Hyperfractionated Cyclophosphamide with High-Doses of Arabinosylcytosine and Methotrexate (HyperCHiDAM Verona 897)

An Intensive and Effective Regimen for Patients with Aggressive, Refractory or Recurrent Non-Hodgkin Lymphomas after Anthracycline-Containing Regimens

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Received November 30, 2004; revision received February 22, 2005; accepted March 9, 2005.

BACKGROUND. Patients who have aggressive, refractory or recurrent non-Hodgkin lymphomas (NHLs) that are refractory to first-line anthracycline-containing regimens (ACRs) have a dismal outcome. Achieving complete remission (CR) is essential for a favorable outcome. To improve the CR rate in these patients, the authors designed a new protocol that contained hyperfractionated cyclophosphamide (CTX), high-dose arabinosylcytosine (HiDAC), and high-dose methotrexate (MTX) delivered sequentially in the same cycle and followed by the administration of granulocyte-colony stimulating factor (G-CSF) (HyperCHiDAM Verona 897).

METHODS. Between February 1998 and May 2002, 28 consecutive adult patients (median age, 44 years) with aggressive NHL (B-lineage in 21%, T-lineage in 7%, and Ki-67 percentage $>$ 50 in 82%) were entered on the protocol after they had failed on ACRs (15 patients with refractory disease, 6 patients with stable disease, 5 patients with recurrent disease, and 2 patients in partial remission). Patients characteristics were as follows: Twenty-two patients had Stage III–IV NHL (78.6%), 19 patients had B symptoms (67.8%), 22 patients had extranodal disease (78.6%), 12 patients had bulky mass (42.8%), 18 patients elevated lactate dehydrogenase levels (66%), and 8 patients had high-intermediate/high International Prognostic Index scores (64.3%). Patients received hyperfractionated CTX (300 mg/m^2) and HiDAC (2 g/m^2) every 12 hours on Days 2–4 and received high-dose MTX (400 mg/m^2 bolus plus 1600 mg/m^2 as a 24-hour continuous infusion on Day 1 with folinic rescue), followed by G-CSF. Subsequently, 15 patients underwent autologous stem cell transplantation (SCT), and 4 patients underwent allogeneic SCT.

RESULTS. A CR was achieved by 18 of 28 patients (64.3%), a partial remission was achieved by 6 patients (21.4%), 4 patients were nonresponders or had progressive disease (14.3%), and there was 1 early toxic death (3.5%). Two of 18 patients developed recurrent disease (11.1%). The median follow-up for all patients was 35 months (range, from 2 months to $\geq$ 74 months). Among the patients who achieved a continuous CR, the median follow-up was 48 months (range, from $\geq$ 32 months to $\geq$ 73 months). At the time of the current report, 13 of 28 patients (46.42%) were event-free.

CONCLUSIONS. HyperCHiDAM Verona 897 was an effective regimen for patients with aggressive NHL who failed on ACRs, and it allowed patients to undergo subsequent SCT. ***Cancer* 2005;104:555–60.** © *2005 American Cancer Society.*

KEYWORDS: non-Hodgkin lymphoma, recurrence, refractory, chemotherapy.

In most patients with aggressive non-Hodgkin lymphomas (NHLs), current regimens remain unsatisfactory because of the large proportion of treatment failures, with $<$ 50% of patients ultimately achieving a cure. Failures are due either to a lack of response to

DOI 10.1002/cncr.21150
Published online 15 June 2005 in Wiley InterScience (www.interscience.wiley.com).

first-line regimens or to disease recurrence. In patients with refractory or recurrent NHLs, various second-line regimens have been proposed, usually followed by autologous or allogeneic stem cell transplantation (SCT).[1–5] Nonetheless, despite the advances obtained with second-line, high-dose chemotherapy (CT), the achievement of complete remission (CR) in patients with these lymphomas remains a major challenge and a sine qua non conditio to subsequently successful SCT. The long-term event-free survival (EFS) rate currently obtained with the most used second-line regimens reported in the literature ranges roughly between 10% and 38%.[1–7]

