·Clinical Research·

Efficacy of modified Hyper-CVAD regimen on non-Hodgkin's lymphoma and safety evaluation

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[Abstract] Background and Objective: The efficacy of standard chemotherapy regimen on aggressive non-Hodgkin's lymphoma (NHL) of certain pathologic types is unsatisfied. This study was to evaluate the safety and efficacy of modified Hyper-CVAD regimen on Chinese patients with aggressive NHL. Methods: Clinical records of 31 NHL patients who received modified Hyper-CVAD regimen in Cancer Hospital of Chinese Academy of Medical Sciences from June 2004 to June 2008 were analyzed in terms of toxicity and response. Results: The 31 patients totally received 91 cycles of regimen A and 41 cycles of regimen B with a median of 4 cycles (ranged 1-7 cycles). The major toxicity was myelosuppresion: the occurrence rates of neutropenia of grades Ⅲ-Ⅳ, thrombocytopenia and febrile neutropenia were 49.5%, 3.3% and 12.1% during treatment of regimen A, and were 80.5%, 82.9% and 46.3% during treatment of regimen B. No treatment-related death was observed. The responses were assessable in 26 patients. The total response rate was 80.8%, and 12 patients achieved complete response (46.2%). Conclusion: Modified Hyper-CVAD regimen is a promising regimen for the patients with intermediate and high grade NHL.

Key words: non-Hodgkine's lymphoma, combined chemotherapy, safety, efficacy

Non-Hodgkins lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders. Different treatment strategies and regimens should employed according to pathological types. Chemotherapy is the mainstay for aggressive and highly aggressive NHLs, and CHOP has been established as the first line therapy of aggressive NHL.[1] However, certain pathological types such as mantle cell lymphoma and precursor lymphoblast lymphoma, are less responsive to standard CHOP. Commonly used strategy is to induce remmision with combined intensive chemotherapy in a short period, then consolidate with high-dose chemotherapy and autologous hematopoietic stem cell transplantation. For those with aggressive or highly aggressive NHLs, no standard therapy has been established. We evaluated the safety and efficacy of modified Hyper-CVAD regimen in 31 patients with aggressive or highly aggressive NHLs treated in our hospital from June 2004 to June 2008. The results are reported as follows.

Materials and Methods

Patients. From June 2004 to June 2008, 31 patients with aggressive or highly aggressive NHL were treated with modified Hyper-CVAD regimen in Cancer Hospital of Chinese Academy of Medical Sciences. The pathologic diagnoses of all patients were reviewed in our hospital.. Of the 31 patients, 24 (77.4%) received modified Hyper-CVAD regimen as first line therapy, five (16.1%) as salvage therapy and two (6.5%) as consolidation therapy. Clinical characteristics of the patients are shown in Table 1.

Regimens. Modified Hyper-CVAD regimens comprised alternative regimen A and B. Hyper-CVAD A regimen: 2-hour intravenous infusion of cyclophosphamide (CTX, 300 mg/m^2), repeated every 12 h on days 1-3; intravenous injection of vincristine (VCR, 2 mg) on days 4 and 11; intravenous infusion of epirubicin (EPI, 80 mg/m^2) on day 4; oral administration or intravenous injection of dexamethasone (DXM, 30-40 mg) on days 1-4 and 11-14. The regimen was repeated every 21 days.

Hyper-CVAD B regimen (HD-MTX+Ara-C): 24-hour intravenous infusion of methotrexate (MTX, 1 g/m^2) on day 1; intravenous infusion of cytarabine (Ara-C, 1 g/m^2), repeated every 12 h on days 2 and 3, 21 days for a cycle. Salvage administration of calcium folinate (CF) was given since 12 h after completion of MTX administration, with 50 mg as the dosage for the first 4 intravenous infusions and 15 mg as the dosage for subsequent 8 oral administrations, repeated every 6 h.

The patients received intrathecal injection of 12 mg MTX on day 2 and 100 mg Ara-C on day 7.

If peripheral leucocytes dropped below 2.0×10^9/L or granulocytes below 1.0×10^9/L, daily subcutaneous injections of granulocyte colony stimulating factor (G-CSF) were initiated until the leucocyte count returned normal. Prophylactic antibiotic administration was not used. If severe non-hematological toxicity or persistent grade IV myelosuppresion occurred, the next cycle was delayed or reduced in dosage by 15%-25%.

