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Original article

Feasibility and toxicity study of a high-dose chemotherapy regimen for autotransplantation incorporating carboplatin, cyclophosphamide and thiotepa

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Summary. Sixteen patients received a high-dose chemotherapy regimen consisting of carboplatin (1600 mg/m^2) and cyclophosphamide (6000 mg/m^2) as daily two-hour infusions over four days (CC). All but two of them also received thiotepa (480 mg/m^2) in eight 30-minute infusions given every 12 hours (CTC). Bone marrow and/or peripheral stem cell (PSC) reinfusions took place 72 hours after the last course of chemotherapy. The major toxicity was bone marrow suppression, the duration of which was markedly reduced in the patients receiving PSC reinfusions. Non-hematological toxicity was relatively mild and consisted of nausea and vomiting, minor mucositis and skin rashes. All but one patient had mild and completely reversible elevations of serum ALAT and/or LDH levels. One patient, who had received full-dose chemotherapy despite a creatinine clearance of 56 ml/min, developed significant toxicity consisting of transient cyclophosphamide-associated pancarditis, reversible neurotoxicity and partially reversible hearing loss and renal function impairment. There were no toxic deaths. In view of the high carboplatin dose, the CTC regimen may be particularly suitable for use in the salvage treatment of germ cell cancer. Since CTC causes no serious organ toxicity, further studies to determine its suitability for double or even triple transplantation programs are warranted.

Key words: carboplatin, cyclophosphamide, thiotepa, autologous bone marrow transplantation

Introduction

Although chemotherapy can induce objective remissions in a variety of solid tumors, the large majority of patients will ultimately relapse and die of disease refractory to cytotoxic agents. One investigational strategy for overcoming this type of drug resistance is dose-intensification [1, 2]. The ability of such an approach to salvage patients who cannot be cured by conventionally-dosed regimens remains to be proven, but there is little doubt that this is the case at least for a subgroup of patients with non-Hodgkin's lymphoma [3] or Hodgkin's disease [4].

Autologous bone marrow transplantation in solid tumors is an area of accelerating research. Its feasibility has increased dramatically with the availability of recombinant human hemopoietic growth factors [5] and the recent introduction of autologous peripheral stem cell transplantations [6]. These advances, though crucially important for the further development of this treatment modality, underscore the urgent need for high-dose chemotherapy regimens that are characterized by: (1) optimal activity against the relevant tumor; (2) little extramedullary toxicity, allowing major dose escalations; and (3) an absence of unpredictable organ toxicity that could account for mortality or cumulative toxicity not related to myelosuppression.

Frei and colleagues have advocated the use of multiple alkylating agents for this purpose because these drugs have little cross-resistance, have a broad spectrum of activity and do not easily induce high-grade drug resistance in vitro [7]. A regimen based on cyclophosphamide, carboplatin and thiotepa was developed by the Boston group [8] which, with only one toxic death in 29 patients (3%) [9], has been used in the treatment of patients with breast cancer.

The dose of carboplatin, however, was just 800 mg/m^2 in this study, which is only twice the dose recommended for use as a single agent without bone marrow support. Although carboplatin is clearly associated with a positive dose-response curve in the clinic, our experience in germ cell cancer suggests that considerably higher doses may be required to induce lasting remissions in patients refractory to standard doses [10]. Higher doses should be possible, since phase I studies have shown that doses up to 2000 mg/m^2 can be administered without bone marrow support or undue toxicity [11]. Furthermore, regimens incorporating higher doses of carboplatin combined with etoposide have been reported in the autotransplantation setting [12, 13]. Thus, we set out to develop a high-dose chemotherapy multiple alkylating agent-based regimen with a carboplatin dose of 1600 mg/m^2.