In an attempt to improve the CR rate in patients with recurrent or primary refractory, aggressive NHLs after failure on anthracycline-containing regimens (ACRs), we designed new protocol with hyperfractionated cyclophosphamide (CTX), high-dose arabinosylcytosine (HiDAC), and high-dose methotrexate (MTX) delivered sequentially in the same cycle and followed by the administration of granulocyte-colony stimulating factor (G-CSF) (the "HyperCHiDAM Verona 897" protocol). In a short period, this protocol concentrates three chemotherapeutic agents with proven effectiveness in the treatment of aggressive lymphomas. Arabinosylcytosine (ARA-C) and MTX usually are not used in conventional first-line regimens, whereas CTX is employed in this new regimen with a different hyperfractionated schedule, which is known to be very active in rapidly growing lymphomas and offers several advantages (hepatic self-induction of the active metabolite 4-hydroxylophosphamide, decreased renal elimination, and a better therapeutic index).[8]

MATERIALS AND METHODS

Patients

Between February 1998 and May 2002, 28 consecutive adult patients (19 males and 9 females; median age, 44 years; range, 19–59 years) were entered on the HyperCHiDAM Verona 897 protocol. Inclusion criteria were high-grade lymphomas or mantle cell lymphomas that were refractory or that recurred after ACRs and age $\leq$ 60 years. Exclusion criteria were positive human immunodeficiency virus (HIV) serology or severe ongoing infections.

Patients' characteristics are summarized in Table 1. All 28 patients had previously received at least a first-line ACR (intensified CTX, etoposide, vincristine, and prednisone[9] MegaCEOP in 13 patients; combined etoposide, adriamycin, CTX, vincristine, and prednisone with bleomycin (VACOP-B) in 10 patients; combined CTX, doxorubicin, vincristine, and prednisone (CHOP) in 4 patients; and other combinations in 1 patient. Nine patients (32%) received $>$ 1 line of CT.

TABLE 1
Patients' Characteristics

Characteristic	No. of patients (%)
Age (yrs)	
Median	44
Range	19–59
Male:female ratio	19/9
Stage III–IV	22/28 (78.6)
B symptoms	19/28 (67.8)
Extranodal disease	22/28 (78.6)
Bone marrow involvement	13/28 (46.4)
Bulky disease (all abdominal)	12/28 (42.8)
Increased LDH serum levels	16/24 (66.6)[a]
Ki-67 $>$ 50%	23/28 (82%)
IPI high intermediate/high	18/28 (64.3)
Primary refractory (induction failure)	15/28 (53.6)
Stable disease	6
Recurrence	5
Partial remission	2

LDH: lactate dehydrogenase; IPI: International Prognostic Index.
[a] Evaluable patients.

The histologic diagnosis was diffuse large B-cell lymphoma (DLBCL) in 13 patients, primary mediastinal large B-cell lymphoma (PMLBCL) in 5 patients, mantle cell lymphoma (MCL) in 3 patients, T-anaplastic large cell lymphoma (T-ALCL) in 5 patients (anaplastic lymphoma kinase [ALK]-negative in 3 patients), and peripheral T cell lymphoma-unspecified [PTCL-U] in 2 patients). The disease status before HyperCHiDAM was no response/progressive disease (NR/PD) in 15 patients, stable disease (i.e., with a response rate $<$ 50%) in 6 patients, recurrent disease in 5 patients, and a partial response (PR) in 2 patients (both with advanced disease and bulky masses that were reduced by 50% after first-line therapy).

Protocol

Before CT, after informed consent was obtained, patients received hydration (3000 ml/m^2 every 24 hours) with bicarbonate and furosemide administered intravenously (IV) to maintain diuresis $>$ 100 mL per hour and oral allopurinol or IV urycase in patients with persistent hyperuricemia. Therapy was started after the urinary pH was $>$ 7.0. Patients received MTX IV (400 mg/m^2 bolus and 1600 mg/m^2 as a 24-hour continuous infusion on Day 1), Ara-C (2 g/m^2 IV every 12 hours on Days 2–4), and CTX (300 mg/m^2 IV every 12 hours on Days 2–4) (Fig. 1).