Hyper-CVAD A and B regimens were alternated. However, if persistent grade IV myelosuppresion or severe liver function impairment occurred, the regimen B was not used. Subsequent treatment such as autologous hematopoietic stem cell transplantation was performed after remission.

Follow-up, evaluation of safety and efficacy and data analysis. All patients were followed up until September 1, 2008. Efficacy evaluation was according to NHL international response criteria, including complete response (CR), complete response uncertain (CRu), partial response (PR), stable disease (SD), progressive disease (PD). Toxicity were assessed according to WHO common toxicity criteria.

Statistics. The primary end points were incidence of toxicity and response rates, and secondary end point ws overall survival. All calculation were performed with the SPSS 11.5 statistical package. Differences in response rates or clinical characteristics among subgroup were analyzed by Fisher exact test. P values less than.05 were considered significant.

Results

Toxicity. Toxicity of all 31 patients were assessable. Myelosuppresion was the most common toxicity. The occurrence rate of grade III-IV neutropenia was 83.9% and that of grade IV neutropenia was 58.1%. The occurrence rate of grade III-IV thrombocytopenia was 58.8%, including 15 cases (48.4%) requiring platelet transfusion. Severe thrombocytopenia was mostly seen during regimen B. The occurrence rates of grades I-II and III-IV anemia were 12.9% and 35.5%, including six cases requiring RBC transfusion. Anemia was common in the late stage of chemotherapy.

Alopecia (100%) and gastrointestinal reactions (93.5%) were the most common non-hematological toxicities. The gastrointestinal reactions were mostly grade I-II, while two cases showed grade III vomiting, both occurred in regimen A, and the symptom was alleviated by palliative therapy without influence on chemotherapy schedules.. Fatigue (22.6%) and neurological toxicity (22.6%) were also commonly seen. One case showed tachycardia. One case presented type I respiratory failure when disease progressed. No treatment related death was observed.

The thirty-one patients had completed 91 cycles of regimen A and 41 cycles of regimen B. Toxicities related to regimen A and B are shown in Table 2. In the 91 cysles of regimen A, the occurrence rate of grade IV neutropenia was 23.1%. The median time of developing severe myelosuppresion was 12 days (6-

Table 1 Clinical characteristics of the 31 patients with aggressive non-Hodgkin's lymphoma (NHL)

Item	Cases	Percentage (%)
Gender		
Male	27	87.1
Female	4	12.9
Age (years)		
≤ 60	30	96.8
> 60	1	3.2
PS (ECOG)		
0–1	24	77.4
2–4	7	22.6
Pathologic subtype		
B-LBL	2	6.5
T-LBL	18	58.1
MCL	5	16.1
PCTL	2	6.5
BL	4	12.9
aa-IPI		
0	8	25.8
1–3	23	74.2
LDH		
Normal	17	54.8
Elevated	14	45.2
Bulky disease		
Yes	17	54.8
No	14	45.2
Extranodal involvement		
No	13	41.9
Yes	18	58.1
Bone marrow involvement		
Yes	7	22.6
no	24	77.4
CNS involvement		
Yes	4	12.9
No	27	87.1
First-line or salvage therapy		
First-line	24	77.4
Salvage	5	16.1
Consolidation	2	6.5
Objective response of the regimen		
CR+CRu	12	46.2
PR	9	34.6
SD+PD	5	19.2

PS, physical status; ECOG, Eastern Cooperative Oncology Group; B-LBL, B-lymphoblastic lymphoma; T-LBL, T-lymphoblastic lymphoma; MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma; BL, Burkitt's lymphoma; aa-IPI, age-adjusted international prognostic index; LDH, lactate dehydrogenase; CNS, central nervous system; CR, complete response; CRu, complete response uncertain; PR, partial response; SD, stable disease; PD, progressive disease. The responses were assessable in 26 patients.

