Chemotherapy of Advanced Hodgkin's Disease : A Long Term Follow-up at Paik Hospital

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Background : There have been few reports regarding the long term effects of chemotherapy on advanced Hodgkin's disease in Korea. We reviewed medical records of Hodgkin's disease patients diagnosed in 1979-91 to study long term results of chemotherapy.

Methods : Localized disease amenable to radiation therapy and advanced disease in violation of our treatment protocol were excluded from the evaluation of 56 patients to have 14 patients left (10 men and 4 women, ages 8-67 with a median of 43). Our regimens consisted of variants of standard MOPP, BCVPP, or ABVD regimen with half to two thirds of dose intensity.

Results : A total of 117 courses of chemotherapy (mean 8.4, range 6-12) was administered for remission induction. Two patients achieved partial remission. Twelve patients (86%) attained complete remission (CR) after a mean of 4.5 cycles of chemotherapy (range 2-9). The duration of CR ranged 8-107 months (median 18). Eight patients (67%) had relapse at a median of 12 months. A total of 64 courses of salvage treatment (mean 9.1, range 6-13) different from induction regimens induced a second complete remission (CR2) in 6 of 7 (86%) patients. Seven patients (50%) were alive disease free at 25-173 months (median 53), 4 in continuous CR (duration 22⁺, 42⁺, 46⁺, 58⁺ months each), and 3 in CR2 (duration 7⁺, 46⁺, 51⁺ months each). The overall survival duration ranged 8-173 months at a median follow-up period of 47 months.

Conclusions : Although 7 of 14 patients (50%) have been alive disease free at 25-173 months (median 53), longer treatment courses for remission induction, higher relapse rate, and high rate of CR2 indicated our regimens should be revised to be faithful to full dose intensity.

KEY WORDS : Hodgkin's disease · Chemotherapy · Survival duration.

Introduction

Since a half chance curability of advanced Hodg-

kin's disease was demonstrated with drug treatment alone^{1,2)}, the MOPP (mechlorethamine, vincristine, procarbazine and prednisone) polychemotherapy for Hodgkin's disease has been a prototype of successful drug combination in the practice of medical oncology. Radiation therapy also has shown a curative potential in localized Hodgkin's disease. Although the treatment strategy for the disease has been evol-

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ving, the original MOPP combination chemotherapy still remains solid as a reference to which newer multi-agent chemotherapies could be compared.

Current chemotherapy for Hodgkin's disease is still on the way to find an optimal treatment. NCI (National Cancer Institute) group in the United States has emphasized dose intensity of MOPP and other standard regimens³⁾. Milan, CALGB (Cancer and Leukemia Group B), Vancouver, and other groups⁴⁾ adapting the Goldie and Coldman hypothesis⁵⁾ propose to use seven or eight drugs from the very start in an attempt to circumvent drug resistance by alternating or hybridizing classical MOPP with presumably non-cross resistant ABVD (doxorubicin, bleomycin, vinblastin and dacarbazine)⁶⁾ devised as a salvage regimen for MOPP failure.

We reviewed our experience for a 13 year period in Hodgkin's disease treated with our own versions of several effective polychemotherapies and sometimes with focal radiotherapy. The chemotherapy regimens were derived from MOPP¹⁾, ABVD⁶⁾, or BC-VPP⁷⁾ (BCNU, cyclophosphamide, vincristine, pro-

carbazine, and prednisone). The purpose of the review was to measure the survival durations of the patients treated with chemotherapy to assess the long term therapeutic effects of our own institutional regimens.

Patients and Methods

Fifty six Hodgkin's disease patients were seen in our institute during the 13 year period from January 1979 through December 1991. Medical records of the 56 patients were reviewed to extract response rate to chemotherapy and survival durations.