Patients, materials and methods

Patients

All patients were in chemotherapy-induced partial or complete remission of advanced malignant disease (breast cancer, germ cell cancer or medulloblastoma). All were considered candidates for an attempt to consolidate their remissions by high-dose chemotherapy. Patients with breast cancer were in their first chemotherapy-induced remissions (all complete or near-complete), the patients with testicular teratoma and the patient with medulloblastoma were in second partial or complete remissions. To be eligible for the study, patients were required to have a satisfactory performance status (ECOG/Zubrod WHO grade 0 or 1), adequate renal function (creatinine clearance $\geq$ 50 ml/min) and hepatic function (bilirubin $\leq$ 20 μmol/L, ALAT and ASAT less than 2 × the upper limit of normal). The bone marrow function had to be normal (WBC $\geq 3.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L) and any infections, regardless of whether they were associated with prior chemotherapy, had to be controlled. Informed consent was obtained from all patients according to institutional guidelines.

Bone marrow and stem-cell harvests

Bone marrow was harvested by multiple aspirations from the iliac crest under general anesthesia. A total of at least 2×10^8 nucleated cells per kg body weight had to be obtained. The theoretical number of granulocyte-macrophage colony-forming units (CFU-GM) available for reinfusion (as indicated by colony-forming assays after freezing and thawing of aliquots) had to exceed 2×10^4 per kg body weight.

Autologous peripheral stem cells were mobilized by administering chemotherapy followed by daily s.c. administration of 300 μg granulocyte-colony-stimulating factor (G-CSF). In the patients with breast cancer, the regimen consisted of fluorouracil (500 mg/m^2), epidoxorubicin (120 mg/m^2) and cyclophosphamide (500 mg/m^2). The chemotherapy was given on day 1 and G-CSF was administered from day 2 on. In the medulloblastoma patient, a mobilizing regimen consisting of cisplatin (60 mg/m^2), ifosfamide (1800 mg/m^2) and etoposide (75 mg/m^2) was employed, followed by G-CSF from day 4 on.

From day 8, daily blood counts and estimates of the CD34-positive nucleated cell fractions in the peripheral blood were performed by fluorescence-activated cell sorting employing an anti-CD34 antibody [14]. Daily hemapheresis sessions began as soon as an unequivocal rise in CD34-positive cell percentage was observed. In all patients except the one with medulloblastoma (patient 16), the chemotherapy used for stem cell mobilization was the last to be administered before high-dose chemotherapy. In patient 16, peripheral stem cells were harvested following the third of six chemotherapy courses. A total yield of 5×10^6 CD34-positive cells per kg body weight was considered adequate for a transplantation procedure. In our hands, this correlates well with a yield of over 20×10^4 CFU-GMs/kg. Further details of the mobilizing strategies and their efficacies will be published elsewhere.

Pre-treatment evaluation

The clinical evaluations prior to high-dose chemotherapy included a full blood count with differential, serum chemistry profile, creatinine clearance, chest x-ray, electrocardiogram and radionuclide ejection fraction. Complete documentation of the remission status included serum markers (CEA and CA 15.3 determinations in breast cancer, βHCG and AFP in testicular teratoma patients) and computed tomography studies whenever appropriate. Other tests, such as pulmonary function studies and audiograms, were done only when clinically indicated.

Treatment regimen

All patients received 400 mg/m^2 carboplatin i.v. as a two-hour infusion and 1500 mg/m^2 cyclophosphamide as a one-hour infusion on days −7, −6, −5 and −4. Mesnum (500 mg) was given 6 times daily for a total of 24 doses, beginning one hour before the first cyclophosphamide infusion. In addition, all patients except the first two received 60 mg/m^2 thiotepa twice daily as a 30 to 60-minute i.v. infusion on days −7, −6, −5 and −4. All infusions were administered through double-lumen Hickman catheters inserted in a subclavian vein. Bone marrow was reinfused on day 0. Patients who also received autologous peripheral stem cell transplantations were reinfused on day −1 (peripheral stem cells) and day 0 (bone marrow). The patient who received autologous peripheral stem cells only was reinfused on day 0.

Antiemetics were employed both prophylactically and as needed and usually included dexamethasone, high-dose metoclopramide and temazepam. Ondansetron was given intravenously (24 mg/day as a continuous infusion from day −7 until day −3) in all patients who were treated after June 1991.

