High-Dose Etoposide: From Phase I to a Component of Curative Therapy

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In 1983, we reported in *Journal of Clinical Oncology*¹ a phase I high-dose escalation study of the chemotherapeutic agent etoposide. By reinfusing autologous bone marrow to assure hematopoietic recovery, we were able to identify the nonmyeloid dose-limiting toxicity of this agent. At the same time, other chemotherapy agents were similarly studied, based on the concept that high-dose therapy might be superior treatment for cancers that were not successfully treated with standard-dose cytotoxic therapy.²⁻⁸ The results of these single-agent studies led to the development of the combination regimens that today remain integral to high-dose anticancer therapy.

The intravenous infusion of marrow-derived hematopoietic stem cells to facilitate marrow ablative cytotoxic therapy was under intense investigation in the 1980s. The fundamentals of such therapy were pioneered, during the previous decade, by Nobel laureate E. Donnell Thomas, MD, and George Santos, MD.⁹ They hypothesized that supra-maximal therapy could overcome resistance to standard-dose therapy and began to unravel the immunologic aspects of allogeneic graft-versus-host disease. Patients with resistant acute leukemia were initially treated, using fresh allogeneic marrow and cytotoxic therapy consisting of total whole-body irradiation (TBI) with cyclophosphamide or busulfan with cyclophosphamide. These therapies provided two predominant functions: (1) profound immunosuppression to allow engraftment of allogeneic cells and (2) cyto-reduction to eradicate leukemia refractory to standard-dose treatment. Despite substantial toxicity, a minority of patients with otherwise incurable acute leukemia achieved long-term complete remission.

Autologous cryopreserved marrow-derived stem-cell transplantation was similarly developed to allow patients to donate their own stem cells, thus avoiding the allogeneic consequences of graft-versus-host disease. The first reports of cryopreserved autologous transplantation, in the 1980s, used large aliquots of marrow aspirates as the cell source with adequate marrow recovery and cure of some patients with resistant lymphoma.^{10,11} In this era, improvements in supportive care for the consequences of neutropenia and thrombocytopenia reduced the morbidity and mortality of transplantation. Gradually, other cancers became targets of high-dose therapy as autologous transplantation and supportive care became more refined. Recently, the preferred source for hematopoietic stem cells are mobilized peripheral-blood cells collected by large-volume leukapheresis.^{12,13}

Etoposide (VP-16-213), a semi-synthetic congener of epidophyllotoxin, has a broad spectrum of clinical activity in hematologic and solid tumors. The standard dose of etoposide is 300 to 500 mg/m²

administered in divided doses over 3 to 5 days and repeated every 3 weeks. With this dose, grade 4 neutropenia and thrombocytopenia (usually of brief duration) is produced in 10% to 15% of patients. We chose this agent to dose escalate because myelosuppression was its dose-limiting toxicity, with other toxicities being infrequent or mild.

Our trial escalated etoposide using a modified Fibonacci scheme from the previous highest dose ever administered to humans (1,500 mg/m²) to 2,700 mg/m² (900 mg/m² per day for 3 consecutive days). A total of 28 patients underwent four dose escalations, with four patients treated at the highest dose and 13 patients at the prior dose level. At 2,700 mg/m², severe mucositis was observed in three of three courses. At the next highest dose (2,400 mg/m²), only two (11%) of 18 courses resulted in severe mucositis, thus defining this dose as the maximally tolerated dose based on extramedullary toxicities. In reviewing these observations 25 years later, it is conceivable that further dose escalation may have been achieved with current methods to mitigate mucous membrane toxicity and prevent herpes simplex virus reactivation.¹⁴

As anticipated, myelotoxicity was severe, but based on the kinetics of marrow recovery, etoposide at these doses appeared not to be marrow ablative. Etoposide produced a prolonged duration of cytopenias at all dose levels, but peripheral blood count recovery (defined as > 500 neutrophils/ μ L and $> 20,000$ platelets/ μ L) occurred before three weeks after transplantation in all except one patient. During this time, we did not routinely measure stem cell content using CD34+ cell number as a surrogate and therefore could not, beyond measuring total nucleated cell count, determine the quality of the marrow infusion. The duration of neutropenia (< 500 neutrophils/ μ L) was similar at all dose levels with a median of 11 days. Our suspicion that dose escalated etoposide was not myeloablative was confirmed in a subsequent study, when high-dose dose of etoposide (1.8 to 4.8 g/m² by continuous infusion) was administered with high-dose cyclophosphamide (50 mg/kg/d $\times$ 3-4 days).¹⁵ In this trial, patients with refractory leukemia or lymphoma recovered their blood counts without autologous stem cell support.