The histologic diagnosis was based on Rappaport classification, the staging on Ann Arbor system. Localized disease amenable to radiation therapy, prior chemotherapy at other institutions, suboptimal courses of chemotherapy, and referral to other institutions excluded 42 patients from the evaluation to have 14 patients left. Patients characteristics and methods of chemotherapy were as tables 1 and 2. The patients consisted of 10 men and 4 women at their ages 8-

Table 1. Patients characteristics

Male to Female ratio :	10 to 4
Ages on Diagnosis :	8-69 with a median of 43
Histology :	Nodular Sclerosis in 5, Mixed Cellularity in 6, Lymphocyte Depletion in 3.
Stage :	III in 6, IV in 8, with B symptoms in 11.

Table 2. Chemotherapy regimens

C-MOPP	: Vincristine 1.4mg/sq m on day 1, Cyclophosphamide 250mg/sq m on days 2-4, Procarbazine 90mg/sq m on days 1-10, Prednisone 40mg/sq m on days 1-5. Repeated every 4 weeks
BCAVP	: Vincristine 1.4mg/sq m on day 1, BCNU 60mg/sq m on day 2, Adriamycin 30mg/sq m on day 3, Cyclophosphamide 250mg/sq m on days 4-6, Prednisone 40mg/sq m on days 1-7. Repeated every 6 weeks
ABVD	: Vinblastine 6mg/sq m on day 1, Adriamycin 30mg/sq m on day 2, Bleomycin 9mg/sq m on days 3-4, Dacarbazine 200mg/sq m on day 5. Repeated every 4 weeks
CHOP	: Vincristine 1.4mg/sq m on day 1, Adriamycin 30mg/sq m on day 2, Cyclophosphamide 250mg/sq m on days 3-5, Prednisone 40mg/sq m on days 1-5. Repeated every 4 weeks
CHOP-Bleo	: Vincristine 1.4mg/sq m on day 1, Adriamycin 30mg/sq m on day 2, Cyclophosphamide 250mg/sq m on days 3-5, Bleomycin 9mg/sq m on days 6-7, Prednisone 40mg/sq m on days 1-7. Repeated every 4 weeks

The dose of vincristine was capped at 2mg in all regimens.

Table 3. Summary of results

UPN	Sex/Age on Dx	Histology	Stage	ChemoRx Regimen (cycles)	Response (cycles to CR)	Duration of Response	Salvage Rx Regimen (cycles)	OSD
1.382851	F/69	LD	IVA	BCAVP(8)	PR			8M
2.644271	F/27	NS	IVB	C-MOPP(11)	CR(9)	14M	BABP(8)	40M
3.680997	M/47	MC	IIIS	CHOP-BLEO(6) C-MOPP(4)	CR(8)	40M ⁺		49M ⁺
4.696752	M/18	NS	IVB	C-MOPP(6)	CR(4)	7M	ABVD(7)	45M
5.753124	F/64	LD	IIIB	BCAVP(9)	CR(2)	51M ⁺		53M ⁺
6.778092	M/53	MC	IVB	BCAVP(7)	CR(2)	43M	C-MOPP(9)	55M ⁺
7.781860	M/68	LD	IVB	BCAVP(6)	PR			8M
8.786043	M/32	MC	IIIA	BCAVP(9)	CR(2)	8M	RT	16M
9.822647	M/69	NS	IIISB	C-MOPP(12)	CR(7)	10M	BCAVP(6)	71M ⁺
10.872053	M/63	MC	IVB	CHOP(8)	CR(6)	10M	C-MOPP(13)	77M
11.875695	M/38	NS	IIIB	C-MOPP(6)	CR(3)	42M ⁺		45M ⁺
12.909884	F/ 8	NS	IVB	C-MOPP(8)	CR(3)	107M	BAVP(9), RT	173M ⁺
13.914275	M/16	MC	IVB	C-MOPP(9)	CR(4)	22M ⁺		25M ⁺
14.916637	M/39	MC	IIIB	BCAVP(8)	CR(4)	14M	C-MOPP(12)	78M

