original paper
Haematologica 1996; 81:521-528

THE F-MACHOP REGIMEN IN THE TREATMENT OF AGGRESSIVE NON-HODGKIN'S LYMPHOMAS: A SINGLE CENTER EXPERIENCE IN 72 PATIENTS

Laura Infanti, Federico Silvestri, Renato Fanin, Flavia Salmaso, Francesco Zaja, Giovanni Barillari, Francesca Patriarca, Antonella Geromin, Michela Cerno, Daniela Damiani, Michele Baccarani

Division of Hematology, University Hospital, Udine, Italy

ABSTRACT

Background. Since July 1991 we have employed the F-MACHOP regimen for the treatment of aggressive non-Hodgkin's lymphomas (NHL). The aim of the present study was to evaluate the response rate and the toxicity of this chemotherapy program.Patients and Methods. Seventy-two consecutive patients entered the study and were treated with the F-MACHOP regimen for 6 planned courses, given every 21 days. G- or GM-CSF were administered whenever required.Results. Sixty-six patients (92%) obtained a response: 38 (53%) a complete remission (CR) and 28 (39%) a partial remission (PR); 4 (6%) proved to be resistant and 2 (3%) died of chemotherapy-related toxicity. Fifty-seven patients with a good performance status were subsequently selected to undergo autologous stem cell transplantation (ASCT). During chemotherapy, grade III-IV neutropenia was observed in 59% of the patients; a significant drop in hemoglobin levels was detected, with blood transfusions being required in 21% of the cases; platelet counts were unaffected. The main extrahematological toxic events were: alopecia (100% of the patients), osteoarthromyalgias (58%), grade I-II neuropathy (53%) and grade I-II hepatic toxicity (43%). Conclusions. Our study confirms the efficacy of the F-MACHOP regimen in obtaining a high rate of response (CR+PR) in most aggressive NHL cases, with an acceptable toxicity and a low rate of toxic deaths. This regimen enables the majority of patients to be selected for ASCT as consolidation therapy without significant toxicity.

Key words: F-MACHOP, aggressive non-Hodgkin's lymphoma.

Chemotherapy (CHT) for aggressive non-Hodgkin's lymphomas (NHL) is still a controversal matter and remains uncodified, since many available regimens are effective. CHOP is still considered by many authors to be as effective as second- and third-generation regimens in inducing high rates of complete remission (CR) and in obtaining long-term overall survivals (OS); it is also less toxic and less expensive.[1-3] If CHOP is the gold standard therapy for high-risk NHL, then all new regimens must be compared to it in terms of efficacy, toxicity and cost. On the other hand, since the introduction of third-generation regimens in the early 80's, many reports of single Institution studies have demonstrated response rates and overall survivals higher than those obtained with CHOP.[4-11]

Since its introduction in 1980, few studies on the F-MACHOP regimen have been reported in the literature. Available data indicate it is effective in most cases, with an overall CR rate of 65% to 80% and an OS rate of 75-80%, still detectable at a median of 5 years (3 to 10) from the start of treatment.[12,13]

In our Institution we have employed the F-MACHOP regimen since 1991 for the treatment of those NHL with intermediate- or high-grade

Correspondence: Federico Silvestri, M.D., Division of Hematology, University Hospital, p.le S. Maria della Misericordia, 33100 Udine, Italy; Tel. international +39.559662-4; Fax. international +39.432.559661.
Received June 26, 1996; accepted September 16, 1996.

histology (according to the *Updated Kiel Classification*)[14] and with at least one of the following risk factors: bulky disease, B symptoms or Ann Arbor stage III-IV. After chemotherapy part of the patients were submitted to radiotherapy (RT) on residual disease; after first-line therapy (CHT±RT), part of them were selected on the basis of performance status and response to therapy to undergo autologous stem cell transplantation (ASCT). Herein we report the results obtained in a group of 72 patients, focusing in particular on the feasibility, toxicity and outcome of the chemotherapy program as a preparative regimen for ASCT.

