CHOP Regimen for Intermediate Grade Non-Hodgkins Lymphoma at Maharat Nakhon Ratchasima Hospital: Efficacy and Preliminary Outcomes

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Abstract: The non-Hodgkins lymphomas (NHL) are a diverse group of diseases that differ with regard to histologic appearance, age of incidence, sites of involvement, clinical course and response to therapy. The objective of this study was to evaluate the efficacy of the CHOP regimen. The eligibility criteria included (1) patients between the ages of 15 and 60 years (2) biopsy-proven NHL of intermediate grade (3) stage II, III, or IV (4) no prior therapy (5) absence of clinically apparent CNS disease (6) clinically adequate heart and lung function, and adequate kidney function. Treatment consisted of cyclophosphamide 750 mg/m^2, doxorubicin 45 mg/m^2 and vincristine 1.4 mg/m^2 IV on day 1. Prednisolone 60 mg/m^2 orally was administered on day 1 to 7. Courses were repeated every 28 days and evaluation was done after 6 courses of chemotherapy. The results of treatment indicated that CHOP regimen was active with 80% complete remission. The median time to complete remission was 2 months. One-year survival rate was 96.7%. CHOP regimen can be administered safely and the complete response rate support the previous studies using CHOP as the standard treatment.

บทคัดย่อ : **ประสิทธิภาพและผลของการรักษาผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองชนิดรุนแรงปานกลางด้วย CHOP regimen ที่โรงพยาบาลมหาราชนครราชสีมา**

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โรค non-Hodgkins lymphoma (NHL) เป็นโรคที่พบแพร่หลายทั้งในและต่างประเทศ ผู้รายงานได้ทำการศึกษาผู้ป่วย NHL intermediate grade อายุตั้งแต่ 15-60 ปี ที่มารับการรักษาที่โรงพยาบาลมหาราชนครราชสีมา ในระหว่างเดือนตุลาคม 2538 ถึงเดือนมีนาคม 2540 จำนวนทั้งสิ้น 30 ราย โดยผู้ป่วยทุกรายมีเกณฑ์ดังต่อไปนี้ คือ (1) มีผลชิ้นเนื้อพิสูจน์ว่าเป็น NHL intermediate grade (2) มี clinical stage II, III หรือ IV (3) ต้องไม่เคยได้รับยาเคมีบำบัดมาก่อน (4) ไม่มี clinical ของ CNS disease (5) มีการทำงานของหัวใจ ปอด และไตปกติ ผู้ป่วยทุกรายได้รับการรักษาด้วย CHOP regimen ซึ่งประกอบด้วย cyclophosphamide 750 mg/m^2, doxorubicin 45 mg/m^2, vincristine 1.4 mg/m^2 ทั้งหมดฉีดเข้าหลอดเลือดดำในวันที่ 1 และ prednisolone 60 mg/m^2 กินวันที่ 1-7 โดยให้ยาเคมีบำบัดทุก 28 วัน และประเมินผลหลังจากได้ยาครบ 6 ครั้ง ผลที่ได้จากการศึกษาพบว่า ผู้ป่วยจำนวน 24 ราย จากทั้งหมด 30 รายได้ complete remission (CR) คิดเป็นร้อยละ 80 และมี median time to CR ประมาณ 2 เดือน อัตรารอดชีวิตที่ 1 ปี เท่ากับร้อยละ 96.7

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The non-Hodgkins lymphomas (NHL) are a heterogeneous group of malignancies with diverse natural histories and clinical presentations. In developed nations such as the United States, the age-adjusted incidence of NHL has steadily increased over the last few decades which now accounts for 4% of all cancer death and 4% of all cancer incidence.[1] In Thailand, NHL is the second most common hematologic malignancy and its incidence has continued to increase for at least 20 years. In recent years, combination chemotherapy has made a major impart in the treatment of patients with intermediate and high grade lymphomas. These disorders, which were previously rapidly fatal in almost all patients, can now be successfully treated in the majority of patients. High complete remission rates and long term disease free survival have been reported with several different combination chemotherapy regimens. The most active chemotherapeutic agents for treating the aggressive lymphomas are cyclophosphamide and doxorubicin such as CHOP regimen. Initial studies using "first-generation" CHOP regimen produced good therapeutic results with complete response rates of 70% to 80% depended on clinical stages and various factors such as performance status, histologic features, etc.

The distribution of histologic features of NHL in Thailand is quite different from that reported from Western countries. It has been documented that diffuse type of NHL has significantly greater proportion than nodular type in Thailand with diffuse to nodular type ratio approximately 19-32 to 1.[2,3] In contrast, many published data from Western countries have reported that the proportion of nodular type of NHL is predominant with ratio of diffuse to nodular type approximately 2-4 to 1.[4,5] With regard to this major difference in histopathologic subtype, the results of treatment may be somewhat effected since nodular type of NHL has been considered to be less aggressive and has better outcomes.