Abbreviations : UPN(unique patient number), Dx(diagnosis), NS(nodular sclerosis), MC(mixed cellularity), LD(lymphocyte depletion), CR(complete remission), PR(partial remission), RT(Radiotherapy), OSD(Overall survival duration), BCAVP(BCNU + cyclophosphamide + adriamycin + vincristine + prednisone), C-MOPP(cyclophosphamide + vincristine + prednisone + procarbazine), BABP(BCNU + adriamycin + bleomycin + prednisone), CHOP(cyclophosphamide + adriamycin + vincristine + prednisone), CHOP-Bleo(CHOP + bleomycin), ABVD(adriamycin + bleomycin + vinblastine + dacarbazine), BAVP(BCNU + adriamycin + vincristine + prednisone)

The numbers in parentheses following chemotherapy regimens indicate courses given. The numbers in parentheses following response mean the courses repeated to achieve CR. The durations of response and survival are indicated in months(M).

67(median 43), with their performance status 3 or less on ECOG(Eastern Cooperative Oncology Group) scale, and normal functions of heart, lung, liver, kidney, and nervous system.

Our protocol required chemotherapy be cycled every four weeks except for nitrosourea containing regimen which was repeated every six weeks. The chemotherapy was given at least two courses after complete remission was attained or occasionally more than two courses in disease with high tumor burden, disease responding slowly to chemotherapy, or persistent residual disease on restaging according to our discretion. Leukocyte count was not monitored routinely to adjust the dose intensity. Radiation was delivered for curative aim in local recurrence or for

palliative aim in chemorefractory disseminated disease. Maintenance chemotherapy was not attempted.

The criteria of response were standard⁸⁾. Stable residual disease on more than 2 courses of treatment was regarded as having been in complete remission (CR). Survival durations were calculated from the starting date of treatment to the date of death or last follow-up.

Results

For remission induction, six patients received BCAVP(BCNU, cyclophosphamide, doxorubicin, vincristine, and prednisone, a derivative of BCVP),

Fig. 1. Durations of CR1, CR2 and Overall Survival.

Fig. 2. Kaplan Meier survival plot.

six C-MOPP(cyclophosphamide, vincristine, procarbazine, and prednisone), one CHOP(cyclophosphamide, doxorubicin, vincristine, and prednisone), and one CHOP-Bleo(CHOP plus bleomycin) followed by C-MOPP. CHOP or CHOP-Bleo regimen was given to patients with clinical manifestation in favor of non-Hodgkin's lymphoma although the histology suggested Hodgkin's disease. Salvage treatment for relapsed disease consisted of ABVD or different regi-

men from first line therapy. Dose modification was not necessary with the regimens, because all the patient showed recovery of marrow suppression before subsequent chemotherapy.

A total of 117 courses of chemotherapy (mean 8.4, range 6-12) was administered for remission induction. Two patients achieved partial remission, who refused salvage treatment. Twelve patients (86%) attained CR after a mean of 4.5 cycles of chemotherapy (range 2-9). The duration of the first complete remission (CR1) ranged 8-107 months with a median of 19. Eight patients (67%) had relapse at a median of 12 months (range 8-107). A total of 64 courses of salvage treatment (mean 9.1, range 6-13) different from induction regimens induced a second complete remission (CR2) in 6 of 7 patients (86%) after a mean of 6.3 cycles (range 5-8) of chemotherapy. One of 8 relapsed patients did not respond to radiotherapy and refused further chemotherapy. The duration of CR2 ranged 7-51 months with a median of 33.5.

Two patients who were believed to be dead could not be traced. Five patients died of their disease. They received third or fourth line chemotherapy plus palliative irradiation. The details of the treatments are not given because they seemed not to impact on survival duration. Seven patients (50%) were alive disease free at 25-173 months (median 53), with 4 in continuous CR1 (duration 25+, 45+, 49+, 53+ months each) and 3 in CR2 (duration 7+, 46+, 51+ months each). The overall survival duration ranged 8-173 months during the median follow-up period of 47 months.

The details of the drug toxicity are not presented here because the end point of our study was survival duration. However, treatment related morbidity was minimal with no case of mortality or long term complication.

