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A phase I trial of AUC-directed carboplatin with infusional doxorubicin and ifosfamide plus G-CSF in patients with advanced gynecologic malignancies

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Abstract The effect of the addition of G-CSF to carboplatin, ifosfamide and doxorubicin (CIA) at the maximally tolerated dose (MTD) was studied in a phase I clinical trial. Nine patients with incurable solid tumors were treated: six endometrial and epithelial ovarian cancers, one colon cancer with pelvic masses and two unknown primary cancers. The carboplatin dose was calculated using the Calvert formula and administered in a standard 30-min intravenous infusion. The initial carboplatin dose was AUC 4.0 mg/ml per min. Fixed doses of ifosfamide (1.25 g/m² per day), mesna (1.0 g/m² per day, and doxorubicin (15 mg/m² per day) were combined and given as a 4-day continuous intravenous infusion in an attempt to decrease nonhematologic toxicity. The dose-limiting toxicity of CIA was myelosuppression, mainly neutropenia and thrombocytopenia. Nonhematologic toxicities were hemorrhagic cystitis, weakness, fatigue, and nausea and vomiting. The MTD for CIA was established at the first dose level of carboplatin (4.0 mg/ml per min). Following this, G-CSF was added to the regimen in an unsuccessful effort to escalate the carboplatin dose. Free and total carboplatin pharmacokinetics were determined using flameless atomic absorption spectroscopy. There was one complete response and one partial response among eight evaluable patients. Both responding patients had advanced ovarian cancer. We conclude that carboplatin dose intensification beyond an AUC of 4.0 mg/ml per min is not made feasible by the addition of G-CSF to infusional doxorubicin and ifosfamide in patients with advanced gynecologic cancer.

Key words Carboplatin · Ifosfamide · Doxorubicin · G-CSF · Combination regimen

Introduction

Carboplatin, ifosfamide and doxorubicin, are three of the most active anticancer agents in solid tumor chemotherapy. Combinations of these drugs, for example, the MAID regimen (mesna, Adriamycin, ifosfamide, and dacarbazine), have demonstrated efficacy against solid tumors, specifically sarcoma [1]. However, myelosuppression is often serious, especially in the elderly patient [2].

Ifosfamide and doxorubicin have proven active as single agents in the treatment of advanced gynecologic [3] as well as soft tissue and endometrial sarcomas [4]. However, the other alkylating component of the MAID regimen, dacarbazine, has demonstrated only limited activity in other solid tumors when used as a single agent. We therefore chose to determine the maximally tolerated doses of a drug combination of ifosfamide and doxorubicin with the addition of carboplatin. Carboplatin has proven to be a potent chemotherapeutic agent with good response rates in ovarian and lung cancer. To ameliorate the anticipated myelosuppression and allow higher drug doses, G-CSF was to be added after defining the maximum tolerated dose (MTD) of the three-drug combination.

Fixed doses of ifosfamide and doxorubicin were used in this study. Total ifosfamide doses of 5 g/m² and doxorubicin doses of 60 mg/m² were employed, as in the MAID regimen [5]. The ifosfamide and doxorubicin doses were delivered via a 4-day continuous infusion in an attempt to decrease nonhematologic toxicities of
doxorubicin (cardiac) and ifosfamide (renal and neurologic) [6].

This phase I clinical and pharmacologic trial of carboplatin, ifosfamide, doxorubicin with and without G-CSF in patients with incurable solid tumors or soft tissue sarcomas had the following objectives: (1) to determine the MTD of carboplatin with and without G-CSF, (2) to determine the duration of hematologic toxicities associated with this regimen, (3) to evaluate nonhematologic toxicities, and (4) to evaluate the accuracy of the carboplatin AUC estimate calculated using the Calvert formula by measuring free and bound carboplatin levels in plasma by atomic absorption spectrometry.

