Interferon as adjuvant therapy with initial radiotherapy of patients with anaplastic gliomas

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In a group of nine patients with anaplastic gliomas, survival following surgery and treatment with interferon and radiotherapy was comparable to survival for a matched group of patients treated with BCNU and radiotherapy following surgery.

KEY WORDS: brain tumor • anaplastic glioma • glioma • chemotherapy

In a previous report, the administration of interferon to nine adult patients with partially resected supratentorial anaplastic gliomas was described. Therapy began 3 weeks after primary surgery and was given during a 3-week period prior to radiotherapy. That report dealt primarily with a Phase I study of the possible toxicities of interferon treatment. Studies of the serum levels of interferon obtained during treatment as well as assays of interferon in the cerebrospinal fluid (CSF) and in a tumor cyst cavity were also reported. We now report the survival data of these patients compared to a matched retrospective group of control patients treated with radiotherapy and BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea).

Summary of Cases
The details of the administration of interferon to the patients in this study appear in our previous report. In brief, nine patients ranging in age from 34 to 71 years and with Karnofsky functional ratings of 70 or greater were begun on treatment with human lymphoblastoid interferon* within 3 weeks following initial surgical resection of an anaplastic glioma. Table 1 lists the histological diagnosis, age, Karnofsky functional rating, and survival data for each patient. Only one patient was receiving glucocorticosteroids at the time of entry into the study.

The interferon was administered intravenously on 3 consecutive days during each of 3 consecutive weeks. The daily dose was 10 MU/sq m during the 1st week, 20 MU/sq m during the 2nd, and 30 MU/sq m during the 3rd. The interferon was diluted in 80 ml of normal saline and administered intravenously by infusion pump over a 4-hour period. At the conclusion of the interferon treatment, each patient received radiation therapy: 4300 rads to the whole head plus a 1720-rad boost to the tumor area over 7 weeks. All patients tolerated the complete treatment satisfactorily. Chills and fever occurred in each instance during the interferon administration, and slight lethargy was observed toward the end of interferon treatment. As mentioned in our previous report, serum interferon levels were proportional to dosage and reached a maximum con-

* Interferon (Wellferon) manufactured by Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, North Carolina.

Table 1

Summary of nine glioma patients in this study

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Diagnosis*</th>
<th>Age (yrs)</th>
<th>Karnofsky Rating</th>
<th>Time to Recurrence (days)†</th>
<th>Survival (days) &amp; Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AA</td>
<td>50</td>
<td>90</td>
<td>none</td>
<td>660, alive</td>
</tr>
<tr>
<td>2</td>
<td>GBM</td>
<td>32</td>
<td>90</td>
<td>346</td>
<td>534, dead</td>
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<tr>
<td>3</td>
<td>GBM</td>
<td>62</td>
<td>80</td>
<td>110</td>
<td>142, dead</td>
</tr>
<tr>
<td>4</td>
<td>AA</td>
<td>71</td>
<td>70</td>
<td>47</td>
<td>491, dead</td>
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<tr>
<td>5</td>
<td>GBM</td>
<td>56</td>
<td>90</td>
<td>219</td>
<td>356, dead</td>
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<tr>
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<td>AA</td>
<td>38</td>
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<td>255</td>
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<td>34</td>
<td>100</td>
<td>none</td>
<td>550, alive</td>
</tr>
<tr>
<td>9</td>
<td>GBM</td>
<td>54</td>
<td>100</td>
<td>450</td>
<td>562, alive</td>
</tr>
</tbody>
</table>

* AA = anaplastic astrocytoma; GBM = glioblastoma multiforme.† None = no recurrence to date.
centration of 2286 U/ml at the end of the 4-hour infusion with the highest dose. Interferon was not detected in lumbar CSF, but fluid from the tumor bed of one patient contained 120 U/ml. Patients have subsequently been followed with serial computerized tomography (CT) brain scans, neurological examinations, and Karnofsky functional rating.

Table 1 lists the time to recurrence and the survival status of each patient as of January 31, 1984, 20 months after initial patient entry. Figure 1 shows the survival curves for patients in this study compared to a retrospective control group of 18 patients who were matched for histological diagnosis, age, and Karnofsky rating before treatment, but were treated with surgery followed by radiation therapy (similar to that used in this study) and a bimonthly course of BCNU (80 mg/sq m daily for 3 consecutive days every 8 weeks). The median survival time was 534 days compared to 445 days for the retrospective control group.

Discussion

The relatively limited experience with immunotherapy of patients with intracranial tumors has been reviewed recently. Interferon has been administered systemically or into the lesion in small groups of patients with central nervous system tumors, with transient beneficial responses having been reported by some. In addition, inhibition of in vitro growth of the U-251 mouse glioma cell line, thought to be due to the effect of interferon upon DNA (deoxyribonucleic acid) synthesis, has been reported as well as interferon inhibition of human glioma cells grown in nude mice. Previous reports of the use of interferon in the treatment of anaplastic gliomas have not been controlled for several factors that obviously may influence the agent’s effectiveness: 1) Karnofsky functional rating of each patient at time of entry into the study; 2) length of time between surgical resection and the beginning of adjuvant therapy; 3) concomitant use of multiple forms of therapy; 4) size of tumor at initiation of therapy; and 5) pathological grade of tumor.

In the study reported here, patients with relatively high Karnofsky ratings, begun on treatment at a uniform time soon after surgery and subsequently treated with a standard dose of radiotherapy, tolerated the administration of interferon well. Survival of this small but relatively uniform group of patients is comparable to that of controls treated with radiation therapy and BCNU and studied retrospectively. Therefore, administration of interferon on this schedule during a 3-week period prior to the beginning of radiation therapy could represent an alternative to the use of BCNU as an adjunct in the management of anaplastic gliomas. The efficacy of interferon as a single agent in the treatment of patients with recurrent gliomas is currently being actively explored in a Phase II study, with responses being documented by serial CT brain scanning.

A next step in the investigation of the role of interferon in improving survival in brain-tumor patients would be to compare results after its administration simultaneously with radiotherapy versus radiotherapy plus BCNU chemotherapy. Such a study would permit evaluation of any possible combined toxicities that could emerge from the simultaneous use of interferon and radiotherapy, with or without chemotherapy. Interferon and BCNU each independently can produce bone marrow suppression. Lethargy is sometimes observed during treatment with either radiation therapy or interferon. On the other hand, if a schedule of therapy with these combined modalities can be derived which does not create prohibitive additive toxicities, overall survival time of patients following surgery for anaplastic gliomas might be extended with the combination of radiotherapy, interferon, and maintenance BCNU chemotherapy.

References


Manuscript received April 23, 1984.

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