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CLINICAL INVESTIGATION **Brain**

PRIMARY BRAIN TUMORS TREATED WITH STEROIDS AND RADIOTHERAPY: LOW CD4 COUNTS AND RISK OF INFECTION

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Purpose: Patients with primary brain tumors are often treated with high doses of corticosteroids for prolonged periods to reduce intracranial swelling and alleviate symptoms such as headaches. This treatment may lead to immunosuppression, placing the patient at risk of life-threatening opportunistic infections, such as *Pneumocystis carinii* pneumonia. The risk of contracting some types of infection may be reduced with prophylactic antibiotics. The purpose of this study was to determine the occurrence of low CD4 counts and whether monitoring CD4 counts during and after radiotherapy (RT) is warranted.

Methods and Materials: CD4 counts were measured during RT in 70 of 76 consecutive patients with newly diagnosed Grade III and IV astrocytoma and anaplastic oligodendroglioma treated with corticosteroids and seen at the Johns Hopkins Hospital. Weekly CD4 measurements were taken in the most recent 25 patients. Prophylactic trimethoprim-sulfamethoxazole (160 mg/800 mg p.o. every Monday, Wednesday, and Friday) or dapsone (100 mg p.o. daily) in those with sulfa allergy was prescribed only if patients developed a low CD4 count. Carmustine chemotherapy wafers were placed at surgery in 23% of patients, evenly distributed between the groups. No patient received any other chemotherapy concurrent with RT.

Results: CD4 counts decreased to $<200/mm^3$ in 17 (24%) of 70 patients. For the 25 patients with weekly CD4 counts, all CD4 counts were $>450/mm^3$ before RT, but 6 (24%) of 25 fell to $<200/mm^3$ during RT. Patients with counts $<200/mm^3$ were significantly more likely to be hospitalized (41% vs. 9%, $p < 0.01$) and be hospitalized for infection (23% vs. 4%, $p < 0.05$) during RT. Overall survival was not significantly different between the groups. All patients with low CD4 counts were treated with prophylactic antibiotics, and no patient developed *Pneumocystis carinii* pneumonia. No patients developed a serious adverse reaction to antibiotic therapy. The mean dose of steroids, mean minimal white blood cell count, and number of patients treated with Gliadel wafers were not significantly different between the groups.

Conclusion: The results of this study have confirmed the clinical impression that the use of high-dose corticosteroids and RT in patients with primary brain cancer is sufficient to result in severe immunosuppression and place these patients at risk of life-threatening opportunistic infections. A protocol of prophylactic antibiotics for those at risk may help prevent a potentially fatal side effect of treatment. A prospective study is underway to determine the frequency, depth, and prognostic implications of this finding. **© 2005 Elsevier Inc.**

Glioblastoma multiforme, Corticosteroids, Radiotherapy, Immunosuppression, CD4.

INTRODUCTION

The treatment of high-grade gliomas often involves surgery followed by radiotherapy (RT), along with concurrent, high-dose corticosteroids to reduce inflammation and relieve symptoms. High doses of corticosteroids are generally given from diagnosis until RT completion, a period of $\geq$8–12 weeks. Prolonged steroid use is associated with a number of side effects, including immunosuppression, putting patients at risk of serious or life-threatening opportunistic infections, such as *Pneumocystis carinii* pneumonia (PCP).

A retrospective study of PCP and primary brain tumors showed that 90% of cases were in patients with high-grade gliomas, all of whom had been taking steroids for a median of 10 weeks. Forty percent of these cases were fatal (1). Partial body RT has previously been shown to cause myelosuppression (2). More specifically, data from a previous high-grade glioma study at our institution showed increased myelosuppression when cranial RT was added concurrently to chemotherapy (3). Because of these data and our clinical experience, we instituted a policy of measuring the CD4 counts in patients with newly diagnosed high-grade glioma during RT. We were specifically interested in estimating the risk of developing clinically significant immunosuppression in this population.

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METHODS AND MATERIALS

Several cases of PCP during RT for high-grade glioma prompted a policy to measure absolute CD4 counts during adjuvant RT in cases of Grade III and IV astrocytoma and anaplastic oligodendroglioma treated with corticosteroids. Specifically, we measured CD4 and total white blood cell counts once during adjuvant external beam RT in 70 of 76 consecutive patients, usually during the first 3 weeks of RT. CD4 and total white blood cell counts were measured weekly in the most recent 25 consecutive patients. Weekly CD4 counts were checked after it was noted that several patients had precipitous declines in CD4 counts during RT. Prophylactic trimethoprim-sulfamethoxazole (160 mg/800 mg p.o. every Monday, Wednesday, and Friday) or dapsone (100 mg p.o. daily in those with sulfa allergy) was initiated if the patient's CD4 count was $<300/mm^3$ to avoid the need for close monitoring as the counts approached the critical level of $200/mm^3$.