16 days), with a median duration of 2 days (1–9 days). Six patients presented infections that had been confirmed by clinical manifestations and imaging studies during regimen A chemotherapy, including one case of sepsis (drug resistant *staphylococcus epideridis*). Fifteen cycles underwent dose adjustment, and eight cycles delayed with the median delayed time of 6 days (1–16 days). In the 41 cycles of regimen B chemotherapy, the occurrence rate of grade IV neutropenia was 56.1%. The median time of developing severe myelosuppresion was 12 days (6–21 days), with a median duration of 3 days (1–10 days). Four patients presented infection, including one case of sepsis (*Klebsiella pneumonia*). The occurrence rate of grade III–IV thrombocytopenia was 82.9% (34/41) with a median duration of 5 days (1–11 days). There were 26 cycles (63.4%) requiring platelet transfusions. Six cycles underwent dose adjustment, and three cycles delayed with a median delayed time of 2 days (1–7 days). The occurrence rates of grade III–IV neutropenia and thrombocytopenia in the 24 patients receiving modified HyperCVAD as first line therapy were 87.5% and 62.5%. And the occurrence rates of grade III–IV neutropenia and thrombocytopenia in the five patients receiving this regimen as salvage therapy were 80.0% and 80.0%, which were not significantly different from those of first line therapy.

Response. The thirty-one patients had completed 91 cycles of regimen A and 41 cycles of regimen B. The median number of Hyper-CVAD A/B chemotherapy cycles were four (1–7), median number of regimen A and B cycles were three (1–6 cycles) and one (0–3 cycles), respectively. Twenty-six patients were eligible for response assessment.

Of the 26 patients eligible for response assessment, the objective response rate (RR) was 80.8%, including 12 (46.2%) CR and nine (34.6%) PR. A total of 24 (77.4%) patients received Hyper-CVAD A/B as first line therapy, and RR and CR rates of the first line therapy were 86.4% and 54.5%. Of the five patients received this regimen as salvage therapy, four were eligible for response assessment., and only two achieved PR. For those with early stage diseases, RR and CR rates were 90.0% and 80.0%; while RR and CR rates of those with III–IV advanced stage diseases were 70.6% and 23.5%, which was significantly worse than that of early stage patients (P=0.007).

Survival. Of the patients that responded to

chemotherapy, nine cases (including eight with CR and one with PR) underwent high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HDT/AHSCT). Additionally, one patients failed to undergo transplantation because of poor stem cell mobilization. And 14 patients received salvage therapy.

Follow-up rate of the whole group was 87.1% (27/31) with a median follow-up time of 12 months (range, 4-36 months). Up to September 1, 2008, there were nine patients died, three lost follow up, 11 had disease-free survival and eight survived with tumor.

Table 2 Toxicity of modified Hyper-CVAD regimen

Adverse event	Grades 1-2	Grades 3-4
Regimen A (91 cycles)		
Neutropenia	46	45
Thrombocytopenia	6	3
Infections	NA	6
Febrile neutropenia	NA	11
Transaminase elevation	17	1
Bilirubin elevation	8	0
Peripheral neuropathy	7	1
Regimen B (41 cycles)		
Neutropenia	8	33
Thrombocytopenia	7	34
Infections	NA	5
Febrile neutropenia	NA	19
Transaminase elevation	10	0
Bilirubin elevation	4	0
Mucositis	1	1

NA, not applicable.

Discussion

At least 50% patients with aggressive and highly aggressive NHL cannot be cured with first-line CHOP regimen, which remains a challenge for clinicians.[1-3] Hyper-CVAD regimen was designed by professor Murphy from MD Anderson Cancer Center, USA. Several strategies in regimen A are directly against the rapid proliferation of moderate-to-high aggressive NHL,including alternate use of several drugs without cross drug resistance, introduction of intensive fractionated CTX, short-term therapy, shortening treatment interval, CNS prophylaxis, and substituting prednisone with DXM. High dose-MTX and Ara-C are critical components of CNS prophylaxis and treatment, which, in conjunction with prophylactic intrathecal injection, can significantly improve the cure rate. The alternate use of regimen A and B can avoid the development of early-stage drug resistance. MD Anderson Cancer Center treated patients with LBL and Burkitt-like adult acute lymphoblastic leukemia with Hyper-CVAD, and 91% and 81% patients achieved CR, respectively.[4,5] The response rate in MCL was 94%, including 38% patients achieving CR. For those MCL patients aged above 65 who received Hyper-CVAD regimen as first-line therapy, a CR rate of 68% was achieved, which was significantly superior to historical controls.[6] In 2008 NCCN guideline, the Hyper-CVAD was recommended as the first line therapy for highly aggressive NHL such as MCL, LBL, BL and PCTL. Since Hyper-CVAD is a new regimen with severe toxicities, and is recommended only in specific pathological types, controlled studies in homogenous cases are hard to carry out. Therefore, this study enrolled patients with varieties of pathological subtypes. The aim of this small, single center clinical trial is to investigate the safety of modified HyperCVAD in Chinese population, and to preliminary evaluate its efficacy, so as guide further clinical trials.