All patients received prophylactic antibiotics, including ciprofloxacin and amphotericin orally as selective bowel decontamination. Penicillin G (1 million units, 4 times daily) and amphotericin B (0.25 mg/kg/day) were given prophylactically from day 0 and were discontinued when the neutrophil count exceeded 0.5×10^9 cells/L. Patients who tested positive for anti-Herpes simplex antibodies received aciclovir prophylactically, in an oral dose of 400 mg twice daily. Irradiated platelet transfusions were administered to maintain platelet counts of at least 10×10^9/L, or in case of hemorrhage, and leukocyte-free irradiated red blood cells were given to maintain hemoglobin levels at or above 5.5 mmol/L. The patients occupied private rooms between day 0 and the end of absolute neutropenia, but no other reverse isolation measures were employed.

G-CSF was administered as a daily s.c. injection of 300 μg, regardless of body weight, from day 1 until the WBC count exceeded 5.0×10^9/L.

Results

A total of 16 patients received autotransplantation with high-dose carboplatin and cyclophosphamide with or without thiotepa in The Netherlands Cancer Institute until January 1992, and all are included in this report. The first two patients (numbers 1 and 2) received only carboplatin and cyclophosphamide. Since neither showed any significant non-hematologic toxicity, it was deemed safe to add a third alkylating agent (thiotepa) to the regimen.

Pertinent patient characteristics are given in Table 1. Six patients received bone marrow reinfusions as hematological support, five patients received bone marrow reinfusions combined with G-CSF, and five patients received autologous peripheral stem cell transplantations followed by G-CSF (four of these patients also received autologous marrow reinfusions, see Table 2). Information on prior treatment and preliminary outcome data are presented in Table 3.

Hematological toxicity

As expected, the main toxicity of the CTC regimen consisted of profound bone marrow suppression. All patients had periods of absolute neutropenia and required platelet transfusions. The duration of neutro-

penia and thrombocytopenia were significantly reduced in the patients who received the peripheral stem cell reinfusions (Table 2). Full engraftment was achieved in 14 of 16 patients. Patient 7 had a refractory mediastinal extragonadal germ cell tumor with pre-existing polycythemia. He remained thrombocytopenic until his death of respiratory failure due to massive lung metastases. Patient 13 developed unexplained myelodysplasia-like abnormalities without evidence of monoclonal cytogenetic abnormalities in the bone marrow. This was associated with persisting anemia and moderate thrombocytopenia 5^+ months after transplantation, possibly related to treatment with tuberculostatics in the immediate post-transplant period (see below).

Table 1. Characteristics of 16 patients receiving high-dose chemotherapy.

Patient number	Sex (m/f)	Age (years)	Creatinine clearance (ml/min)	Tumor	Autograft[a]
1	m	35	84	Teratoma	ABMT
2	m	23	97	Teratoma	ABMT
3	m	23	119	Teratoma	ABMT
4	f	25	141	Breast	ABMT
5	m	51	127	Teratoma	ABMT
6	m	29	124	Teratoma	ABMT
7	m	44	87	Teratoma	ABMT+G-CSF
8	f	41	135	Breast	ABMT+G-CSF
9	m	43	132	Teratoma	ABMT+G-CSF
10	m	28	56	Teratoma	ABMT+G-CSF
11	m	22	102	Teratoma	ABMT+G-CSF
12	f	39	98	Breast	ABMT+PSCT
13	f	49	115	Breast	ABMT+PSCT
14	f	48	123	Breast	ABMT+PSCT
15	f	46	104	Breast	ABMT+PSCT
16	m	32	116	Medullo-blastoma	PSCT

[a] ABMT: Autologous bone marrow transplantation not employing hemopoietic growth factors; ABMT+G-CSF: Autologous bone marrow transplantation employing 300 μg G-CSF (Amgen) from the first day after transplantation until WBC recovery; ABMT+PSCT: Combined autologous bone marrow transplantation and peripheral stem cell reinfusion, employing G-CSF until WBC recovery (see text); PSCT: Peripheral stem cell transplantation without ABMT.