Patients and Methods

From July 1991 to January 1996, 72 unselected, previously untreated patients with aggressive NHL were diagnosed and treated with the F-MACHOP regimen at the Division of Hematology of Udine, Italy. A lymphoma was defined as aggressive if intermediate- or high-grade histology (according to the *Updated Kiel Classification*)[14] and at least one of the following risk factors was present: bulky disease, B symptoms or Ann Arbor stage III-IV.

Diagnosis was performed on pathologic specimens (fixed in 10% buffered formalin, processed using routine techniques and embedded in paraffin) and was based on morphologic and immunophenotypic criteria according to the *Updated Kiel Classification*.[14] A comparison with the more recent *Revised European-American Classification of Lymphoid Neoplasms* (R.E.A.L.)[15] is also provided in Table 1. Staging was defined according to the Ann Arbor criteria. Bulky disease (both nodal and extranodal) was defined as the presence of a mass larger than 10 cm in diameter; bulky mediastinum was defined as an MT ratio >0.33 (MT ratio, the ratio between the maximum mediastinal diameter and the maximum thoracic diameter at level T5-T6, as detected by standard posteroanterior chest radiographs). Performance status (P.S.) and chemotherapy-related toxicity criteria were assessed according to the *Eastern Cooperative Oncology Group* (ECOG).[16] Prediction of relative risk of death was made retrospectively using the age-adjusted *International Prognostic Index,* which was developed in 1993 by the *International NHL Prognostic Factors Project* and based upon tumor stage, serum lactate dehydrogenase (LDH) levels and P.S.[17] A detailed history was collected from each patient and everyone underwent physical examination, blood tests, serology for HBV, HCV and HIV infection, chest radiographs, computed tomography (CT) scans of chest and abdomen and bone marrow aspirate and biopsy. Other examinations were performed as clinically indicated. All the patients with bulky disease were also entered into an ongoing study comparing CT, magnetic resonance imaging (MRI) and ^{67}Gallium-scintigraphy (^{67}GA-S) for the evaluation of residual mass after therapy. Patients were assessed with the three imaging techniques at diagnosis, at the end of therapy and every 6 months thereafter.[18]

Updated Kiel Classification	R.E.A.L. classification	No.
T large cell anaplastic (Ki-1 pos.) L.	Anaplastic large cell L., T and null-cell type	12
Pleiomorphic T-cell L.	Peripheral T cell L., unspecified	14
Centroblastic/centrocytic diffuse L.	Follicle centre L.	5
MALT L.	Marginal zone L.	4
Centrocytic L.	Mantle cell L.	2
Centroblastic L.	Diffuse large B cell L.	16
Immunoblastic L.		6 35
B large cell anaplastic (Ki-1 pos.) L.		13

L. = lymphoma.

Table 1. Histologic diagnosis of the 72 patients studied.

Two patients with stage IV disease underwent RT (1 on the left humerus and 1 on the dorsolumbar spine) as the first therapeutical intervention due to the presence of lymphoma (bulky in one case) in those sites. Another 7 patients, 6 with stage IV and 1 with stage IE disease, underwent surgery (6 on the gastrointestinal tract and 1 splenectomy) for diagnostic or debulking purposes as the first therapeutical intervention. All patients were then hospitalized (5 days/cycle of CHT) to undergo CHT with the F-MACHOP regimen for 6 planned courses, given every 21 days. Each course of therapy included: vincristine (0.5 mg/m^2, i.v. bolus hour 0 and 12), cyclophosphamide (800 mg/m^2, i.v. bolus hour 36), 5-fluorouracil (15 mg/kg, i.v. 6-hour infusion hour 36), cytosine-arabinoside (1000 mg/m^2, i.v. 6-hour infusion hour 42), doxorubicin (60 mg/m^2, i.v. bolus hour 48), methotrexate (500 mg/m^2, i.v. 6-hour infusion hour 60), prednisone (60 mg/m^2 p.o. daily from day 1 to 14) and folinic acid rescue (20 mg/m^2, i.v. bolus hours 84, 96, 108 and 120).