The objective of this study was to evaluate the efficacy of CHOP regimen in the treatment of intermediate grade NHL which is aggressive and also frequently found in Thailand. This study assessed the complete response rate, the median time to complete remission, one-year survival rate and toxicity. The study was based on patients diagnosed to be intermediate grade NHL treated at Maharat Nakhon Ratchasima Hospital between October 1995 and March 1997.

Patients and Methods

Between October 1995 and March 1997, patients diagnosed to be intermediate grade NHL treated at Maharat Nakhon Ratchasima Hospital were enrolled in this study. The eligibility criteria included (1) patients with ages between 15 and 60 years (2) biopsy-proven non-Hodgkins lymphoma of intermediate grade using National Cancer Institute (NCI) working formulation[6] (3) stage II, III, or IV disease according to the Ann Arbor system[7] (4) no prior treatment (5) absence of clinically apparent CNS disease (6) clinically adequate heart and lung function and adequate kidney function as measured by a creatinine clearance of at least 60 ml/min. Patients were required to evaluate before treatment as evidenced by history taking, complete physical examination, evaluation of performance status using Eastern Cooperative Oncology Group scale, chest film, bone marrow examination and/or biopsy, abdominal computerized tomography and/or

ultrasonography, laboratory profiles included liver function test, CBC, serum LDH, ESR, BUN, creatinine and uric acid.

Treatment consisted of cyclophosphamide 750 mg/m^2 IV on day 1; doxorubicin 45 mg/m^2 IV on day 1; vincristine 1.4 mg/m^2 IV on day 1; and prednisolone 60 mg/m^2 orally was administered on day 1 to 7. Courses were repeated every 28 days. After 6 courses of chemotherapy, patients underwent systemic restaging for occult disease. If a documented complete remission was achieved after 6 courses of induction treatment, patients were then assigned to receive another 6 courses of the same treatment. Patients who experienced only partial response or stable disease after the first 6 courses of treatment were assigned to receive additional treatments with radiation or debulking surgery then follow by another 6 courses of the same regimen. Patients who failed to achieve at least stable disease after 6 courses of induction treatment were taken off study.

Definition of Response

Standard criteria were used to define a nonsurgically documented response to treatment in patients with non-measurable disease.[8]

Complete response (CR) – complete disappearance of all known disease for at least four weeks.

Partial respone (PR) – estimated decrease in tumor size of 50% or more for at least four weeks.

Stable disease (SD) – estimated decrease of less than 50% and lesions with estimated increase of less than 25%.

Progressive disease (PD) – appearance of any new lesions not previously identified or estimated increase of 25% or more in existent lesions.

Results

Between October 1995 and March 1997, 57 patients diagnosed to be intermediate grade NHL were treated at Maharat Nakhon Ratchasima Hospital. Fifteen patients subsequently were found to be ineligible, leaving 42 patients evaluable for survival. Data are not available to assess response in twelve patients, leaving 30 patients evaluable for response. All ineligible patients were over 60 years of age. Patient characteristics are summarized in Table 1. Importantly, 50% of the patients had stage II disease and the median age was 46 years. The majority of patients had performance status 0 or 1. The most common histology was diffuse large cell 63.3% with 30% diffuse mixed small and large cell and 6.7% diffuse small cleaved subtype. Constitutional B symptoms and signs, characterized by weight loss, fever and night sweats occurred in 16.7% of patients.

Table 1 Clinical characteristics of 30 patients

	No.(%)
Sex	
Male	21 (70.0)
Female	9 (30.0)
Performance status ECOG	
0–1	26 (86.7)
2	4 (13.3)
Histological classification	
Diffuse small cleaved	2 (6.7)
Diffuse mixed	9 (30.0)
Diffuse large cell	19 (63.3)

Table 1 (cont.) Clinical characteristics of 30 patients

	No.(%)
Stage	
II	15 (50.0)
III	7 (23.3)
IV	8 (26.7)
Systemic symptoms	
A	25 (83.3)
B	5 (16.7)
Bone marrow involvement	
No	24 (80.0)
Yes	6 (20.0)
Liver involvement	
No	28 (93.3)
Yes	2 (6.7)

Remission rates by treatment are shown in Table 2. The overall rate of documented CR for the CHOP regimen was 80%. Following 6 courses of induction treatment, the overall response rate (CR+PR) was strikingly 93.3%. Two patients (6.7%) remained in stable disease. None of these 30 patients was detected to have progressive disease while receiving CHOP chemotherapy. Median time to complete remission was 2 months. Twenty-nine patients (96.7%) survived 1 year from the time of initiation of chemotherapy. One patient developed pneumonia and septicemia during the 4th course of chemotherapy and finally died.

Table 2 Results of treatment of 30 patients

	No.(%)
Complete remission (CR)	24 (80.0)
Partial remission (PR)	4 (13.3)
Stable disease (SD)	2 (6.7)
Progressive disease (PD)	–

Toxicity of treatment with CHOP regimen was evaluated for 30 patients. Table 3 summarizes the toxicity experienced during the entire treatment courses. Nausea and vomiting were more common side effects of treatment with the CHOP regimen due to the rapid intravenous administration of large doses of doxorubicin and cyclophosphamide. The majority of patients had toxicities that were generally mild and tolerable. Life-threatening or fatal infection was seen in 3.3% of patients and leukopenia in 16.7%.