The prominent problem of Hyper-CVAD regimen is the severe toxicity and the grade IV myelosuppresion was reported 100% in Caucasians, and the incidence of neutropenia-related side effects such as infection ranged from 20% to 30%.[4,7,8] Grade IV thrombocytopenia, as reported, occurred in 100% of the patients receiving regimen B,[9] and 35% of them requiring dose adjustment to complete the regimen.[8] In addition, grade III-IV liver function impairment occured in more than 10% patients.[4] All of these studies were carried out in international renowned centers where the supportive care (including speedy platelet supply) and complication management are much better than those of most Chinese medical centers. Thus, considering the physical condition of Chinese patients and practicing environment of China, our study aimed to achieve a balance between safety and efficacy through modifying the regimen, and to improve the feasibility of clinical application of the regimen. Previous studies have investigated the doses of MTX and Ara-C, and the highest doses reached 8 g/m^2 and 3 g/m^2, respectively. It was found even lower dose could achieve similar response rate.[10,11] Regarding the tolerability of Chinese patients, and there is no

definite evidence that decreasing Ara-C doses will influence its short or long-term efficacy, we adjusted the dose of Ara-C to 1 g/m^2.

Although myelosuppresion remains prominent after dose adjustment, most patients could complete chemotherapy after supportive care, and no treatment related death was observed. Moreover, the incidences of severe myelosuppresion and hepatic function impairment were lower than that reported in literatures,[4,8,9] indicating the improved safety after dose adjustment. The most common toxicities are myelosuppresion and its relevant complications. Prophylactic G-CSF treatment is a component of the regimen in most foreign studies. Weiser et al.[12] investigated the timing of G-CSF administration and concluded that G-CSF initiation on the tenth day of the course would not increase the treatment related risk of infection. In our study, prophylactic antibiotics and G-CSF were not used, instead, G-CSF adminidtration was initiated when the patient presented grade II or above neutropenia, and antibiotics were initiated when febrile neutropenia or infection signs were identified. Median time of grade III-IV neutropenia development was 12 d in our study, and most patients had received G-CSF administration on the tenth day. The incidence of infection and duration of neutropenia were not higher than reported in other studies, and the therapeutic measrue was acceptable to patients financially. There were no significant differences of infection, duration and incidence of severe neutropenia, dose adjustment and time delay between regimen A and B. Severe thrombocytopenia occurred primarily in regimen B, and most patients required platelet transfusion, which remarkably limited the use of regimen B, thus, 31 patients completed only 41 cycles. Because the present study was not a strictly designed prospective study, the small number of regimen B cycles was attributed to various reasons. Besides the toxicity of the regimen and disease progression of part of the patients during regimen A therapy, the limited experiences of this regimen during initial phase, cautious attitude of clinicians and worries of the patients also contribute to the limited use of regimen B. With accumulation of experiences, these problems can be solved. And we will conduct well designed prospective study to evaluate the efficacy and safety of this regimen more accuately in future.

The RR and CR rates of the study were 80.8% and 46.2%, which were higher than those of CHOP regimen.[3,13] However, this is still worse than that reported in literatures, which is likely to be attributed to following reasons: ① Only 77.4% patients received this regimen as first line therapy. RR and CR rates of first line therapy were 86.4% and 54.5%, respectively; and RR rate of salvage therapy was 50.0%, none achieved CR. ② Ara-C dose of adult was 3 g/m^2, which adjusted to 1 g/m^2 for the elderly in foreign literatures. Dose in our study was 1 g/m^2 regardless of patients ages. In addition, some patients did not undergo regimen B due to severe side effects. We are to investigate means to improve compliances by enhancing supportive treatment. ③ Populations enrolled in foreign literatures are Caucasians whose genetic background is different from Chinese population.

The single center study investigated the safety and efficacy of modified Hyper-CVAD in treating aggressive and highly aggressive NHL. The result showed that modified Hyper-CVAD regimen improved the safety, and response rate was higher than CHOP regimen. The long-term outcome remains to be determined. HDT/AHSCT after remission by chemotherapy is a feasible strategy. A prospective study focusing on the efficacy of modified Hyper-CVAD in the treatment of certain types of NHL is carried out in our hospital, and the results of the underway study will help to define the safety, efficacy and feasiblity of wider application of this regimen in Chinese patients.

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