The intensity of the CHT dose given to patients was calculated according to the Hryniuk and Bush model[21] as the ratio of the actual dose to the planned dose, multiplied by the ratio of the planned time to the actual time. The planned dose was calculated based on the patient's weight; the planned time was 21 days/cycle.

After completing CHT, RT was then performed on residual mediastinal disease in 7 patients.

The first 28 patients, as part of an Italian NHL National Study Group trial, were randomized to receive or not receive granulocyte-macrophage colony-stimulating factor (GM-CSF; Mielogen; Sandoz, Milan, Italy) 300 μg s.c. daily from day +5 to day +15 after CHT. In the next 44 patients granulocyte colony-stimulating factor (G-CSF; Filgrastim; Granulokine; Roche, Milan, Italy) 300 μg s.c. daily for a total of 3-6 doses was administered whenever required. In particular, as previously reported,[19,20] it was given to anyone after any course who presented the following: 1) neutropenia $< 1\times10^9$/L during the interval between courses; 2) delay in cycle schedule due to ANC $< 1\times10^9$/L on the planned day of treatment; 3) onset of fever or a documented infection between courses, regardless of the ANC.

After completing first-line therapy (CHT± RT) all patients were evaluated for response by means of blood examinations, CT scans and bone marrow aspirate and biopsy. Complete remission (CR) was defined as no evidence of disease for at least 4 weeks; partial remission (PR) was defined as a reduction of at least 50% in tumor mass; resistance (R) as a reduction of less than 50%.

Part of the patients, selected on the basis of a P.S. of 0-1 and response to therapy (at least a PR), subsequently underwent autologous stem cell transplantation with BAVC as the conditioning regimen [BCNU 200 mg/m^2 i.v. on day -4; cytarabine 150 mg/m^2 i.v. every 12 h on days -5, -4, -3, -2; etoposide (VP-16) 150 mg/m^2 every 12 h on days -5, -4, -3, -2; cyclophosphamide 45 mg/kg b.w. i.v. on days -5, -4, -3, -2].[26,27] The source of stem cells was bone marrow (BM) in 30 patients and peripheral blood (PB) (after priming with filgrastim at a daily dose of 16 μg/kg b.w. for 3 days) in 3 patients.

Results

Patients

Histologic diagnoses are reported in Table 1. All patients were affected by high-grade NHL (including 35 diffuse large B cell lymphomas, 14 T large cell anaplastic lymphomas, 12 pleiomorphic T cell lymphomas, and 4 high-grade MALT lymphomas) or intermediate-grade NHL (5 centroblastic-centrocytic diffuse lymphomas and 2 centrocytic lymphomas). General characteristics of the patients and clinical features at presentation are listed in Table 2. There was a slight male prevalence (56%) and the median age was 42 years (15-60). Most of the cases (#52, 72%) were diagnosed at an advanced stage (III or IV) with only 2 patients in stage I disease (bulky liver and bulky colon disease, respectively). B symptoms were present in 36 patients (50%), bulky disease in 39 patients (54%), with the mediastinum accounting for the majority; extranodal disease was detectable in 42 patients (58%), with 2 or more sites of involvement in 19 (26%). LDH levels were elevated in 27 patients

(37%) and 22 (31%) showed a P.S. ≥2. Among the 20 stage I-II patients, the 2 in stage I had both bulky disease and B symptoms, while among the other 18 stage II patients 12 presented bulky disease, 9 B symptoms and 5 elevated LDH. The relative risk of death according to the age-adjusted *International Prognostic Index* was as follows: low 14 patients (19%), low-intermediate 27 patients (37%), high-intermediate 18 patients (25%), high 13 patients (18%).

Outcome

After CHT 38 patients (53%) reached a CR; 28 (39%) a PR and 4 patients (6%) were resistant. Two patients (3%) died of CHT-related toxicity (acute renal failure in both cases) while on therapy. Overall, 92% (66/72) of the patients obtained a response. In 7 cases in PR, RT was performed after CHT on previously bulky mediastinal masses, allowing 3 additional patients to become free of disease.

