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How do patients with aggressive non-Hodgkin's lymphoma treated with third-generation regimens fare in the long-term?

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ABSTRACT

Background and Objectives. **To examine the long-term clinical course and prognostic factors of patients with advanced aggressive non-Hodgkin's lymphoma (NHL) treated with third-generation regimens as front-line chemotherapy.**

Design and Methods. **A total of 348 patients aged <60 years received MACOP-B or F-MACHOP regimen between September 1988 and August 1993 for advanced stage aggressive NHL.**

Results. **Of these, 249 (71.5%) obtained a complete response (CR); 65 / 249 (26%) subsequently relapsed. The CR rates for MACOP-B and F-MACHOP were 70.5% and 72%, respectively, while the relapse-free survival rates (RFS) at 9 years were 66% and 74%, respectively. The overall survival rate at 9 years was 61% for MACOP-B and 67% for F-MACHOP patients. Of the relapses, 78.5% were early (<24 months) and 21.5% late. Eleven out of 65 (17%) patients are in continuous second CR with a median follow-up of 45 months; most of them have been salvaged with high-dose therapies. The validity of the International Prognostic Index was confirmed in long-term analysis.**

Interpretation and Conclusions. **With a 9-year RFS, it is possible to consider cured 50% of the patient with aggressive NHL treated with a third-generation regimen. About a quarter of the CRs relapse and late relapse occurs in roughly 20% of all relapsed patients. In these patients high-dose chemotherapy followed by autologous bone marrow or hematopoietic stem cell transplantation seems to be a very reliable approach in terms of long-term second CR. Finally, the IPI score maintains its pivotal role in terms of stratifying patients according to different risk subsets also in long-term analysis.**

Key words: MACOP-B, F-MACHOP, aggressive NHL, long-term outcome, late relapses

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The literature offers a wide range of therapeutic schemes for aggressive non-Hodgkin's lymphomas (NHL) ranging from first- to third-generation regimens.[1-8] Although satisfactory results have generally been recorded, the reports tend to be heterogeneous, being based on work done at individual centers with small series of patients.

The data available from the few randomized, prospective trials[9-14] recommend CHOP as the standard therapy for aggressive NHL. Nevertheless, assessment of poor prognostic factors[15-17] at the time of diagnosis in conjunction with rapid evaluation of response could permit the utilization of specific chemotherapeutic approaches for different risk groups, including high-dose therapy with autologous bone marrow transplantation or autologous hematopoietic stem cell support for poor risk patients.

Few data currently exist regarding the rates of cure in patients treated with conventional chemotherapy (first- to third-generation regimens),[18-21] but the concept of long-term relapse-free survival (RFS) appears very important in order to gain a broader view of the real impact of a chemotherapeutic regimen not so much in terms of isolated CR rates but, rather, of RFS at >5 years. As yet, we know little about the real trends regarding the distribution of relapses during follow-up, or the various possibilities of salvage treatment at different relapse times. We do know that up to 30-40% of patients with aggressive NHL who respond to first-line polychemotherapy relapse. Although it is commonly believed that most, if not all, relapses occur within the first 2 years, reports do exist of later relapses.

In order to elucidate the natural history of aggressive NHL in terms of outcome and relapses, we conducted a multicenter retrospective study of 348 patients with advanced aggressive NHL who were all treated with either F-MACHOP or MACOP-B, two different third-generation regimens.

Design and Methods

Patients

From September 1988 to August 1993, a total of 348 patients with previously untreated aggressive NHL were enrolled in 9 Italian institutions to receive combination chemotherapy with either MACOP-B or F-MACHOP. A conspicuous number of them had been previously enrolled in a randomized, prospective phase III clinical trial.[14] However, because of the lack of subsequent compliance by a few centers participating in the study, some patients were lost to long-term follow-up in terms of data collection. On the other hand, the remaining centers kept treating patients according to the original chemotherapy regimens, although without any randomization. As a consequence, as many as the 348 patients reported here were suitable for this retrospective analysis. Eligibility criteria included: a confirmed histologic diagnosis of any of the varieties of aggressive NHL included in the R.E.A.L. classification,[22] namely diffuse large B-cell lymphoma (DLBCL), anaplastic large cell lymphoma (ALCL), small non-cleaved cell lymphoma (SNCL), primary mediastinal large B-cell lymphoma (PMLBCL) and peripheral T-cell lymphoma (PTCL); stage II-IV disease according to the Ann Arbor staging system,[23] including stage I patients with bulky mediastinal disease; age between 15 and 60 years; an ECOG[24] performance status score ≤ 3; and normal renal, pulmonary and hepatic functions. The diagnosis was reviewed by a panel of pathologists during the study period. The characteristics of the 348 patients are shown in Table 1.