Table 2. Duration and severity of myelosuppression in 16 patients receiving high-dose chemotherapy.

	ABMT[a] (N = 6)	ABMT+G-CSF[b] (N = 5)	APSCT[c] (N = 5)
Day neutrophils[d] >500/μl	26 (23–45)[e]	15 (12–27)	9 (9–12)
Day of platelet transfusion independence[f]	28 (14–61)	33 (24–51)	16 (9–19)
Blood transfusions (units)	12 (6–18)	13 (5–31)	6 (4–9)
Number of platelet transfusions	8.5 (3–10)	27 (9–30)	4 (2–4)
Days of fever >38 °C	11 (0–27)	9.5 (7–13)	4.5 (0–6)

[a] ABMT, autologous bone marrow transplantation not employing hemopoietic growth factors.
[b] ABMT+G-CSF, autologous bone marrow transplantation followed by G-CSF administration until neutrophil recovery.
[c] APSCT, autologous peripheral stem cell transplantation with (N = 4) or without (N = 1) bone marrow reinfusion.
[d] Day after bone marrow reinfusion stem cell reinfusion (patient 16).
[e] median (range).
[f] Day after ABMT or APSCT (patient 16) on which platelets remained stable at or over 20 × 10^9/L without transfusions.

Nine of the sixteen patients had microbiologically documented infections. These included St. epidermidis catheter infections (8 patients), Corynebacterium catheter infections (3 patients), and positive blood cultures for Streptococci (2 patients). Patient 13 developed a pneumonia due to acid-fast rods that did not grow in culture. She recovered with antibiotics directed against Mycobacteria (isoniazid, rifampicin and ethambutol).

Gastro-intestinal toxicity

Nausea and vomiting were common and occurred in all patients despite intensive antiemetic therapy for a median of 5 days (range 1–18 days). Some degree of diarrhea was noted in 14 of the 16 patients, usually lasting for about one week (range 1–18 days). Both vomiting and diarrhea usually commenced on the third or fourth days of the intensive chemotherapy.

Mucositis was mild. It did not occur in six patients, was grade 1 in six and was over grade 1 in only four patients (2 × grade 2, 1 × grade 3, 1 × grade 4).

Organ toxicity

Symptomatic tinnitus and hearing loss were noted in two patients. This toxicity was completely reversible in one, and partially reversible in the second. Hearing aids were not required. Both patients also complained of increased sensory loss and dysesthesias in feet and hands, ascribed to worsening of their pre-existent cisplatin neuropathies. The symptoms eventually returned to pre-transplant levels in both.

Renal toxicity as evidenced by rises in serum creatinine levels were seen in 3 of 16 patients. In two patients, the serum creatinine level rose to 1.5 × the initial value, returning to base-line levels within a few weeks. However, in a third patient (patient 10) with a creatinine clearance of 56 ml prior to CTC, the serum creatinine level rose from 128 μmol/l to a maximum of 293 μmol/l, and then slowly decreased to 140 μmol/l over a period of six weeks.

Mild hepatic toxicity was seen in all patients except one of the two who did not receive thiotepa. It usually consisted of ALAT elevations to a median maximum of 2.8 times the upper value of normal (range 1.3–17.5 times), which invariably peaked on day −1 or day 0. In 11 of these patients, accompanying rises in LDH were seen. Both ALAT and LDH elevations were completely reversible, usually within one or two weeks. Brief elevations of the serum bilirubin (maximum 1.6–3.0 times upper value of normal) were observed in 5 of 16 patients.

Table 3. Prior treatment and preliminary efficacy data of C.T.C. in 16 patients.