MTX serum levels were monitored at 0 hours, 24 hours, 42 hours, 48 hours, 72 hours after the end of MTX infusion. Leucovorin rescue IV was started 42

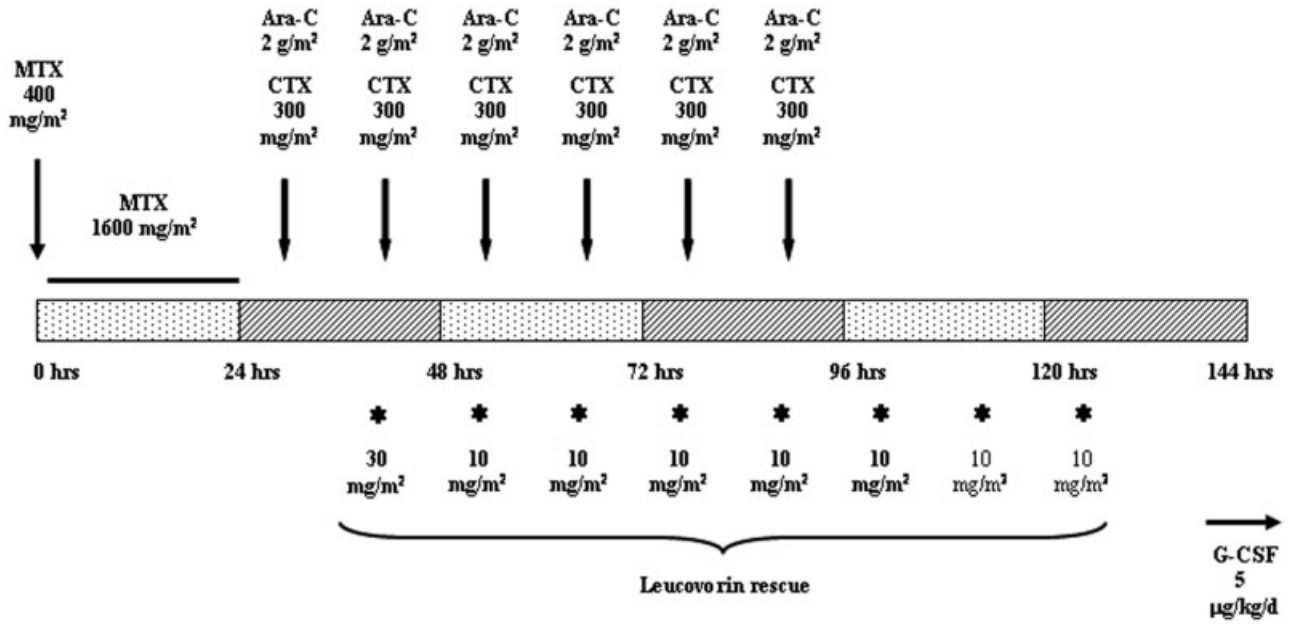

FIGURE 1. This chart illustrates the HyperCHiDAM Verona 897 protocol that contained hyperfractionated cyclophosphamide (CTX), high-dose arabinosylcytosine (Ara-C), and high-dose methotrexate (MTX) delivered sequentially in the same cycle followed by granulocyte-colony stimulating factor (G-CSF) administration.

hours after the beginning of MTX at a dose of 30 mg/m^2 followed by 10 mg/m^2 every 6 hours for a total of 6 doses; after this, it was continued only if the MTX serum level was $>$ 0.1 μMol/L. G-CSF (5 μg/kg per day) was started 48 hours after the last dose of Ara-C/CTX and was continued until the polymorphonuclear (PMN) cell count was $>$ 1000/μL for 2 consecutive days.

It was planned that patients would receive two cycles of HyperCHiDAM before SCT, with the second cycle delivered at the time of hematologic recovery. After patients achieved a response, they underwent autologous or allogeneic SCT (when available, a human leukocyte antigen [HLA]-matched sibling donor). Patients who previously had developed severe major infections were excluded from both of these procedures.

After they completed CT, patients were monitored regularly every month in the first 6 months and every 3 months thereafter. The long follow-up allowed us to confirm the achievement of a continuous CR.

Antiinfectious Prophylaxis

Patients received oral ciprofloxacin (500 mg twice daily), oral amphotericin B and clorexidine (oral cavity, three times daily), oral itraconazole (200 mg per day), and oral trimethoprim-sulfamethoxazole (TMP/SMZ) (1 tablet 3 $\times$ per week). Prophylactic antibiotics were administered before starting CT until the PMN cell count was $>$ 1000/μL for at least 2 consecutive days.