Treatment program

Of the 348 patients enrolled, 91 were submitted to the MACOP-B regimen and 257 to the F-MACHOP regimen. As previously reported,[25] F-MACHOP was given every 4 weeks for a total of six cycles. The MACOP-B regimen was administered as originally described by Klimo and Connors.[3] All patients received *Pneumocystis carinii* prophylaxis with co-trimoxazole (two days per week) during the entire course of therapy. The average relative dose intensity was 93% for MACOP-B patients and 89% for F-MACHOP. There was no formal policy with regard to therapy on relapse and the following were used: radiation therapy (n=1), combination chemotherapy (n=47) and high-dose chemotherapy/radiation therapy with rescue of autologous bone marrow or hematopoietic stem cell transplantation (n=17).

Response criteria and statistical methods

CR was achieved if 1 month after completion of treatment there was resolution of constitutional symptoms and normalization of abnormal physical findings, serum enzyme elevations, and radiologic abnormalities related to disease. All survival data were censored at the closing date or the date of last contact when this preceded the closing date. Survival curves were estimated using the Kaplan-Meier[26] method. RFS was measured from the date of achievement of CR to the date of relapse in those patients who responded. Fifteen patients who died in CR of unrelated causes were not considered treatment failures and had their disease-free time censored at the time of death. Overall survival (OS) was measured from the date of diagnosis to the date of death for all patients who died, whatever the cause of death.

Information on eight prognostic factors - age, presence or absence of B symptoms, stage according to the Ann Arbor staging system (I-II vs III-IV),[23] serum LDH level, presence or absence of bulky disease, histologic subtype according to the R.E.A.L. classifica-

Table 1. Characteristics of all 348 patients.

	F-MACHOP	*MACOP-B*	*Total*
N. of patients	257	91	348
Sex			
Male/female	155/102	50/41	205/143
Age			
median	35	38	36
range	15-60	15-60	15-60
Stage			
I	10	2	12
II	120	43	163
III	39	18	57
IV	88	28	116
Symptoms			
No/Yes	166/91	57/34	223/125
Histology			
DLBCL	127	42	169
ALCL	83	30	113
SNCL	10	5	15
PTCL	16	6	22
PMLBCL	21	8	29
Performance status			
0	86	37	123
1	104	28	132
2	56	23	79
3	11	3	14
LDH			
normal level	161	63	224
≥1 normal level	96	28	124
Extranodal sites			
<1	149	54	203
≥1	108	37	145
Bulky disease			
Yes/No	99/158	54/37	203/145
Response			
CR	185 (72%)	64 (70.5%)	249 (71.5%)
IPI			
0	88	33	121
1	83	27	110
2	48	16	64
3	38	15	53

CL= diffuse large B-cell lymphoma; ALCL= anaplastic large cell lymphoma; SNCL= small non-cleaved cell lymphoma; PTCL= peripheral T-cell lymphoma; PMLBCL= primary mediastinal large B-cell lymphoma.

tion,[22] performance status (0-1 vs 2-3), and the extranodal sites (≤ 1 vs > 1) was associated with outcome of all the patients. To assess the effect of covariates on the relapse-free survival time, a Cox's proportional hazards model was fitted.[27] The Chi-square test was used whenever appropriate for comparison of groups or of group variables. Two-sided *p* values were used throughout. For both the OS and RFS curves, all patients were analyzed according to International Prognostic Index (IPI) criteria.[17]

Results

Response

The CR rate was 70.5% (64/91) for MACOP-B and 72% (185/257) for F-MACHOP; the overall CR rate was 71.5% (249/348). At the time of closing the study period, the relapse rate was 26% (65/249) at a median follow-up of 72 months (range, 58-112) after achievement of initial CR. Relapses occurred in 20/64 (31.2%) patients treated with MACOP-B and 45/185 (24.5%) with F-MACHOP (*p*= 0.35). The median follow-up after attaining initial CR was 83 months for MACOP-B patients and 66 months for F-MACHOP patients, respectively. Early relapses (<2 years from first CR) occurred in 51/65 (78.5%) patients and late relapses (≥ 24 months) in 14/65 (21.5%). At the time of relapse, a few of the patients had further biopsies, and all the remaining were assigned to aggressive categories, based upon a subjective interpretation, at the time of the retrospective chart review, of the rate of growth of the relapse. All patients had complete restaging before starting second-line treatment. Table 2 summarizes the time from the achievement of initial CR to first relapse. Concerning the early relapses, 41/51 (80.5%) occurred within the first year and the remaining 10 (19.5%) were recorded during the second year. Among the late relapses, 11/14 (78.5%) occurred between 25 months and 60 months and the other 3 patients relapsed within 7 years.