Of the 66 patients (41 in CR and 25 in PR) who responded to CHT±RT, 57 (86%) were selected as previously described to undergo ASCT, while 9 were excluded because of poor PS. Of the 57 patients selected, 2 died in CR and PR, respectively, of unrelated causes while waiting for transplant; 17 (11 in CR and 6 in PR) are still waiting for the procedure to be completed; 4 (2 in CR and 2 in PR) relapsed while waiting for stem cell harvest and are currently on salvage therapy; 1 patient in CR refused the procedure; 33 (23 in CR and 10 in PR) have been already transplanted. The harvest was performed at a median of 3 months (2-7) after the end of therapy, and the transplant after a median of 3.5 months (1-10) from the harvest. A median of 0.43 (0.19-1.9) BM mononuclear cells (MNC) $\times 10^8$/kg b.w. or 5.3 (1.0-7.5) PB MNC $\times 10^8$/kg were reinfused. The median number of days to PMN ≥ 0.5×10^9/L and to Plt 20×10^9/L was 13 and 14, respectively.

Neither transplant-related deaths nor major complications occurred. Twenty-two patients (67%) became febrile during the period of post-transplant aplasia (median of 4 days/patient) and median hospitalization time from reinfusion was 18 days (11-32).

Currently 32 of the 33 transplanted patients are alive without disease, while 1 patient who was transplanted in PR and never achieved a CR, progressed 24 months after ASCT and is currently on salvage therapy. Overall survival of

Table 2. Clinical features at diagnosis of the 72 patients studied.

Characteristics	*No.*	*%*
Male	40	56
Female	32	44
Age ys. median (range)	42 (15-60)	
Ann Arbor stage:		
I-II	20*	27
III-IV	52	72
B symptoms	36	50
Bulky disease:	39	54
nodes**	17	24
mediastinum	13	18
liver	3	4
spleen	3	4
lung	3	4
colon	2	3
bone	2	3
soft tissues	1	1
Extranodal disease:	42	58
bone marrow	12	17
lung	10	14
GI tract	8	11
liver	7	10
spleen	6	8
pleura	5	7
skin	4	6
bone	4	6
parotid	2	3
colon	2	3
pericardium	2	3
others	5	7
No. of extranodal sites:		
0	27	37
1	26	36
2	19	26
Serum LDH level > normal	27	37
Performance status (ECOG):		
0-1	50	69
2-4	22	31
A.A. international index:		
low	14	19
low-intermediate	27	37
high-intermediate	18	25
high	13	18

**Only 2 patients had stage I disease (bulky liver and bulky colon disease, respectively). **Including 7 cases with peripheral adenopathy, 8 cases with intrabdominal adenopathy and 2 cases with retroperitoneal adenopathy.*

the 33 patients is 100% at a median of 37 (9-61) months from diagnosis, and disease-free survival is 100% at a median of 26 (3-58) months from the time CR was attained.

Of the 9 patients not selected for ASCT because of poor PS, 4 are alive in CR 40 months (20-58) from diagnosis, 2 are alive with stable disease, 1 progressed and is currently on salvage therapy and 2 died of disease progression.

Toxicity and dose-intensity of chemotherapy

Table 3 lists the toxic events recorded during CHT. Hematologic toxicity was predominantly due to neutropenia (59% of patients), but severe neutropenia (grade IV = $< 0.5\times10^9$/L) was observed in only 19 patients (26%). Overall, this caused a delay in starting 12 cycles of CHT. During neutropenia 11 episodes of FUO and 2 of sepsis (1 due to *Staphylococcus epidermidis* and 1 to *Staphylococcus alpha hemolyticus*) were documented and because of this 7 other cycles of CHT were delayed. Four more cycles were delayed as a result of toxic hepatitis (#2 cycles), enterocolitis and an unrelated problem. Overall, 23/260 (9%) cycles were delayed (median cycle delay was 8 days, range 3-15); consequently the dose intensity delivered to patients was 91%.