Discussion

There is no controversy in that chemotherapy is

indicated in disseminated stage IV Hodgkin's disease. Since the advent of MOPP polychemotherapy¹⁾, a variety of MOPP version appeared to be as effective as MOPP including ChlVPP (chlorambucil, vinblastine, procarbazine and prednisone)⁹⁾ and MVPP¹⁰⁾ (mechlorethamine, vinblastine, procarbazine and prednisone). ABVD regimen was devised to rescue MOPP failure and later put in the first line treatment to be proved as effective as and less toxic than MOPP. BCVPP regimen developed by ECOG and proved comparable to MOPP is no longer recommended because of high mutagenicity of BCNU¹¹⁾.

Although chemotherapy for early Hodgkin's disease was reported as effective as irradiation¹²⁾, radiation therapy is still regarded as a standard treatment for stage I and II Hodgkin's disease¹³⁾. B symptoms in stage II disease confer a systemic rather than a localized disease and chemotherapy is preferred to radiation therapy. Massive mediastinal disease is thought to need both chemotherapy and irradiation for better local control.

Combined modality treatment for stage III patients used to be regarded as a standard treatment. Nowadays, chemotherapy alone is being preferred to avoid complications given the equivalent results of combined modality to those of chemotherapy only. The results of chemotherapy were reported superior to those of radiotherapy in stage III disease. The current sole indication for combined modality treatment is a massive mediastinal disease or a bulky disease where local control is difficult to achieve with chemotherapy only.

Current controversy in the treatment of Hodgkin's disease is whether to be faithful to the dose intensity of the standard regimens or to combine more agents to overcome the drug resistance^{3,4)}. NCI group advocates the importance of dose intensity. According to their meta-analysis of various regimens, the therapeutic outcome correlated with dose intensity of vin-

cristine and alkylating agents. Other groups contend that MOPP plus non-cross resistant agents is superior to MOPP alone and their data support the Goldie and Coldman hypothesis. NCI team compared MOPP with hybrid or alternating regimens with regards to dose intensity, and they claimed there is no advantage of MOPP plus over MOPP alone provided the same dose intensity is kept in both regimens. The success of very high dose chemotherapy rescued by bone marrow transplant in a subset of otherwise lethal chemorefractory patients^{14,15)} is quoted as another example verifying their theory of dose response relationship. However, both of them agree with that ABVD alone or ABVD analogues plus MOPP are less toxic than MOPP, a merit of ABVD or ABVD based hybrids with MOPP for easier compliance with dose intensity.

Contemporary chemotherapy is expected to cure at least two thirds of disseminated Hodgkin's disease patients. Complete remission is achievable in more than 80% of patients, less than 40% of whom relapse, leaving a half of patients to be cured with primary chemotherapy. The salvage chemotherapy for relapsed patients was reported to add 10-15% of cure rate. The outcome of salvage chemotherapy mainly depends on the disease free interval. If the duration of CR1 is longer than one year, CR2 can be achieved in most of the relapsed patients and half of the patients who entered CR2 can maintain durable remission. However, long term follow-up results at 10 years showed a reduction of long term survivors to 25% due to secondary malignancies and late complications. Less than one third of patients in CR1 shorter than 1 year can achieve CR2 after salvage chemotherapy and only 10% can be cured. Very high dose chemotherapy supported by bone marrow rescue is being on trial revealing roughly a half chance of CR even in patients heavily exposed to chemotherapy. One quarter to one half of the patients who achieved CR is expected to be cured although the

follow-up period is not long enough.

Our regimens were mainly derived from standard MOPP, BCVPP, and ABVD combination chemotherapies. The comparison of three regimens was beyond deduction from our limited data. In light of small contributory role of corticosteroids in the treatment of Hodgkin's disease, the dose of our regimens excluding prednisone was compared with dose of standard regimens. The relative dose intensity versus standard MOPP, BCVPP, and ABVD ranged from half to two thirds. The high relapse rate and longer median course needed for remission induction than that of NCI MOPP(3 courses)¹³⁾ seem to reflect underdosing of our regimen. The fact that most of the relapsed patients had CR1 longer than 1 year, 86% of the relapsed patients entered CR2, and two thirds of them maintained durable remission also suggests dose intensity was less than optimal in our primary chemotherapy. On the other hand, the suboptimal chemotherapy could produce several long term disease free survivors and lower dose may be curative for a subset of patients. Whether those who attained CR2 can maintain long term remission is uncertain for our relatively short observation period. It seems theoretically impossible to get better result than that of primary chemotherapy considering emergence of drug resistant tumor cell clones on repeated drug exposure.