After the detection of cytomegalovirus (CMV) antigenemia, serum pp65 levels were measured systematically every week (twice per week in patients with fever). When they were positive for CMV, patients received gancyclovir (5 mg/kg IV every 12 hours) in addition to antibacterial and antifungal prophylaxis. Patients who had hypo-γ-globulinemia (immunoglobulin G [IgG] $<$ 600 mg/dL) received Ig (0.4 g/kg IV on Day 1 and 0.2 g/kg IV on Day 2) every 21 days.

Statistics

Criteria used to establish a CR were those used commonly based on the normalization of the previously positive findings (through computed tomography scans, bone marrow biopsies, etc.). Event-free survival (EFS) was defined as the interval between the end of treatment (HyperCHiDAM Verona 897) and the first documented evidence of PD, or recurrence, or death from any cause. Progression-free survival (PFS) was defined as the interval between the end of treatment (HyperCHiDAM Verona 897) and the first documented evidence of PD or disease recurrence; patients who died of causes unrelated to lymphoma were censored at the time of death. Overall survival, EFS, and PFS were calculated according to the Kaplan–Meier method.

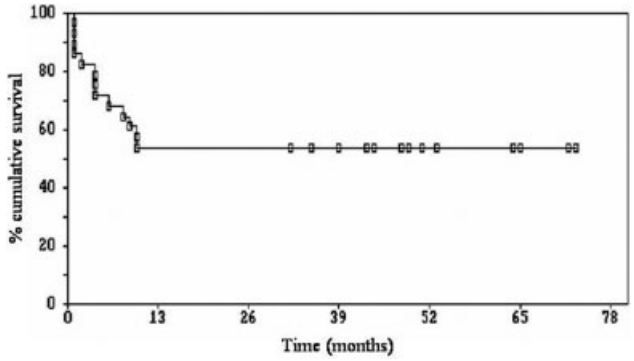

FIGURE 2. This progression-free survival curve shows a plateau after 12 months.

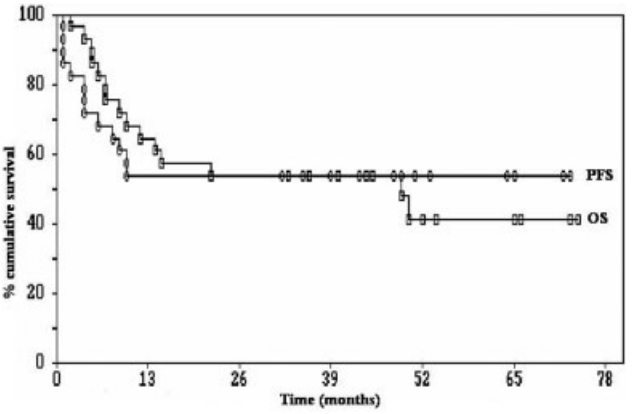

FIGURE 3. These curves illustrate progression-free and overall survival.

RESULTS

All 28 patients were evaluable. Overall, 51 courses of HyperCHiDAM were delivered. Seven patients received 1 course only (1 patient due to an early toxic death after the first cycle, 4 patients due to PD, 2 patients because they underwent SCT soon [autologous SCT in 1 patient, allogeneic SCT in 1 patient] after they achieved a CR). All remaining patients received two courses of CT, with the exception of two patients who underwent three courses because they were judged unsuitable or were waiting for SCT, respectively. Overall, 18 of 28 patients achieved a CR (64.3%), 6 patients achieved a PR, and 4 patients had NR/PD.

Among the 18 patients who achieved a CR, 2 patients developed recurrent disease, 1 patient died early of toxic death, and 2 patients died late (after autologous SCT) of congestive cardiomyopathy and lung toxicity, respectively. The two recurrences were observed after 7 months and 9 months, respectively. Thus, 15 of 28 patients (53.57%) remained progression free (Fig. 2).