Three episodes of FUO and 2 severe neutropenias were recorded in patients randomized to receive no growth factor. Five episodes of FUO, 14 neutropenias and 1 sepsis were detected in the group of patients randomized to receive GM-CSF. Three episodes of FUO, 3 of neutropenia, 1 sepsis and the enterocolitis were observed in patients receiving G-CSF. Of the 44 non-randomized patients, 34 (77%) required the introduction of G-CSF into therapy during CHT according to the above mentioned criteria. Overall, 8 (11%) patients needed to be hospitalized for the treatment of CHT-related toxic events.

A significant ($p < 0.0001$) drop in hemoglobin levels was observed during treatment (from 12.66±1.77 g/dL before starting to 10.84±1.29 one month after the end of CHT), with 21% of the patients requiring blood transfusions (a mean of 2.5 units/transfused patient). On the other hand, platelets were unaffected (from $305.0\pm154.4\times10^9$/L to $302.4\pm163.0\times10^9$/L, p = 0.9763), with their counts never falling below 50×10^9/L and no patient complaining of bleeding or requiring platelet transfusions.

Table 3. Toxicity of chemotherapy.

Toxic events	*No. of patients*	*%*
Hematologic		
neutropenia grade III [1]	24	33
neutropenia grade IV [2]	19	26
anemia grade III [3]	15	21
thrombocytopenia grade III [4]	–	–
Non hematologic		
infections grade III-IV [5]	3	4
fever grade II-III [6]	11	15
herpetic infections [7]	11	15
alopecia grade II [8]	72	100
transient osteoarthromyalgias	42	58
oral mucositis grade III-IV [9]	6	8
local phlebitis	7	10
nausea and vomiting grade I-II [10]	14	19
diarrhea grade I-II [11]	10	14
paresthesias grade I-II [12]	38	53
constipation grade I-II [13]	6	8
weakness grade I-II [14]	24	33
headache grade I-II [15]	6	8
hepatic grade I-II/III-IV [16]	31/2	43/3
acute renal failure grade I-II/III-IV [17]	2/2	3/3
other*	31	43

[1]<1.0x10^9/L; [2]<0.5x10^9/L; [3]requiring transfusional support; [4]<50x10^9/L; [5]debilitating-life threatening; [6]>38°C–>40°C; [7] #9 HS labialis, #1 HS keratitis and #1 thoracic HZ; [8]severe; [9]ulcers, can-cannot eat; [10]controllable; [11]without-with dehydration; [12]mild-severe; [13]mild-severe; [14]mild; [15]mild-moderate; [16]SGOT, Alk Phosp, bilirubin 1.5-5/ >5 x normal; [17]creatinine 2.1-4.0/>4.0 mg/dL.
*#19 mild conjunctivitis, #4 transitory hyperglicemia, #6 weight loss > 10%, #1 renal colic, #1 deep phlebitis.

Due to the regular use of tropisetron (Navoban; Sandoz, Milan, Italy), nausea and vomiting were mild and occurred only in 19% of the patients. In 100% of the cases a reversible alopecia was observed. The other most frequent side effects observed were: osteoarthromyalgias (in 58% of the patients, due to steroid withdrawal, vincristine or growth factor administration), grade I-II peripheral neuropathy (in 53%), grade I-II hepatic toxicity (in 43%) and grade I-II weakness (in 33%). Herpes infections were recorded in 15% of the patients and severe (grade III, but never grade IV) oral mucositis in only 8% of the patients. The only 2 fatal toxic events were related to acute renal failure, probably caused by methotrexate.

Discussion

Despite a high percentage of initial responses, a high relapse rate is observed in patients with aggressive NHL treated only with CHT, with long-term progression-free survival being approximatively 50%.[17]

There is increasing evidence that ASCT (either from BM or PB) performed as consolidation of first remission is needed to increase the proportion of patients who can be cured.[22-28] Data from the *European Blood and Bone Marrow Transplant* registry showed that status at transplant is the most important prognostic factor for overall and progression-free survival. Patients autotransplanted in first CR have a much better outcome than those autotransplanted in second CR, in progression or with resistant disease.[29] Moreover, it has been demonstrated that achieving a PR after first-line therapy does not appear to be an adverse prognostic factor for outcome to subsequent ASCT, especially if dose-intensive therapy is performed before disease progression.[30-33]

If this is the case, the ideal CHT regimen to be employed as first-line therapy should lead to the highest percentage of remissions (CR+PR) with the lowest toxicity for the patients.

