Methotrexate With Thymidine Protection or Rescue in Advanced Head and Neck Cancer: A Phase II Study

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The usefulness of leucovorin in the reversal of methotrexate (MTX) toxicity has been shown in numerous clinical studies (1,2). It is well-known from experimental as well as clinical studies that MTX toxicity can also be reversed by thymidine (TdR) alone or in combination with a source of purine, as reviewed recently (3). In the treatment of advanced head and neck cancer, MTX is an effective drug with an overall response rate of 43% and minimal toxicity when given at moderate doses (100-1000 mg/m^2) followed by leucovorin rescue (4). The present phase II study was undertaken to investigate further the effectiveness of TdR in the control of MTX toxicity and to evaluate the clinical response of head and neck cancer to the combination of MTX and TdR.

PATIENTS AND METHODS

Initially, ten patients (six males; four females) with recurrent or metastatic squamous cell carcinoma of the head and neck were treated with MTX (600 mg/m^2 in a 24-hr infusion), with simultaneous or sequential infusion of TdR (8 g/m^2/day for 72 hrs). The median age was 59 years (range, 36–86). One patient had an Eastern Cooperative Oncology Group performance status (PS) of 3, four had a PS of 2, and five had a PS of 1. All patients had received prior radiotherapy, six patients had had surgery, and one patient had received cyclophosphamide but > 2 years previously.

Twelve patients (nine males; three females) were treated subsequently with MTX (600 mg/m^2 in a 24-hr infusion), with simultaneous or sequential infusion of TdR (1.5 g/m^2/day for 72 hrs). The median age in this group was 60 years (range, 46–75). Three patients had distant metastases; all others had recurrent or locally advanced disease. One patient had a PS of 3, six had a PS of 2, and five had a PS of 1. Eleven patients had received prior radiotherapy and five had had prior surgery. One patient had received a combination of MTX, cisplatin, and bleomycin (no response); another patient had received prior treatment with bleomycin and cisplatin.

MTX and TdR infusions were started simultaneously ("protection"); courses were given every 3 weeks in the first part of the study and every 2 weeks in the second part. If after two courses of simultaneous MTX and TdR infusion no effect on the tumor was observed, the 72-hr infusion of TdR was started at the end of the MTX infusion ("rescue"). If still no effect on the tumor was observed after another two cycles, the patient was removed from the study.

Blood cell counts were performed daily during drug infusion and at least once a week between courses. Blood chemistry was checked at least once a week. MTX and TdR plasma levels were monitored throughout each infusion by enzyme-inhibition assay and high-pressure liquid chromatography, respectively (5,6).

Standard criteria for response were used (7). Toxicity was graded according to World Health Organization recommendations (7).

RESULTS

In the first part of the study, the ten patients received a total of 28 courses of MTX-TdR, 21 with concurrent TdR and seven with TdR as rescue. Three patients had only one course, two because of grade 2 renal toxicity; one patient refused further treatment. Another patient refused further treatment after two courses and died within 4 weeks of progressive disease. No hematologic toxicity was recorded during or following 28 MTX-TdR infusions. Phlebitis was observed in 50% of the courses. Ten courses (three patients) were associated with mucositis, grade 3 in one patient and grade 2 in two others. Three courses were followed by transient grade 1 elevation of SGOT/SGPT. Nausea occurred in eight of 28 courses. No patient achieved partial or complete response.

In the second part of the study, 12 patients received 49 courses of MTX-TdR, 29 with TdR as protection and 20 with TdR as rescue; courses were repeated every 2 weeks. Two patients died, one shortly after the third course and

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one after the fourth course of MTX-TdR. Both died of rapidly progressive disease without any signs of MTX toxicity. Toxicity was as follows: 21 courses were associated with episodes of hematologic toxicity, six of which were grade 3. Hematologic toxicity was the same during simultaneous and sequential administration of MTX and TdR. Other forms of toxicity were the same as those seen in the first part of the study and are summarized in table 1. In two patients a partial remission was achieved, four had no change, and six had progressive disease.

During MTX infusion, plasma MTX levels were 7.5 ± 3.2 (SD) μM. After the end of the infusion, normal decay curves for MTX were observed in all patients regardless of TdR dose. The pretreatment plasma TdR levels were 0.35 ± 0.17 (SD) μM. During infusion of TdR (8 g/m²/day), TdR plasma levels were fivefold to sixfold higher than the pretreatment levels (data not shown). TdR levels during infusion with 1.5 g/m²/day were not significantly different from pretreatment levels.

DISCUSSION

In this phase II study, the combination of MTX and TdR was given as first-line chemotherapy to all patients but two, in contrast with previous studies (8-12), in which the combination was tried in heavily pretreated patients, without substantial therapeutic effect. The results of this study show that concurrent or delayed infusion of TdR (8 g/m²/day for 72 hrs) prevented the development of serious toxicity from MTX (600 mg/m² in a 24-hr infusion) in patients with head and neck cancer. There was no indication of myelosuppression. However, grade 3 mucositis occurred in ten of 28 courses and nausea occurred in eight of 28 courses, indicating that TdR at this dose did not completely reverse all toxicity of MTX.

Prompted by the report of Howell et al (10) that the minimum dose of TdR required for (partial) protection against MTX toxicity in humans was approximately 1 g/m²/day and by the dismal therapeutic effect in our first ten patients, we continued the study but reduced the dose of TdR (1.5 g/m²/day for 72 hrs). We increased the frequency of treatment to every 2 weeks in a further attempt to improve the results. With this lower dose of TdR, substantial hematologic toxicity from MTX was observed, with a leukocyte count nadir of 1.1 × 10⁹/L and a platelet count nadir of 38 × 10⁹/L. It is unlikely that the increase in hematologic toxicity was due only to the more frequent MTX administration, since this schedule is generally tolerated without any problems with leucovorin rescue (2). Interestingly, the reduced dose of TdR was not associated with an increased incidence of mucositis or nausea (table 1), suggesting that these forms of toxicity are independent of plasma TdR concentrations but perhaps related to an antipurine effect of MTX. Phlebitis was a problem in 50% of courses in the first part of the study and was clearly related to the concentration of TdR (1.5% vs 0.3% in 0.6% NaCl), since it was seen only once in 49 courses of MTX with low-dose TdR.

Unfortunately, the reduction of the TdR dose was not accompanied by a significant increase in therapeutic effect, since only two partial remissions were seen in 12 patients, ten of whom had not had prior chemotherapy. A further decrease in TdR dose would lead to unacceptable toxicity (10).

The study was discontinued because this form of treatment appeared to be too complicated, requiring at least 4 days of hospitalization, and provided only minor antitumor effects.

In summary, 22 patients with advanced head and neck cancer received MTX at a dose of 600 mg/m² in 24 hrs concomitant with or followed by a 72-hr infusion of TdR at a dose of 8 g/m²/day in the first ten patients and 1.5 g/m²/day in the last 12 patients. No response or major toxicity was observed in the first ten patients, whereas two partial responses and substantial hematologic toxicity were seen with the lower dose of TdR. Considering the limited antitumor effect and the logistic problems (4 days of hospitalization per course), we cannot recommend this regimen for the treatment of patients with advanced head and neck cancer.

REFERENCES