Because 1 patient died after 47 months (from a recurrent, preexisting breast carcinoma) and 1 patient died after 48 months (from myelodysplastic syndrome), at the time of this writing, 13 of 28 patients (46.42%) remained event-free. Overall, there were 13 deaths that occurred after a median of 6.5 months after HyperCHiDAM (range, 1.5–12.0 months). The causes of death related to lymphoma were early toxic death (1 patient), PD or recurrent disease (10 patients), and lung and cardiac toxicity after autologous SCT (2 patients). Overall survival and PFS curves are shown in Figure 3.

Among 24 patients who responded to HyperCHiDAM, 15 patients underwent autologous SCT, and 4 patients underwent allogeneic SCT (2 standard SCT procedures and 2 nonmyeloablative SCT procedures).

TABLE 2
Therapeutic Results According to Status of Disease Before Hyperfractionated Cyclophosphamide, High-Dose Arabinosylcytosine, and High-Dose Methotrexate Delivered Sequentially in the Same Cycle Followed by Granulocyte-Colony Stimulating Factor Administration

Status	No. of patients	PFS (%)
Progression, refractory disease	15	10/15 (66.6)
Stable disease	6	3/6 (50.0)
Partial remission	2	1/2 (50.0)
Recurrence	5	1/5 (20.0)

PFS: progression-free survival.

Among 18 patients who achieved a CR, 16 patients underwent SCT (either autologous or allogeneic), and 2 patients were not deemed suitable for SCT due to preexisting breast carcinoma and a poor performance status, respectively. Among six patients who achieved a PR, three patients underwent SCT, and three patients did not undergo SCT due to progressive disease after PR in 2 patients or mycotic pneumonia in 1 patient. Patient outcomes according to lymphoma status and cell lineage before HyperCHiDAM are reported in Tables 2 and 3, respectively.

Outcome According to the International Prognostic Index

There were no low-risk patients. There were 11 low-to-intermediate risk patients and 17 high/intermediate-to-high risk patients. Eight of 11 patients achieved a CR (72.7%) in the low-to-intermediate risk group compared with 10 of 17 patients (58.8%) in the high/intermediate-to-high risk group (a nonsignificant difference).

TABLE 3
Therapeutic Results According to Lineage Affiliation and Histology

Lineage/histology	No. of patients	CR	PFS (%)
DLBCL	13	10/13	7/13
PMLBCL	5	1/5	1/5
MCL	3	2/3	2/3
B-lineage	21	13/21	10/21 (47.6)
T-ALCL	5	3/5	3/5
PTCL-U	2	2/2	2/2
T-lineage	7	5/7	5/7 (71.4)
Total	28	18/28	15/28 (53.6)

CR: complete response; PFS: progression-free survival; DLBCL: diffuse large B-cell lymphoma; PMLBCL: primary mediastinal large B-cell lymphoma; MCL: mantle cell lymphoma; T-ALCL: T-anaplastic large-cell lymphoma; PTCL-U: peripheral T-cell lymphoma-unspecified.

CD34-Positive Cell Harvest

After HyperCHiDAM (Cycle 2), CD34-positive cells were collected in 15 of 28 patients with a median stem-cell mobilization of 10×10^6/Kg (range, 2.5–31.8 $\times 10^6$/Kg).

Myelotoxicity

The median duration of neutropenia (PMN cells $< 500/\mu L$) was 8 days (range, 4–13 days). Platelet counts were $< 20{,}000/\mu L$ for a median of 7.5 days (range, 2–30 days). The median interval between cycles was 27 days (range, 16–110 days).

Side Effects

Most of the reported side effects were due to infections, including bacteremia in 11 patients, FUO in 9 patients, pneumonia in 4 patients (2 bacterial infections and 2 fungal infections), CMV infections in 6 patients, Herpes Zoster in 2 patients, tuberculosis in 4 patients (lung in 2 patients, bone in 2 patients). Other side effects were oral mucositis in 5 patients, transient cerebellar toxicity in 2 patients, and exfoliative dermatitis in 1 patient.

Long-Term Results

All of the 13 patients who remained alive and free of disease had an event-free duration that exceeded 24 months (median, 48 months; range, from $>$ 32 months to $>$ 73 months). The median follow-up for all patients was 35 months (from 2 months to $>$ 74 months).