Because the therapeutic protocol for aggressive NHL in our Institution has since 1991 included ASCT performed after first-line therapy (CHT± RT) for patients in CR or PR with a good (0-1) P.S., the aim of the present study was to evaluate the response rate and toxicity of F-MACHOP employed as a preparative regimen for ASCT.

In our hands the overall percentage of responses obtained was 92%, with 53% CR and 39% PR. Compared to the results reported in the original studies on F-MACHOP,[12,13] in which a CR was reported in 65-80% of cases, our CR rate appears to be lower. However, it must be pointed out that the evaluation of response in our patients was very accurate and performed using three highly sophisticated imaging techniques: CT, MRI and ^{67}Ga scintigraphy. Therefore many cases that could have been considered in CR if restaged with traditional techniques are currently considered in PR.[18] This improvement in the evaluation of residual masses after therapy implies that those patients with a remarkable reduction in but not a complete disappearance of the original mass must also be considered as responders to CHT and therefore candidates for consolidation therapy with ASCT.

If compared with other studies reported in the literature,[4-11] the results achieved with the F-MACHOP regimen are similar to those obtained with third-generation regimens. In particular, a recent randomized study performed on a large sample of patients by the *Italian Cooperative Study Group on Aggressive NHL* showed an absolute overlapping of results between the F-MACHOP and the MACOP-B regimens.[34]

The toxicity due to chemotherapy observed in our patients was greater than that reported for CHOP,[2] but similar to what had already been reported by others employing the same regimen.[12,13,34] The most common events were mild and transitory side effects such as alopecia, peripheral neuropathy, osteoarthromyalgias and hepatic toxicity, while, as recently reported in the study by Mazza *et al.*,[34] we confirm the low incidence of severe mucositis, grade III-IV extrahematologic toxicity and toxic deaths. On the other hand, hematologic toxicity was very common, with neutropenia being recorded in most of the cases as the direct or indirect (fever or sepsis) cause of the delay in cycle schedule. Retrospective evidence suggests that the dose intensity delivered to patients is the most important factor affecting the success of treatment.[35,36] Since myelosuppression, principally neutropenia, is the condition that most affects cycle delay (and thus dose intensity), the use of hematopoietic growth factors between cycles is often necessary to prevent dose-limiting neutropenia. Our previous experience in the treatment of lymphomas with conventional-dose CHT,[19,20] and the experience of other Institutions with third-generation regimens,[11,37,38] support this statement. In fact, of the 44 non-randomized patients in the present study, 34 (77%) needed the introduction of growth factors during the CHT program, according to the criteria previously mentioned.

The low rate of extrahematological toxicity with the CHT regimen and the prevention and care of main hematological toxicity through the

use of growth factors allowed the majority of our patients to finish first-line therapy in good enough condition (P.S. 0-1) to be selected for the subsequent high-dose therapy program. Eighty-six percent of our patients (57 of 66) were in fact chosen for ASCT; of these, 33 have already been transplanted and 17 are awaiting completion of the entire procedure. Both the harvesting and the autotransplant were carried out without any significant problems.[39] In particular, it must be emphasized that neither transplant-related deaths nor major complications were observed. Though a comparison in terms of outcome between transplanted and non-transplanted patients is not advisable since ASCT itself would be the bias between the two populations, it is worthwhile to mention the good outcome of the 33 transplanted patients: 100% overall survival at 37 (9-61) months and 100% disease-free survival at 26 (3-58) months.

In conclusion, our study showed that the F-MACHOP regimen is well tolerated by the majority of patients, that toxicity is acceptable and that the therapy produces a high percentage of responses (CR+PR). Therefore it can be considered a modern induction-remission regimen for the treatment of aggressive NHL candidates for ASCT in first remission.

