292**: 825–8.
17. Di Costanzo F, Malacarne P, Zironi S, *et al.* Preliminary report of high dose folinic acid and 5-fluorouracil alone or combined with hydroxyurea in advanced colorectal carcinoma: a randomized trial of the Italian Oncology Group for Clinical Research. *J Surg Oncol* 1991; **Suppl 2**: 137–40.
18. Lee G, Pitman WS, Bertino JR. Weekly hydroxyurea in squamous head and neck cancer. *Proc Am Soc Clin Oncol* 1985; **4**: 147.
19. Vogl SE, Camacho F, Kaplan BH, *et al.* Hydroxyurea fails to improve the results of MBD chemotherapy in cancer of the head and neck, but reduces toxicity. *Cancer* 1983; **52**: 2011–6.
20. Vokes EE, Panje WR, Schilsky RL, *et al.* Hydroxyurea, fluorouracil, and concomitant radiotherapy in poor prognosis head and neck cancer: a phase I–II study. *J Clin Oncol* 1989; **7**: 761–8.

(Received 3 March 1992; revised version received 13 May 1992; accepted 25 May 1992)