DISCUSSION

HyperCHiDAM Verona 897 is an intensive protocol that was designed with the objective of improving the CR rate in patients with primary refractory/recurrent, aggressive NHLs. In the same cycle, it concentrates three chemotherapeutic agents that usually are employed separately.

Patients who have received conventional first-line regimens had not been exposed previously to MTX or ARA-C. In the study regimen, CTX was delivered according to a hyperfractionated schedule with known effectiveness against rapidly growing NHLs.[10]

Compared with single high-dose CTX delivered in other protocols,[9] hyperfractionated CTX is more effective because, by acting repeatedly, it increases the apoptotic rate of rapidly dividing lymphoma cells. ARA-C and MTX are S-phase drugs that are particularly effective against aggressive lymphomas characterized by an elevated growth fraction, which describes the majority of lymphomas in this series. In addition, high-dose MTX and high-dose ARA-C reach high tissue levels and are particularly suitable in patients with extranodal disease, including central nervous system involvement, which occurs frequently (82% in our series) in patients with refractory/recurrent lymphomas.

The most important finding from our experience is that HyperCHiDAM achieved a CR in the majority of patients (64%) who had previously failed ACRs. It is noteworthy that 72.2% of these patients (46.4% of all patients entered), including 2 patients who did not undergo SCT, currently are event-free after a prolonged follow-up. Because the patients developed recurrences early, and because the median follow-up for patients who achieved a continuous CR was 38 months (range, from $\geq$ 24 months to $\geq$ 68 months), it is conceivable that most of these patients were cured of their disease. These salutary results were achieved despite very unfavorable clinical characteristics (Table 1).

In the current series, it may be tempting to explain the dismal outcomes observed in patients with recurrent disease who received HyperCHiDAM by indicating the histologic type of lymphoma (4 of 5 patients had PMLBCL, which imply a particularly poor outcome[11]) or the incidence of early disease recurrence.[12] Although the numbers of T-cell lymphomas of our series were too small to draw any conclusion, the rates of CR and PFS seemed to show a better trend in patients who had T-lineage lymphomas compared with patients who had B-lineage lymphomas (71.4% vs. 47.6%, respectively; *P* nonsignificant) (Table 3).

After they received HyperCHiDAM, the majority of patients who responded were able to undergo autologous or allogeneic SCT as consolidation. Autologous SCT was made possible by the good harvest of CD34-positive cells after HiDAC and high-dose MTX administration. Thus, HyperCHiDAM, in addition to being very active, appears particularly effective for an ade-

quate CD34-positive cell harvest, allowing subsequent transplantation procedures. The myelotoxicity of the study regimen was limited, as demonstrated by the short duration of neutropenia and low platelet counts, and only one early toxic death was observed.

The regimen studied required hospitalization and careful supportive therapy, including the use of G-CSF, surveillance of pp65 protein levels, antiviral preemptive therapy, prophylactic TMP/SMZ, and, occasionally, prophylactic IV human Ig. Infections occurred frequently and were related mostly to a decreased cell-mediated immunity (viral and tubercular infections). It is noteworthy that the prevalence of latent tubercular infection in Italy (10–11 per 100.000 population) may explain the relatively high number of reactivations we observed after HyperCHiDAM administration.

Because it has been confirmed that the sensitivity of CT is the most important prognostic factor for patients with aggressive, refractory or recurrent NHLs,[13,14] it is of utmost importance to rely on an effective regimen before patients undergo SCT. Our preliminary results suggest that HyperCHiDAM fulfills these requirements, allowing an effective response and an adequate CD34-positive cell harvest.

The additive effects provided by anti-CD20 immunotherapy to other regimens in the treatment of patients with DLBCL[15,16] suggest that the addition of rituximab to HyperCHiDAM may improve the CR rate further in patients with these lymphomas. Conversely, the use of alemtuzumab in conjunction with HyperCHiDAM for the treatment of PTCL-U[17] appears to be hazardous given the impaired cell-mediated immunity caused by this regimen.

The salutary results obtained with HyperCHiDAM suggest that it also may be employed as part of intensive, first-line therapy in patients with aggressive high-risk lymphomas (e.g., PTCL-U) in an effort to increase the rates of CR and PFS. Obviously, a larger series of patients and a multicenter study will be needed to confirm our single-institution experience.

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