References

1. Gordon LI, Harrington D, Andersen J, et al. Comparison of a second generation combination chemotherapeutic regimen (m-BACOD) with a standard regimen (CHOP) for advanced diffuse non-Hodgkin's lymphoma. N Engl J Med 1992; 327:1342-9.
2. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1002-6.
3. Cooper IA, Wolf MM, Robertson TI, et al. Randomized comparison of MACOP-B with CHOP in patients with intermediate-grade non Hodgkin's lymphoma. J Clin Oncol 1994; 12:769-78.
4. Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. Ann Intern Med 1985; 102:596-602.
5. Connors JM, Klimo P. MACOP-B chemotherapy for malignant lymphomas and related conditions: 1987 update and additional observations. Semin Hematol 1998; 25:41-6.
6. Costa MA, Rabinowits M, Froimtchuk MJ, et al. Long-term results with MACOP-B in the treatment of aggressive non-Hodgkin's lymphomas. Am J Clin Oncol 1994; 17:323-7.
7. Dana BW, Dalhberg S, Miller TS, et al. m-BACOD treatment for intermediate and high-grade malignant lymphomas: a Southwest Oncology Group phase II trial. J Clin Oncol 1990; 8:1155-62.
8. Skarin AT, Canellos GP, Rosenthal DS, et al. Improved prognosis of diffuse histiocytic and undifferentiated lymphoma by use of high-dose methotrexate alternating with standard agents (M-BACOD). J Clin Oncol 1983; 1:91-8.
9. Fisher RI, DeVita VT, Hubbard SM., et al. Diffuse aggressive lymphomas: increased survival after alternating flexible sequences of ProMACE and MOPP chemotherapy. Ann Intern Med 1983; 98:304-9.
10. Miller TP, Dahlberg S, Jones SE, et al. ProMACE-CytaBOM is active with acceptable toxicity in patients with unfavorable non-Hodgkin's lymphomas: a group wide SWOG study (Abstract). Proc Am Soc Clin Oncol 1987; 6:197a.
11. Pettengel R, Gurney H, Radford JA, et al. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. Blood 1992; 80:1430-6.
12. Guglielmi C, Amadori S, Anselmo AP, et al. Sequential combination chemotherapy of high-grade non-Hodgkin's lymphoma with 5-Fluorouracil, Methotrexate, Cytosine-Arabinoside, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (F-MACHOP). Cancer Invest 1987; 5:159-69.
13. Guglielmi C, Amadori S, Martelli M, Dragoni F, Mandelli F. The F-MACHOP sequential combination chemotherapy regimen in advanced diffuse aggressive lymphomas: long-term results. Ann Oncol 1991; 2:365-71.
14. Stansfeld AG, Diebold J, Kapanci Y, et al. Updated Kiel classification for lymphomas. Lancet 1988; 1:292.
15. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84:1361-92.
16. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-55.
17. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: a predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329:987-94.
18. Zaja F, Russo D, Silvestri F, et al. Computed tomography, magnetic resonance and 67 gallium scintigraphy for the imaging of residual lymphoma. Haematologica 1995; 80:569-71.
19. Silvestri F, Velisig M, Fanin R, et al. Granulocyte colony-stimulating factor (G-CSF) allows the delivery of effective doses of CHOP and CVP regimens in non-Hodgkin's lymphomas. Leuk Lymph 1995; 16:465-70.
20. Silvestri F, Fanin R, Velisig M, et al. The role of granulocyte colony-stimulating factor (filgrastim) in maintaining dose intensity during conventional-dose chemotherapy with ABVD in Hodgkin's disease. Tumori 1994; 80:453-8.
21. Hryniuk WM, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. J Clin Oncol 1984; 2:1281-8.
22. Fanin R, Geromin A, Silvestri F, et al. Consolidation treatment in aggressive non-Hodgkin's lymphoma with autologous bone marrow transplantation (Abstract). Bone Marrow Transplant. 1995; 15(Suppl. 2):S99.
23. Fanin R, Silvestri F, Geromin A, et al. Primary systemic CD30 (Ki-1) positive anaplastic large cell lymphoma of the adult: sequential intensive treatment with the F-MACHOP regimen (± radiotherapy) and autologous bone marrow transplantation. Blood 1996; 87:1243-8
24. Haoiun C, Lepage E, Gisselbrecht Ch, et al. Autologous bone marrow transplantation (ABMT) versus sequential chemotherapy for aggressive non-Hodgkin's lymphoma (NHL) in