Pat. nr.	Prior treatment	Remission status before CTC	Remission status after CTC	Progression-free survival	Overall survival	Current status of disease
Germ cell cancer patients:						
1	BOP/VIP, 3 × HD-CE	progression (βHCG, lung metastases)	P.R.	4	9	D.O.D.
2	4 × CE, 2 × PVB, 2 × HD-CE, CDDP/VP16, lung metastasectomy	progression (βHCG, lung, mediastinum)	P.R.	1	9	D.O.D.
3	BOP/VIP, 2 × HD-CE	C.R.	C.R.	31+	31+	N.E.D.
5	4 × BEP, metastasectomy brain, mediastinal exploration, 2 × HD-CE	C.R.	C.R.	20+	20+	N.E.D.
6	4 × BEP, metastasectomy lung, 2 × HD-CE	P.R. (lung and mediastinal metastases)	C.R.	16+	16+	N.E.D.
7	BOP/VIP, mediastinal exploration: necrosis, 2 × HD-CE	P.R., βHCG elevation, lung metastases	P.R., βHCG normalized	4	6	D.O.D.
9	3 × BEP, 2 × HD-CE, RPLND: vital tumor	C.R.	C.R.	7+	7+	N.E.D.
10	4 × BEP, 2 × EP, RPLND: necrosis, 2 × HD-CE	P.R. (multiple lung metastases)	C.R.	5+	5+	N.E.D.
11	BOP/VIP + 2 × VIP, RPLND: necrosis, 2 × HD-CE	P.R. (multiple lung metastases, βHCG elevation)	P.R. (vital teratoma at surgery)	2	4+	N.E.D. (surgical C.R.)
Breast cancer patients:						
4	RT, 6 × AVMFP	C.R.	C.R.	4	11	D.O.D.
8	7 × cyclophosphamide + doxorubicin	C.R.	C.R.	9+	9+	N.E.D.
12	5 × CAF, 1 × FEC	P.R. (skin metastases)	C.R.	9	11+	A.W.D.
13	4 × FEC, surgery	surgical C.R., chemoresponsive	C.R.	6	7+	A.W.D. (brain metastases)
14	4 × FEC, surgery	surgical C.R., chemoresponsive	C.R.	5+	5+	N.E.D.
15	4 × FEC, surgery	surgical C.R., chemoresponsive	C.R.	4+	4+	N.E.D.
Medulloblastoma patient:						
16	RT brain and medulla, 6 × VIP	C.R.	C.R.	5+	5+	N.E.D.

AVMFP : Doxorubicin, vincristine, methotrexate, fluorouracil and prednisone.
A.W.D. : Alive with disease.
BEP : Bleomycin, etoposide and cisplatin [18].
BOP/VIP : 3 courses of bleomycin, vincristine and cisplatin, followed by by three courses of etoposide, ifosfamide and cisplatin [19].
CDDP/VP16 : High-dose cisplatin and etoposide (unpublished].
CAF : Cyclophosphamide, doxorubicin and fluorouracil.
CE : Carboplatin and etoposide for low-volume disease
D.O.D. : Dead of disease.
EP : Cisplatin and etoposide [20].
FEC : Fluorouracil 500 mg/m^2, epidoxorubicin 120 mg/m^2 and cyclophosphamide 500 mg/m^2 for locally advanced breast cancer [unpublished].
HD-CE : High-dose carboplatin and etoposide for relapsing or refractory disease [10].
N.E.D. : No evidence of disease.
RPLND : Retroperitoneal lymph node dissection.
RT : Radiation therapy.
PVB : Cisplatin, vinblastine and bleomycin.
VIP : Cisplatin, ifosfamide and etoposide.

Possible cardiopulmonary toxicity was present in 4 patients. One patient had pulmonary infiltrates that cleared after administration of amphotericin B for Aspergillosis. Two patients had unexplained transient and minor pleural effusions with pleural friction rubs but without obvious signs of heart failure. A fourth patient (patient 10) developed pleural and pericardial effusions. A chest x-ray disclosed signs of pulmonary congestion, suggesting cyclophosphamide-induced pancarditis. All abnormalities had cleared after 10 days.

Other toxicity

Twelve patients developed a skin rashes, all between days 2 and 14 after reinfusion. In all cases, the rash disappeared after discontinuation of one or more antibiotics.

One patient briefly complained of blurred vision on the days immediately following completion of the chemotherapy regimen.