All patients received three-dimensional conformal RT to a mean dose of 5927 cGy (range, 4500–6120 cGy). The mean duration of RT was 43 days. The mean time from surgery to the start of RT was 30 days. The mean time from surgery to the end of RT, a rough surrogate measure for the duration of corticosteroid treatment, was 73 days. Carmustine chemotherapy wafers were placed at surgery in 23% of patients.

Statistical analysis for categorical variables used chi-square analysis. We used the Kaplan-Meier method to analyze the survival data (4).

Table 1. Demographic data

Patients (*n*)	76
Age (y)	
Mean	55.7
Range	25–82
Sex (*n*)	
Male	53 (70)
Female	23 (30)
Race	
White	69 (91)
Black	6 (8)
Asian	1 (1)
Diagnosis	
AA	15 (20)
GBM	58 (76)
AO	3 (4)
Dose (cGy)	
Mean	5927
Range	4500–6120
Time from surgery to start of RT (d)	
Mean	30
Range	13–75
RT duration	
Mean	43
Range	33–54
Time from surgery to end of RT (d)	
Mean	73
Range	47–118

Abbreviations: AA = astrocytoma; GBM = glioblastoma multiforme; AO = anaplastic oligodendroglioma; RT = radiotherapy.
Data in parentheses are percentages.

RESULTS

We measured the CD4 counts in 70 of 76 consecutive patients. The counts were not obtained in 6 patients because of unanalyzable samples ($n = 5$) and patient refusal ($n = 1$). The demographic data are presented in Table 1. Patients were predominantly male (70%), white (91%), and had glioblastoma multiforme (76%).

The data for the 70 patients was categorized into two groups by absolute CD4 count: $>200/mm^3$ and $<200/mm^3$ (Table 2). Of the 70 patients with absolute CD4 measurements, 24% had counts $<200/mm^3$. For the 25 patients with weekly CD4 counts, the lowest measurement was used.

A total of 12 patients (17%) were hospitalized during RT. Significantly more patients were hospitalized in the $<200/mm^3$ group (7 of 17, 41%) than in the $>200/mm^3$ group (5 of 53, 9%; $p < 0.01$). Fever/infection was the most common reason for admission. Significantly more patients were hospitalized for infection in the $<200/mm^3$ group (4 of 17, 23%) than in the $>200/mm^3$ group (2 of 53, 4%; $p < 0.05$). The types of infection that required admission included urosepsis ($n = 2$), gastroenteritis (1 patient), pneumonitis (1 patient) (all tests for PCP were negative), and unknown source ($n = 2$). Other reasons for admission include deep venous thrombosis ($n = 2$), mental status changes, drug rash, headache, and pregnancy termination.

The median survival was slightly shorter for the $<200/mm^3$ group (16.4 months) than for the $>200/mm^3$ group (17.2 months), but this difference was not statistically significant. A subgroup analysis including only patients with glioblastoma multiforme also failed to show a statistically significant difference in median survival.

The minimal white blood cell count measured during treatment is given in Table 2. On average, the total white blood cell count was slightly lower in the $<200/mm^3$ group (mean, 6389; range, 3180–11,750) than in the $>200/mm^3$ group (mean, 7197; range, 3630–13,630). The difference between the groups was not statistically significant.

The dose of corticosteroids during treatment was not easily summarized, because patients often required adjustments to their dosing regimen on the basis of clinical criteria. For all patients, the median dose of dexamethasone at the start of RT was 24 mg/d (mean, 24.2; range, 2–80; Table 2). The mean dose for the $<200/mm^3$ group was 23.1 mg/d (range, 4–40) vs. 24.7 mg/d (range, 8–80) for the $>200/mm^3$ group (p = not significant).

The last 25 consecutive patients had weekly CD4 counts measured during RT. Of these patients, 6 (24%) were in the $<200/mm^3$ group. The mean CD4 count for each week is plotted in Fig. 1. The mean count decreased each week until Week 5 and then leveled off during Week 6.

All patients with CD4 counts $<300/mm^3$ were treated with prophylactic antibiotics, and none developed PCP. Only 1 patient developed an allergic reaction to trimethoprim-sulfamethoxazole and was switched to dapsone.

Gliadel wafers were implanted in 23% of patients, evenly distributed between the groups. No patient received other concurrent chemotherapy.