Survival and statistical analysis

Global 9-year OS was 65% (Figure 1). Global 9-year RFS was 70% (Figure 2). Figures 3 and 4 show the OS and RFS curves of patients treated by MACOP-B and F-MACHOP, respectively. No significant differences in the 5 histologic subgroups were recorded between the F-MACHOP and MACOP-B groups. The global OS and RFS curves are shown in Figures 5 and 6, respectively. Information on the 3 main prognostic factors (performance status, LDH level, and stage) that were correlated with OS and RFS for patients younger than

Table 2. Relapse rate with time at relapse.

Time (months)	*F-MACHOP (n= 45)*	*MACOP-B (n= 20)*	*Total (n=65)*
1-12	27 (60%)	14 (70%)	41 (63%)
13-24	8 (18%)	2 (10%)	10 (15%)
25-36	3 (7%)	0	3 (5%)
37-60	7 (15%)	1 (5%)	8 (12%)
61-84	0	3 (15%)	3 (5%)
85-120	0	0	0

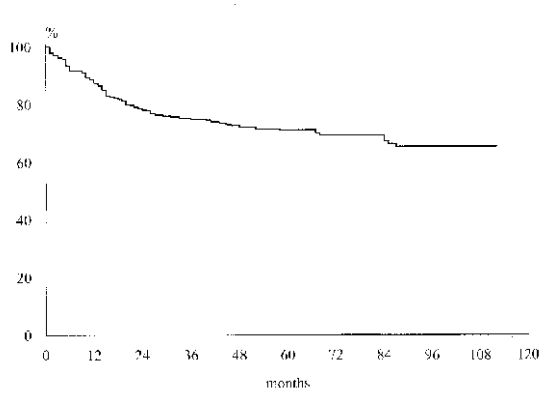

Figure 1. Global overall survival curve of 348 patients with aggressive NHL.

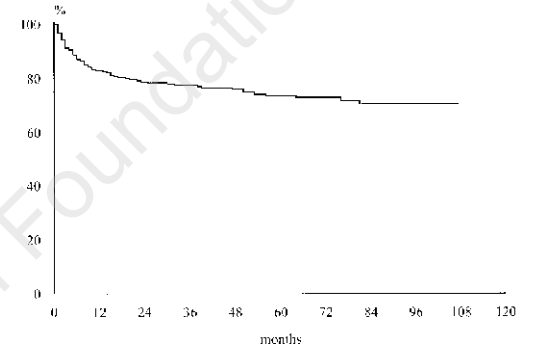

Figure 2. Global relapse-free survival of 249 complete responders.

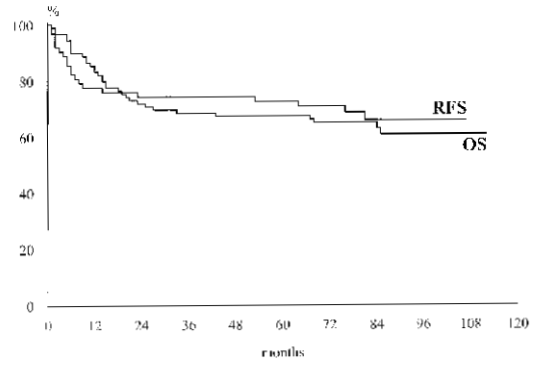

Figure 3. Overall survival and relapse-free survival curves of the MACOP-B group.

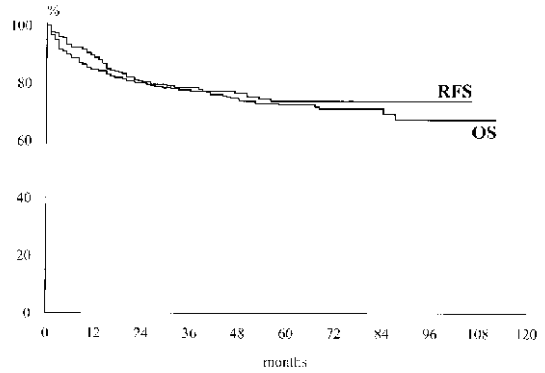

Figure 4. Overall survival and relapse-free survival curves of the F-MACHOP group.