**Patients and methods**

All carboplatin doses were determined based upon a targeted plasma concentration area under the curve (AUC) using the Calvert formula [7]. The Calvert formula allows for adjustment of the carboplatin dose on the basis of kidney function. Calvert et al. have used the AUC to adjust the carboplatin dose, as a single agent or in combination with other chemotherapeutic agents, while maintaining safe levels of myelosuppression. The Calvert formula assumes a fixed non-renal clearance of carboplatin of 25 ml/min. It is defined as follows: carboplatin dose (total mg) = carboplatin AUC x (GFR + 25) where the glomerular filtration rate (GFR) can be measured or estimated from serum creatinine levels.

The initial dose of AUC 4 mg/ml per min was selected because it is well tolerated in patients who have had heavy, prior chemotherapy exposure and who will be receiving combination chemotherapy [6]. Additionally, at the maximally tolerated dose of carboplatin, we evaluated the accuracy of the Calvert formula in predicting the actual assayed amount of carboplatin ultrafiltrate in plasma.

**Patient selection**

All subjects were required to have histologic proof of advanced-stage malignant solid tumor or soft tissue sarcoma not curable with surgery, radiation therapy or standard chemotherapy. In addition, all participants had to have a performance status of 2 or less (ECOG), to be greater than 18 years of age, and to have an anticipated life expectancy of at least 12 weeks. Measurable disease, while desired, was not required. Patients were required to have adequate bone marrow function (total white cell count greater than 4000/μl and platelets greater than 100,000/μl), liver function (total serum bilirubin less than 2.0 mg/dl), and renal function (serum creatinine less than 2.0 mg/dl). Patients who had received prior doxorubicin therapy were excluded, as were those with previous myocardial infarction. All participants were informed of the experimental nature of the study and provided consent in accordance with institutional and federal guidelines.

**Pretreatment evaluation and follow-up studies**

Before each course of treatment, a complete history and physical examination were performed. Weekly laboratory studies included complete blood count (CBC), differential white blood count (WBC), platelet count, chemistries (including renal and liver function studies), appropriate serum tumor marker, and urinalysis. Twice-weekly CBC, differential WBC, and platelet counts were evaluated in patients receiving G-CSF. Radiologic studies to evaluate tumor response were performed prior to every third course of treatment.

**Study design**

A minimum of three patients were to be studied at each carboplatin dose level. Carboplatin doses were combined with fixed doses of ifosfamide/mesna and doxorubicin. Toxic side effects were graded based on the Common Toxicity Criteria (SWOG) [8]. If significant toxicity (grade 2 or greater) was observed, an additional three patients were to be treated at that same dose level. The MTD was defined as the dose level at which the majority of patients experienced a dose-limiting toxicity of at least moderate severity (grade 3 or more). Once the MTD was established, G-CSF was to be added to the regimen in an effort to escalate the carboplatin dose further and allow additional courses of chemotherapy. Dose reductions for myelotoxicity were performed on subsequent courses as shown in Table 1.

Patients were able to continue study treatment as long as their disease did not progress and a cumulative doxorubicin dose of 750 mg/m² (given by continuous infusion) was not exceeded. Criteria for removal of patients from the study included disease progression after two courses of therapy, development of unacceptable toxicity, or patient decision to withdraw from the study. All patients treated were evaluated for toxicity. All treatment courses were administered in the outpatient setting.

**Drug administration**

Carboplatin was administered by a 30-min intravenous (i.v.) infusion on day 1 of each course. The target AUC of 4.0 mg/ml per min was derived from the Calvert formula using the Cockcroft-Gault method of estimating GFR using serum creatinine levels.

Ifosfamide 1.25 g/m² per day, mesna 1.0 g/m² per day, and doxorubicin 15 mg/m² per day were combined in 1 l normal saline and administered over 24 h by continuous i.v. infusion. The influ-

<table>
<thead>
<tr>
<th>Table 1 Dose adjustments</th>
<th>Value</th>
<th>Dose adjustment</th>
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<td><strong>Parameter</strong></td>
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<td>Carboplatin</td>
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<td><strong>Platelet nadir</strong></td>
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<td>(cells/mm³)</td>
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<td>&lt;25,000, with bleeding</td>
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<td><strong>Total WBC nadir</strong></td>
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<td>(cells/mm³)</td>
<td>&lt;1000 for 5 consecutive days</td>
<td>G-CSF dose increased to 10 μg/kg/day</td>
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