In our study, patients with refractory hematologic or solid tumors were eligible, and objective responses were seen in acute lymphocytic leukemia, germ cell tumor, glioblastoma multiforme, and Hodgkin's lymphoma. Overall, tumor responses occurred in 36% of all patients, but most responses were of brief duration. Five of six patients with refractory germ cell tumors responded, four of whom were refractory to regimens containing standard-dose etoposide. We therefore concluded, based on responses observed in this study, that

high-dose etoposide should be explored in phase II studies or used in combination chemotherapy.

Dose escalation of cytotoxic therapy may alter the pharmacokinetics measured with standard-dose therapy by increasing peak levels or the area under the concentration-time curve. Regional distribution can be improved, especially to “sanctuary” sites with high-dose therapy. As part of our study, we measured plasma, urine, and CSF etoposide concentrations in 12 adult patients to determine the pharmacokinetics of this drug at these elevated dosages.¹⁶ Increasing the etoposide dose produced proportionally higher peak plasma etoposide concentrations (27 to 114 $\mu\text{g/mL}$) and total areas under the concentration-time curve. The etoposide mean terminal half-life and plasma clearance, however, were independent of the dosage given. CSF etoposide concentrations were $1.8\% \pm 1.7\%$ of the simultaneously measured plasma levels. Pleural fluid removed from one patient at 18 hours post-therapy contained etoposide at 1.8 $\mu\text{g/mL}$. Our data, combined with previously published data, indicated that the pharmacokinetics of high-dose etoposide are linear within the dosage range tested. They also suggested that etoposide penetrates poorly into the CSF.

High-dose etoposide in combination with other cytotoxics continues to be a component of high-dose therapy for the treatment of refractory hematologic neoplasms, including acute leukemia, non-Hodgkin's lymphoma, and Hodgkin's lymphoma.¹⁷⁻²⁴ These regimens produce substantial myelotoxicity and mucositis, as well as occasional pulmonary and hepatic toxicity.²⁵ Whether adding etoposide to other high-dose regimens or to TBI regimens (eg, cyclophosphamide and TBI) yields superior results to these regimens without etoposide has not been determined.^{26,27} Nonetheless, it is generally believed that maximal antitumor cytotoxicity should be delivered with autologous transplantation. However, the profound antitumor effect of allogeneic graft-versus leukemia has led to the evaluation of reduced-intensity preparative regimens designed for immunosuppression rather than cytotoxicity for patients not projected to be able to tolerate allogeneic marrow transplantation with full-dose preparative regimens.²⁸

In contrast to the continued role of high-dose therapy in the treatment of hematologic malignancies, this approach has not been useful in most solid tumors. Early studies with high-dose etoposide produced higher response rates, but responses were of brief duration.²⁹⁻³³ Randomized trials have subsequently failed to demonstrate any advantage of high-dose therapy when compared with standard dose in metastatic breast or ovarian cancer.^{34,35} An exception may be testicular cancer. A recent report suggested improved survival (compared with historical controls) when patients in first or second relapse received two successive treatments with high-dose etoposide plus carboplatin followed by autologous stem-cell support.³⁶

Twenty-five years after the first dose-escalation studies, high-dose etoposide remains a routine component of potentially curative high-dose therapy for patients with several hematologic malignancies. However, the administration of high-doses of etoposide (as well as other cytotoxic agents) has made no contribution to the therapy of common solid tumors. Recent improved understanding of cancer stem cells suggests that these quiescent cells are resistant to standard cytotoxic agents, regardless of dose.³⁷ Further improvements in therapy will require continued definition and exploration of molecular mechanisms unique to cancer cells.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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