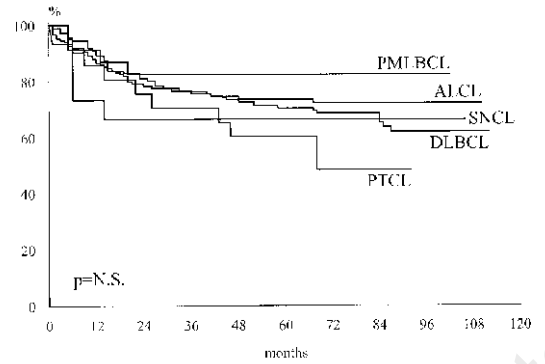

Figure 5. Overall survival curves according to histologic subtypes.

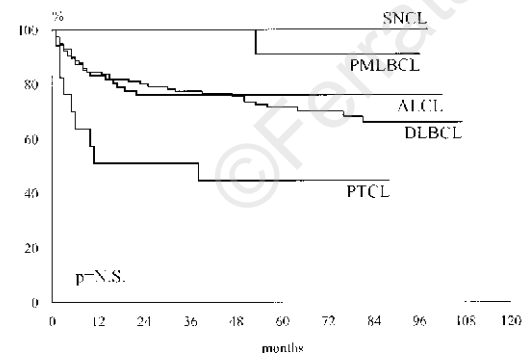

Figure 6. Relapse-free survival curves according to histologic subtypes.

60 years in the age-adjusted IPI was complete for all of the 348 patients of the study. As can be seen from Table 3, the fit of the IPI model to our set of patients was good. Figures 7 and 8 show the significant bearing of IPI risk factors (0-1 vs 2-3) on OS ($p< 0.0000$) and RFS ($p=0.02$), respectively.

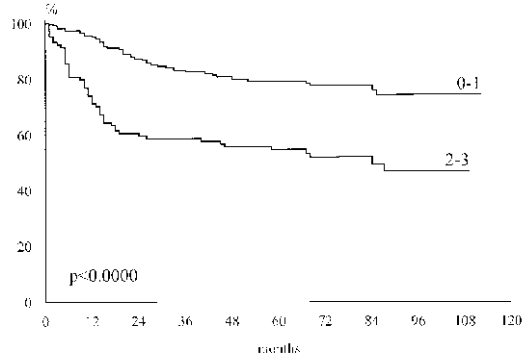

Figure 7. Overall survival curves according to IPI score.

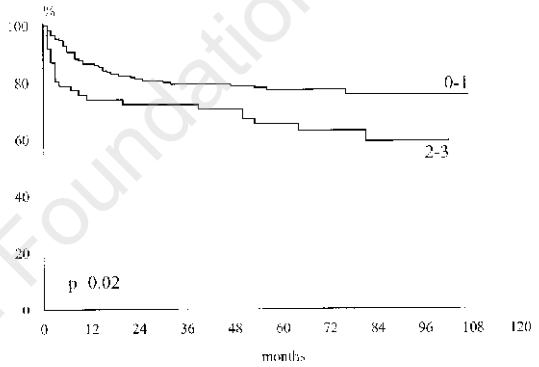

Figure 8. Relapse-free survival curves according to IPI score.

Lower CR rate was correlated to the presence of bulky disease ($p=0.002$), B symptoms ($p=0.02$) and advanced stage ($p=0.001$). The prognostic factors associated with longer RFS in univariate analyses (log-rank test) were localized stage, good performance status and bulky disease. In a Cox multivariate analysis, the prognostic factors most significantly associated with longer OS or longer RFS were localized disease stage ($p=0.001$) and good performance status ($p=0.002$).

Table 3.Outcome according to the International Prognostic Index.

