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Short communication

High-dose carboplatin, cyclophosphamide, and BCNU with autologous bone marrow support: excessive hepatic toxicity*

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Summary. Intensive doses of carboplatin, cyclophosphamide, and BCNU with autologous bone marrow support were given to four patients with advanced melanoma. Three developed clinically diagnosed, severe veno-occlusive liver disease, which was fatal in two cases. The dose of carboplatin (450 mg/m^2) was comparable with that used in ambulatory regimens. At the doses and schedule employed, this three-drug combination produced excessive hepatic toxicity. Caution is suggested when giving carboplatin in combination with intensive doses of other chemotherapeutic agents with known hepatotoxic potential.

Introduction

Therapeutic and toxic results of high-dose alkylating-agent therapy with cyclophosphamide, cisplatin, and BCNU (CPA/CDDP/BCNU) with autologous bone marrow support (ABMS) have previously been reported [5, 6]. Among 39 patients with stage IV breast cancer recently treated with this regimen, 5 (13%) died of hepatic veno-occlusive disease, but the complete response rate was 68% [3]. On this regimen, the doses of the three agents (CPA, 1,875 mg/m^2 daily for 3 days as a daily 1-h infusion; CDDP, 55 mg/m^2 daily for 3 days as a continuous infusion; BCNU, 600 mg/m^2 as a 2-h infusion immediately following the completion of the CDDP infusion) were the highest tolerated during a phase I trial [5].

The CDDP dose could not be increased beyond twice the conventional ambulatory dose range. Escalation of the dose of CDDP beyond 165 mg/m^2 resulted in intolerable hepato- and nephrotoxicity when combined with BCNU. We therefore proposed to explore the substitution of carboplatin (CBDCA) for CDDP in this regimen (CPA/CBDCA/BCNU). The dose-limiting toxicity of CBDCA in conventional use is myelotoxicity, not nephrotoxicity [2], suggesting that it might be more suitable than CDDP for ABMS programs.

Patients and methods

Four female patients with measurable, biopsy-proven, advanced or recurrent melanoma were treated. Three of the patients had visceral metastases and the fourth had a subcutaneous melanoma nodule. All had normal renal (creatinine clearance, >60 cm^3/min), hepatic (SGOT, SGPT, bilirubin, and alkaline phosphatase levels, <1.5 times normal), pulmonary [●(DLCO), >60% of the predicted value], and cardiac function [●(MUGA) scan showing a left ventricular ejection fraction at rest of >45%] prior to treatment. The patients' age ranged from 35 to 39 years. The treatment protocol was approved by the Duke University Institutional Review Board, and signed informed consent was obtained from each patient prior to initiation of therapy. CBDCA was supplied by the National Cancer Institute, and CPA and BCNU were obtained from commercial suppliers.

The chemotherapy protocol was identical to the CPA/CDDP/BCNU program described above, except that CBDCA (150 mg/m^2 daily for 3 days as a continuous i. v. infusion) was substituted for CDDP (Fig. 1). Supportive care was identical to that given on the CDDP-containing regimen. Specifically, vigorous i. v. hydration (minimum, 150 ml/m^2 normal saline per hour) was maintained throughout the CBDCA infusion.

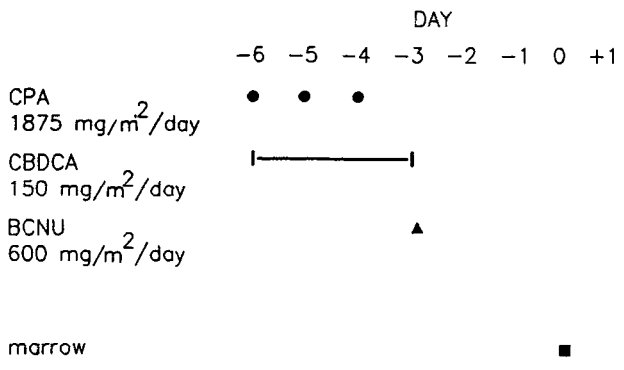

Fig. 1. Scheme for the CPA/CBDCA/BCNU treatment program

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Results

Toxicity

Three of four patients receiving this regimen developed severe, clinically diagnosed hepatic veno-occlusive disease (VOD) following therapy. The diagnosis was based on the triad of ascites, painful hepatomegaly, and jaundice [4]. VOD was confirmed at autopsy in the two patients who experienced fatal hepatic toxicity; their maximal serum bilirubin measurements were 47 and 59 mg/dl, respectively. The third patient survived in spite of developing a serum total bilirubin value of >30 mg/dl. A fourth patient, whose maximal serum bilirubin level was 2.2 mg/dl, succumbed to uncontrollable gastrointestinal bleeding as a result of refractory thrombocytopenia and did not show pathologic evidence of VOD at autopsy.

Antitumor effect

One patient with a biopsy-proven pulmonary metastasis experienced a complete response, but this was documented at autopsy after death due to VOD. Two patients experienced a partial response, and the fourth showed stable disease following therapy.

Discussion

Hepatic VOD is a common complication of marrow transplantation programs. BCNU and CPA given at high doses have both been associated with this toxicity [7], although with the CPA/CDDP/BCNU regimen we have previously explored, life-threatening or fatal VOD was seen in <15% of patients.

Three of four patients treated with the CPA/CBDCA/BCNU regimen at the dose and schedule outlined above experienced life-threatening (one patient) or fatal (two cases) toxicity from hepatic VOD. The mild bilirubin elevation in the fourth patient suggests that early hepatic toxicity may have occurred in that instance. The fourth patient developed a fatal hemorrhage, but refractory thrombocytopenia in the setting of ABMS and high-dose chemotherapy occurs sporadically with many regimens and may relate more to alloimmunization from multiple, transfused blood products than to specific chemotherapy regimens.

Although CDDP used as a single agent has not been associated with hepatic toxicity, high-dose CBDCA (>2,000 mg/m^2 over 4 days as a continuous infusion) with ABMS has been reported to cause hepatic injury [8]. Because of its alkylating properties and predominant myelotoxicity at high doses, however, CBDCA is being increasingly investigated for use in intensive regimens with ABMS.

The total CBDCA dose of 450 mg/m^2 used in the present study is comparable with that given in ambulatory treatment regimens [1] and is not associated with hepatic toxicity. This dose represents <25% of the maximally tolerated dose that can be given as a single agent with ABMS. Thus, it is clear that CBDCA acts in concert with BCNU and/or CPA to produce the hepatic toxicity seen with our regimen. We presume that lowering the CBDCA dose would ameliorate this toxicity, but dose reduction below the ambulatory level in a regimen using ABMS would be at philosophic odds with the wish for maximal exploitation of dose intensity.

These data strongly suggest that the CPA/CBDCA/BCNU combination, given at the dose and schedule outlined, produces excessive hepatic toxicity and should not be further explored. Although the small number of patients in this series precludes statistical analysis, the toxicity is striking compared with that obtained using our CDDP-containing regimen. Additionally, these results suggest caution when combining CBDCA at high doses with other chemotherapeutic agents that produce hepatic toxicity.

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