Table 3 Toxicity

	No.(%)
Nausea, vomiting	
mild	21 (70.0)
moderate	3 (10.0)
Mucositis	–
Dyspepsia	5 (16.7)
Paresthesia	7 (23.3)
Fatigue	13 (43.3)
Weight loss	2 (6.7)
Anorexia	1 (3.3)
Mild infection	4 (13.3)
Fatal infection	1 (3.3)
Leukopenia	5 (16.7)
Granulocyte < 500 mm^3	–

Discussion

CHOP regimen has been widely used as active and standard chemotherapeutic combination for treatment of NHL patients for over two decades. The efficacy of CHOP regimen has been well established for treating early and advanced stage diseases. In recent years, a number of investigators have demonstrated that NHL patients treated with CHOP regimen obtain CR in approximately 50-80%.[3,9,10,11] As shown in this study, CHOP regimen resulted in 80% CR which was similar to previous reports. The other response treatment programs such as methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisolone and bleomycin (MACOP-B) achieves CR in about 80% of patients.[12] However, analysis of toxicity indicates that the majority of patients experienced toxicity that was severe (30%) or life-threatening (29%).[10] ProMACE-CytaBOM, the regimen consisted of cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate with leucovorin rescue, has produced a significantly superior complete response rate but with high treatment-related deaths (5%).[13,10] Of particular significance, the CR rates achieved with MACOP-B and ProMACE-CytaBOM were no better statistically than that achieved with CHOP regimen. Whereas the toxicity of CHOP regimen was generally mild and tolerable, the side effects and toxicity of both MACOP-B and ProMACE-CytaBOM were significant and fatal. For these reasons, CHOP regimen has been using as the standard, first-line treatment for NHL patients. Depending on this study, the median time to complete remission of 24 documented CR patients was 2 months. However, this median time to complete remission appeared to be shorter than that of the initial reports using the same regimen, median time 13 weeks.[14]

The increase in therapeutic results have been a subtle and complex interaction of many factors such as tumor characteristics, host tolerance and drug dosing. At one time or another, multiple factors, including advanced stage, the number of extranodal sites, bone marrow involvement, central nervous system and kidney involvement, bulky lymphadenopathy and elevated serum lactic dehydrogenase (LDH) levels have all been considered to be poor prognostic factors.[15] For the most part, these factors may have simply reflected variable expressions of the volume and/or turnover of the disease. Of the 6 patients who did not achieve CR, all were demonstrated to have bulky tumor. When the tumor burden is greatest, few cells actually in cycle and vulnerable of chemotherapeutic attack. Therefore, to achieve the maximal probability of cure, the total tumor burden should be reduced as much as possible by any means. At the time of assessment, the additional treatments including radiation and debulking surgery were applied to these 6 patients to increase the CR rate and minimize local recurrence. However, in this study, the number of patients was rather small that important prognostic determinants could have been overlooked.

Of the 30 patients treated with CHOP regimen, only 1 patient died as a consequence of pneumonia and septicemia. One year survival in this study was 96.7% which was significantly better when compared with the results from the previous reports. In some categories, the results demonstrated one-year survival rate of 53%.[14] However, some

studies revealed significantly low one-year survival such as that from Ramathibodi Hospital which was only 38%.[16] In fact, the difference in survival of the NHL patients was affected by multiple factors that reflected in a poorer survival such as elderly patients, stage of disease, patient variables including coexistent disease, performance status and details of treatment. Thus, it is difficult to compare treatment outcomes in different series of patients. Of note, all patients older than 60 years were excluded from this study. As usual, older patients are less able to tolerate intense chemotherapy. Response rates are lower, relapse rates are higher and treatment morbidity is greater in the elderly.[17,18] Therefore, these ineligible patients could result in both high CR rate and high one-year survival rate. Furthermore, patients in this study all had good performance status (0-2) and the vast majority of patients had no systemic symptoms. As was demonstrated, these factors which were considered to be good prognostic factors influenced better survival outcomes.

In summary, CHOP regimen is active drug regimen for patients with intermediate grade NHL. This regimen can be administered safely with mild and tolerable toxicity. This study resulted in high CR rate that support the initial trials considering CHOP as the standard and initial treatment for NHL patients. In general, the results obtained do not appear to be much different than other reports in the literature. Patients without poor prognostic factors generally have over a 90% chance of obtaining a complete response. However, for certain poor prognostic subsets, such as bulky tumor, etc., the additional treatments including radiation and debulking surgery as well as second-line chemotherapy should be considered. Based on this study, the poor prognostic factors could not be determined due to the small number of patients. Long term follow up will be required to discern any potential benefit as well as toxicity of the adriamycin containing combination, and to define the long-term overall survival rate. Finally, the use of more aggressive and more toxic therapies in patients likely to be cured with conventional combination chemotherapy regimens should be carefully thought.

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