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BRIEF REPORT
Ifosfamide/Carboplatin/Etoposide (ICE), an Effective Salvaging Therapy for Recurrent Malignant Non-Hodgkin Lymphoma of Childhood: A Pediatric Oncology Group Phase II Study

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Recurrent malignant non-Hodgkin lymphoma (NHL) carries a grave prognosis. The interval between initial response and subsequent relapse is usually brief and the survival rate dismal. In 1990 the Pediatric Oncology Group (POG) initiated a pilot study to determine the maximum tolerated dose (MTD) of carboplatin while testing the efficacy of the combination of ifosfamide, carboplatin, and etoposide (ICE) in the treatment of recurrent malignant solid tumors of childhood. During the study, it was noted that children with malignant non-Hodgkin lymphoma responded exceptionally well to ICE. Therefore, when the MTD of carboplatin was established in 1992, and the pilot protocol for this purpose was closed, the resultant ICE regimen was applied to children with recurrent NHL. ICE then consisted of ifosfamide, 1.5 gm/m^2 iv on days 1–3; carboplatin, 635 mg/m^2 iv on day 3 only; etoposide 100 mg/m^2 iv on days 1–3; mesna, 500 mg/m^2 iv 15 min prior to, then q 3 hr × 2 after ifosfamide infusion daily × 3. Courses were repeated every 3–4 weeks when the absolute neutrophil count (ANC) recovered to >1,000/μl.

From July 1990 to July 1993, a total of 21 evaluable patients with ages ranging from 2 to 20 years (median 12 years) were entered on study. The male-to-female ratio was 3:1. Sixteen of the 21 patients had stage III/IV disease (Murphy staging), and 6 had spotty bone marrow involvement (<25% abnormal cells). They all had previously been heavily treated with a median of five drugs (range, 3–8); 16 had received cyclophosphamide. The patients were given one to six courses of ICE therapy on study (median, two courses). The median interval between courses was 3 weeks.

Myelosuppression was the dose-limiting toxicity. Sixteen patients (76%) developed ANCs <500/μl, 12 (59%) developed platelet counts <25,000/μl, and 1 (5%) a hemoglobin of <6.5 gm/dL. Fever and neutropenia requiring hospitalization and intravenous antibiotic therapy were common occurrences. However, only three episodes of sepsis were reported and none were fatal. Microscopic hematuria was seen in two patients. No renal Fanconi-like syndrome was reported.

Most patients responded after only one to two courses of ICE therapy. Prior exposure to cyclophosphamide had no effect on the response rate. The overall remission rate was 71% (15 patients), with 43% complete remissions (CR) and 28% partial remissions (PR).

DISCUSSION

Ifosfamide, etoposide, and a platinum compound used either as single agents or as components of various combinations have induced remission in patients with recurrent or refractory NHL with a CR + PR rate ranging from 48%–56% [1–3]. The past POG experience had shown no response in 10 patients treated with etoposide alone [4], and 12% CR + PR in 17 patients treated with etoposide/ifosfamide [5]. When all three agents were used together in the ICE therapy reported here, the CR + PR rate increased to 71%. The response was achieved quickly, usually after only one or two courses of therapy. The main toxicity was myelosuppression; patients did not exhibit other complications. Unfortunately, because the study was originally designed for all types of childhood malignant solid tumors, neither the histology nor the immunophenotype of the lymphoma had been requested. Hence, these data are not available. Our prelimi-

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nary observations on ICE as salvaging therapy for refractory NHL are encouraging. More study is needed to confirm our findings and to delineate which subtypes of NHL are most responsive to ICE therapy.

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