Discussion

A high-dose carboplatin and cyclophosphamide-based pre-transplantation chemotherapy regimen was administered to 16 patients in complete or partial remission of metastatic solid tumors. Fourteen of these patients additionally received a third high-dose alkylating agent, thiotepa. The regimen (CTC) was relatively well-tolerated and there were no toxic deaths. Because of the heterogeneity of the patient group and the brevity of follow-up (Table 3), no estimate of its efficacy in preventing relapse can be given. This will have to await the outcome of phase II studies, which are now in progress in our institute.

As anticipated, the main toxicity of CTC was myelosuppression. Neutropenia was less of a problem after G-CSF became commercially available and could be used in these patients. An important further reduction of both neutropenia and thrombocytopenia was achieved by exploitation of the novel techniques of autologous peripheral stem cell harvesting and reinfusion (Table 2), which essentially confirms recent reports in the literature [6]. Although the number of patients in this study is too small for meaningful statistical analysis, the differences in time to hematological recovery are impressive and completely consistent with our experience in lymphomas as well [Richel D.J. et al, manuscript in preparation].

A potentially very important property of the CTC regimen is that it causes no serious organ toxicity. Although some elevation of liver enzymes was observed, it was minor and transient. There was no indication of veno-occlusive disease such as has been observed with some other pre-transplantation regimens. The potential occurrence of hearing loss, neurotoxicity and renal toxicity were of particular concern with a high-dose carboplatin based regimen. These toxicities were, however, significant in only one patient (patient 10), who received CTC in full dose despite a preexistent cisplatin-related renal function impairment with a creatinine clearance of 56 ml/min. It is reasonable to assume that the toxicity was enhanced by the very high AUC that may have been caused by carboplatin [15]. Although most of the toxicity was readily reversible, it would probably be advisable to adjust the carboplatin dosage in future studies.

CTC incorporates three alkylating agents that have major activity as single agents in a wide variety of solid tumors. The high dose intensity of carboplatin may be very important in the salvage treatment of germ cell tumors, but could also be advantageous in breast cancer in which carboplatin was recently shown to be an active agent as well [16]. The next step in the exploitation of the dose-response concept is clearly the development of double or even triple transplantation programs. In this way even higher dose intensities should be achievable, possibly resulting in long-term remission of solid tumors that cannot be cured by conventional therapy. Preliminary data on a double autologous bone marrow transplantation program employing cyclophosphamide and carboplatin in doses comparable to those in this study have recently been presented [17], suggesting that these programs are feasible. We believe that the CTC regimen, combined with autologous peripheral stem cell support, is well-suited for repeated use in such a program. Whether or not multiple administrations of CTC are associated with increased organ toxicity is currently the subject of further study.

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Book review

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Eicosanoids and other bioactive lipids in cancer and radiation injury. K. V. Honn, L. J. Marnett, S. Nigam et al. (eds). Kluwer Academic Publishers, Boston/Dordrecht/London, 1991. 544 pp, $ 125.00, £ 82.75, Dfl. 280.00.

The universal desire to decrease radiation and chemotherapy-induced injuries certainly provided the incentive for this review on interactive mechanisms between bioactive lipids and cancer physiopathology. It comprises the proceedings of the 'First International Conference on Eicosanoids and other Bioactive Lipids' which was held in Detroit in 1989.

Briefly, the scope of this review is an assessment of the diverse roles played by these substances in biological phenomena such as the participation of lipid oxidation in carcinogenic pathways, modulation of tumor growth or tissue injury, and protection by or enhancement of cancer therapy. The first part of the book is dedicated to studies of the role of bioactive lipids in carcinogenesis and radiation injury in a framework of in vitro assays. Particular emphasis is placed on both physiopathological aspects, namely, interactions with tumor growth, and metastases and treatment modulation such as the potential radioprotective role of eicosanoids.

The latter part of the book presents interesting data on the clinical implications of these interactions, notably inhibition of prostaglandin production in malignant tumors, and clinical anticancer effects of substances capable of inhibiting this prostaglandin activity. The paradoxical roles of eicosanoids (stimulation/inhibition of injury processes) are the primary subjects of the investigations reviewed in this book. It will be of great interest to both researchers and clinicians.

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