Risk group *Age-adjusted index (pts age ≤60 yrs)*	*No. of risk factors*	*OS* *5-yr rate*	*OS* *8-yr rate*	*RFS* *5-yr rate*	*RFS* *8-yr rate*
Low	0	87%	80%	87%	85%
Low-intermediate	1	70%	68%	65%	64%
High-intermediate	2	60%	60%	58%	52%
High	3	43%	21%	51%	25%

Response to salvage treatment

All relapsed patients were treated with curative intent. Of the 51 early relapses, 28 (55%) patients achieved a second CR following salvage treatment. Of these, 10 (36% of the responders and 20% of all the early relapses) remained in second CR with a median follow-up of 52 months. Among the 14 late relapsed patients, 3 (21.5%) obtained a second CR: only one (33% of the responders and 7% of all the late relapsers) of them is in continuous CR after 30 months. Globally, there were 11/65 (17%) second CRs with a median follow-up of 45 months; 8/11 (73%) of these patients received high-dose chemotherapy/radiation therapy with rescue of autologous bone marrow or hematopoietic stem cell transplantation.

Discussion

Few reports exist on follow-up data of 5 years or more regarding patients with advanced aggressive NHL submitted to third-generation polychemotherapy regimens.[18-21] We set out to address some of the questions left largely unanswered due to the relative dearth of such information. In particular, long-term outcome analysis of RFS is important to interpret the real curative value of the induction regimen. Although late relapse of aggressive NHL (>2 years from diagnosis) is believed by most hematologists to be an unusual occurrence, this has been shown to be an erroneous belief.[1,28] Another common dogma is that after relapse death from lymphoma is inevitable. In addition, the prognostic factors that are predictive of short-term survival might not necessarily turn out to be equally valid for long-term survival: one theme of the present study was to assess whether the effect of the main IPI prognostic factors measured at diagnosis decays as time passes.

The present long-term analysis extends the patients' follow-up to a minimum of 58 months with a median of 6 years for all surviving patients. The results of this analysis demonstrate that both MACOP-B and F-MACHOP produce similar results in terms of 9-year OS (61% vs 67%, respectively) and 9-year RFS (66% vs 74%, respectively). The global 9-year OS and RFS were 65% and 70%.

Of the 249 patients who obtained CR, 65 (26%) subsequently relapsed. In terms of relapse, no differences were observed between the two regimens. As regards the timing of the relapses, there were 51 (78.5%) early relapses (< 24 months) and 14 (21.5%) late relapses (≥ 24 months) without any significant differences between the two regimens. It should be underlined that a relapse was recorded as late as the seventh year after diagnosis.

Concerning the histologic subsets, the RFS rate was better in the PMLBCL and the rare SNCL subgroups and worse in the PTCL one, with the ALCL and DLBCL subgroups having a rate lying midway. However, no statistically significant differences were observed.

It is important to note that the lower risk groups of the IPI[17] significantly correlated with OS and RFS ($p < 0.0000$ and $p = 0.02$, respectively).

In conclusion, these data suggest that: i) about 50% of patients with an initial diagnosis of aggressive NHL can be reasonably believed to be cured by standard third-generation polychemotherapy regimens, since our median follow-up is 6 years with a 9-year RFS; ii) about a quarter of the CR patients will ultimately relapse, with late relapses occurring in roughly 20% of all relapsed patients. This figure is similar to those of the Dana-Farber (32%) and British Columbia (25%) experiences; iii) contrary to common belief, however, death from lymphoma after relapse does not appear to be inevitable: median follow-up after relapse was 45 months with a CR rate of 17%. Long-term survival is therefore possible and appropriate therapy for relapsed aggressive NHL should be instituted. High-dose chemotherapy with marrow transplantation might be the treatment of choice: 8/11 (73%) of the patients with second continuous CR recorded by us were treated at the time of relapse with this intensive approach; iv) the IPI score remains valid for long-term analysis and retains its pivotal role in terms of stratifying the patients according to the different risk subsets.

In the future, the presence of new biological prognostic factors (sCD30, sCD44, bcl-2, bcl-6, interleukin-6, etc)[29-35] could integrate the initial clinical prognostic score to stratify patients for different therapies (standard polychemotherapy vs standard polychemotherapy plus high-dose approaches). In addition, a better understanding of the long-term dependent covariates, combined with an analysis of the prognostic factors after relapse, may help to identify those patients who could benefit from intensive salvage chemotherapy followed by autologous bone marrow transplantation.

Contributions and Acknowledgments

PLZ and MMar were the principal investigators involved in the conception of the study and its design. MMag and FG helped the principal investigators (PLZ and MMar) with the data analysis interpretation. FZ, SS, EP, VML, ADR, MG, MBo, FR, LS, FP, MBe, VS and CC collected the study data. PLZ wrote the paper. ST and FM critically revised the paper and gave the final approval for its submission.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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