Clinical Study

Pre-irradiation chemotherapy in children with high-grade astrocytoma: Tumor response to two cycles of the ‘8-drugs-in-1-day’ regimen
A Childrens Cancer Group study, CCG-945

Jonathan L. Finlay¹, J. Russell Geyer², Patrick A. Turski³, Allen J. Yates⁴, James M. Boyett⁵, Jeffrey C. Allen⁶ and Roger J. Packer⁷
¹ Memorial Sloan-Kettering Cancer Center, New York, NY; ² Children’s Hospital/University of Washington, Seattle, WA; ³ University of Wisconsin Hospital & Clinic, Madison, WI; ⁴ Ohio State University Division of Neuropathology, Columbus, OH; ⁵ St. Jude Children’s Research Hospital, Memphis, TN; ⁶ New York University Medical Center, New York, NY; ⁷ The Children’s National Medical Center, The George Washington University, Washington, D.C., USA

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Summary

Purpose. This study was undertaken to evaluate the radiographic response to two cycles of chemotherapy prior to irradiation in newly diagnosed children with high-grade astrocytomas.

Patients and methods. One hundred and thirty children less than 21 years of age with newly-diagnosed high-grade astrocytoma were treated with the ‘eight-drugs-in-one-day’ chemotherapy regimen as part of a phase III multi-institutional Childrens Cancer Group (CCG) trial. Computerized Tomographic (CT) or Magnetic Resonance Image (MRI) scans, obtained after two cycles of chemotherapy had been administered, were compared with post-operative scans to determine treatment response. Scans were evaluated by institutional radiologists, and were reviewed centrally by a single neuroradiologist.

Results. Of 79 patients with evaluable post-operative residual tumor on CT or MRI scans, 26 (33%) were determined on institutional evaluation to have had an objective response. However, central review of scans documented responses on only 14/79 (18%). A significantly higher response rate on central review was observed for those children 36 months of age or less at study entry than for older children (33% v 11%; p < 0.001). However, a higher disease progression rate was also observed for those children 36 months of age or less than for older children (21% v 2.6%; p < 0.001).

Conclusion. In this study, the largest yet reported in newly-diagnosed children with high-grade astrocytomas, the chemotherapy regimen has activity in younger children. The differences in response rates reported by institutional and central review highlight the difficulties inherent in assessing response to brain tumor therapy. However, the study does demonstrate the consistent ability of radiologists to identify disease progression within the institutional and central reviews.

Introduction

Following initially encouraging reports on the response of recurrent pediatric brain tumors, including gliomas, to the ‘8-drugs-in-1-day’ chemotherapy regimen [1], the Childrens Cancer Group (CCG), in April 1985, embarked upon a randomized phase III trial in patients newly diagnosed with high-grade astrocytomas. Half of the randomized patients received two cycles of the ‘8-in-1’ chemotherapy prior
to irradiation (Fig. 1) while the remaining randomized patients received adjuvant chemotherapy following initial irradiation. The primary intent of this evaluation of 'up-front' chemotherapy was to assess the response rate, by neuro-radiologic imaging studies, of previously untreated tumor. A second issue addressed by the study was the correlation of the institutional radiologists' determinations of response on imaging with those determinations made by a single review neuro-radiologist. The results of this study form the basis for this report.

Methods

Study design

Between April 1985 and November 1991, patients less than 21 years of age with newly diagnosed high-grade astrocytomas were registered onto the CCG-945 study. This study sought to compare in a randomized fashion, for children with intra-cranial primaries over 36 months of age, two regimens: Regimen A, with 'up-front' irradiation and vincristine followed by adjuvant vincristine, CCNU and prednisone, and Regimen B, with two cycles of the '8-in-1' chemotherapy administered prior to irradiation as well as following irradiation (Fig. 1).

Children less than 36 months of age at study entry were also entered on study, non-randomly assigned to receive the '8-in-1' chemotherapy regimen with a delay in administration of irradiation.

Children with primary spinal cord tumors were also eligible for this study, but do not form part of this report, because of the distinct problems in evaluating radiographic tumor responses in the spine.

The '8-in-1' regimen includes the following drugs: vincristine (1.5 mg/M² max. dose 2.0 mg intravenously (iv)), methylprednisolone (300 mg/M² × 3 doses q6h iv), CCNU (100 mg/M² by mouth (po)), Procarbazine (75 mg/M² po), hydroxyurea (3000 mg/M² po), cisplatin (90 mg/M² over 6 hours iv), cytosine arabinoside (300 mg/M² iv) and DTIC (150 mg/M² iv), all within a 12 hour period.

Patient data

A total of 133 patients were treated with the '8-in-1' chemotherapy regimen on the CCG-945 study. This includes 87 randomized to receive and treated with the '8-in-1' chemotherapy regimen prior to irradiation, and 42 children less than 36 months of age at diagnosis assigned non-randomly to receive '8-in-1' chemotherapy. Additionally, one patient randomized to Regimen A was actually treated with Regimen B, and 3 patients over 36 months of age were non-randomly treated on Regimen B.

Of the 133 patients, 105 (78.9%) were fully evaluable for tumor response and/or progression upon central review. In a total of 28 of 133 (21%) patients, a central review evaluation of response to chemotherapy could not be made for the following reasons: post-chemotherapy scans not performed (n = 7), unknown if post-chemotherapy scans performed (n = 4), post-chemotherapy scans performed after initiation of irradiation (n = 3), disease progression and death prior to administration of 2 cycles of chemotherapy (n = 1), Neuroradiology Response Evaluation Forms and/or Scans performed but not submitted for central review (n = 10), and submitted scans inadequate for assessment (n = 3).

Of the 105 patients, 26 on central review were considered to display no radiographically measurable or identifiable residual disease post-operatively, and are thus not evaluable for tumor response to chemotherapy but are evaluable for assessment of disease progression on chemotherapy. Thus, a total of 105 patients are evaluable for assessment of tumor progression, and 79 are evaluable for assessment of tumor response.