The retrospective comparison of MOPP trials showed a correlation between MOPP dose intensity and outcome¹⁶⁾. When the dose intensity of NCI MOPP was used as a reference standard, actual relative dose intensities of NCI, Stanford, ECOG, and Milan groups were 0.85, 0.64, 0.60, and 0.53-0.66. The corresponding CR rates were 84, 72, 73, and 74% respectively, and the disease free survival rates 55, 30, 37, and 36% respectively¹⁶⁾. Reduction of dose intensity caused reduction of CR as well as long term survival rate. Our data were also in accord with the results of study groups using relatively low dose intensity,

leading to the conclusion that our regimens should be revised to be faithful to full dose intensity. An important cause of treatment failure in our regimens seems to be suboptimal treatment rather than drug resistance in view of relapse rate as high as two thirds and durable CR2 as long as CR1. With the availability of hematopoietic growth factors, chemotherapy in full dose intensity seems to be possible with less problems caused by myelotoxicity.

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= 국문 초록 =

진행병기의 호지킨 림프종에 대한 항암화학요법 : 백병원에서의 장기추적

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배 경 : 진행병기에 있는 호지킨 림프종 환자의 항암화학요법과 그 장기추적에 대한 보고는 우리나라에서 드문 편이다. 이에 1979년부터 1991년까지 인제대학교 백병원에서 진단 받은 호지킨 림프종 환자의 의무기록을 검토하여 항암화학요법의 결과와 장기생존율을 조사하였다.

방 법 : 의무기록상의 56명 중 방사선으로만 치료한 국소적 질환을 가진 환자, 본원의 치료 방침에 어긋난 환자, 타원에 전원된 환자를 제외한 14명이 평가되었으며 이중 남자는 10명, 여자는 4명이었고 연령의 중앙치는 43세(범위 8-67)이었다. 본원에서 사용한 항암화학요법은 MOPP, BCVPP, ABVD 복합요법의 변형을 사용하였고 그 용량강도는 1/2에서 2/3 정도였다.

결 과 : 총 117회(평균 8.4, 범위 6.12)의 관해유도 항암화학요법이 시행되었고 완전관해율은 86%로서 완전관해에 이르기까지 평균 4.5회(범위 2-9)의 항암화학요법이 소요되었다. 관해지속기간은 8-107 개월(중앙치 18개월)로서 8명(67%)이 재발하였고 이중 7명에게 총 64회(평균 9.1, 범위 6-13)의 새로운 관해유도 항암화학요법이 시행되었으며 6명(86%)에서 2차 완전관해가 이루어졌다. 현재 7명(50%)이 무병상태로 생존하고 있으며(중앙치 53개월, 범위 25-173개월), 이 중 4명은 지속적인 1차 관해 상태(기간 22⁺, 42⁺, 46⁺, 58⁺ 개월)에 3명은 지속적인 2차 관해 상태(기간 7⁺, 46⁺, 51⁺ 개월)에 있으며, 환자 모두의 총 생존기간은 8-173 개월로서 그 중앙치는 47개월이었다.

결 론 : 환자의 절반에서 장기생존(중앙치 53개월, 범위 25-173개월)이 가능하였으나 관해유도에 이르기까지 소요된 항암화학요법의 횟수, 높은 재발율, 높은 2차관해율 등은 본원에서 사용된 항암화학요법의 용량강도가 미흡함을 시사하며 호지킨 림프종의 치료에 있어 항암화학요법의 용량강도가 중요한 예후인자라는 고전적인 학설에 상응하고 있다.