first complete remission (CR): a study of 542 patients (LNH87-2 Protocol) (Abstract). Blood 1995; 86(Suppl 1):1816a.
25. Vitolo U, Cortellazzo S, Liberati AM, et al. Intensified chemotherapy followed by myeloablative therapy and autologous stem cell transplantation (ASCT) as first line therapy in high risk diffuse large cell lymphoma (DLCL) (Abstract). Blood 1995; 86(Suppl.1): 1819a.
26. Vose JM, Bierman PJ, Anderson J, Bishop MR, Kessinger A, Armitage JO. Patients with diffuse aggressive non-Hodgkin's lymphomas (NHL) transplanted within one year from initial diagnosis: improved outcome with transplantation planned as part of initial therapy (Abstract). Blood 1995; 86(Suppl.1): 1820a.
27. Tavkorian T, Canellos GP, Ritz J, et al. Prolonged disease free survival after autologous bone marrow transplantation in patients with non-Hodgkin's lymphoma with a poor prognosis. N Engl J Med 1987; 316:1499-505.
28. Rohatiner AZS, Freedman A, Nadler L, Lim J, Lister TA. Myeloablative therapy with autologous bone marrow transplantation as consolidation therapy for follicular lymphoma. Ann Oncol 1994; 5 (Suppl.2):S143-6.
29. Fielding AK, Philip T, Carella AM, et al. Autologous bone marrow transplantation for lymphoma: a 15-year European bone marrow transplant registry (EBMT) experience of 3325 patients (Abstract). Blood 1994; 84(Suppl.1):536a.
30. Gribben JG, Goldstone AH, Linch DC, et al. Effectiveness of high dose combination chemotherapy and ABMT for patients with NHL who are still responsive to conventional dose chemotherapy. J Clin Oncol 1989; 7:1621-9.
31. Colombat P,Gorin NC, Lemonnier MP, et al. The role of autologous bone marrow transplantation in 46 patients with NHL. J Clin Oncol 1990; 8:630-7.
32. Philip T, Hartmann O, Biron P, et al. High-dose therapy and autologous bone marrow transplantation in partial response after first line induction therapy for diffuse NHL. J Clin Oncol 1988; 6:118-24.
33. Gulati SC, Shank B, Black P, et al. Autologous bone marrow transplantation for patients with poor prognosis lymphoma. J Clin Oncol 1988; 6:1303-13.
34. Mazza P, Zinzani PL, Martelli M. et al. MACOP-B vs F-MACHOP regimen in the treatment of high-grade non-Hodgkin's lymphomas. Leuk Lymphoma 1994; 881-94.
35. Hryunk WM. The importance of dose intensity in the outcome of chemotherapy. Adv Oncol 1988; 3:121-42.
36. De Vita VT jr. Principles of chemotherapy. In: De Vita VT, jr, Hellman S, Rosenberg SA, eds. Cancer, Principles and Practice of Oncology. 3rd ed, Philadelphia:J.B. Lippincott Co., 1989:276-300.
37. Miggiano MC, Gherlinzoni F, Visani G, et al. Hematological recovery after autologous bone marrow transplantation for high-grade non Hodgkin's lymphomas: a single center experience. Haematologica 1994; 79:225-32.
38. Hovgaard DJ, Nissen NI. Effect of granulocyte-macrophage colony-stimulating factor on chemotherapy-related neutropenia in patients with non-Hodgkin's lymphomas - A phase I/II study of dose and mode of administration. Leuk Lymphoma 1991; 6:39-48.
39. Rinaldi C, Savignano C, Silvestri F, et al. Autologous bone marrow transplantation in non-Hodgkin's lymphomas: prediction of mononuclear cell yield in bone marrow harvests. Haematologica 1995; 80:443-7.