original paper
Haematologica 1997; 82:309-313

IDARUBICIN IN PATIENTS WITH DIFFUSE LARGE CELL LYMPHOMAS: A RANDOMIZED TRIAL COMPARING VACOP-B (A = DOXORUBICIN) vs VICOP-B (I = IDARUBICIN)

MARILENA BERTINI,* ROBERTO FREILONE,* BARBARA BOTTO,* ROBERTA CALVI,* ANDREA GALLAMINI,° ANNA MARIA GATTI,# ANNA MARIA LIBERATI,@ VITTORIO MENEGHINI,^ ESTER ORLANDI,§ LORELLA ORSUCCI,* MICHELE PIZZUTI,** DELIA ROTA SCALABRINI,°° FLAVIA SALVI,## GIUSEPPE TODESCHINI,^ UMBERTO VITOLO,* LUIGI RESEGOTTI*

**Divisione di Ematologia, Azienda Ospedaliera S. Giovanni Battista, Torino; °Divisione di Ematologia, Azienda Ospedaliera S. Croce e Carle, Cuneo, #Istituto Scientifico di Medicina Interna, Università di Genova, Genova; @Cattedra di Clinica Medica, Università degli Studi, Perugia; ^Cattedra di Ematologia, Università degli Studi, Verona; §Cattedra di Ematologia, IRCCS Policlinico S. Matteo di Pavia; **Divisione di Ematologia, Ospedale S. Carlo, Potenza; °°Divisione di Ematologia, Ospedale Mauriziano, Torino; ##Divisione di Ematologia, Azienda Ospedaliera S. Antonio e Biagio, Alessandria; Italy*

ABSTRACT

Background and Objective. Idarubicin is an effective drug in acute leukemia but its use in non-Hodgkin lymphomas (NHLs) is not yet well established. We evaluated its efficacy in patients with diffuse large cell lymphoma (DLCL) by means of a randomized trial comparing two 12-week regimens (VACOP-B and VICOP-B) which differed only in the anthracycline drug used (doxorubicin vs idarubicin).

Methods. From January 1992 to December 1994, 104 patients aged less than 65 years with *de novo* advanced stage DLCL, were enrolled. Fifty-two patients were treated with VACOP-B (doxorubicin 50 mg/sqm) and 52 with VICOP-B (idarubicin initially 8 mg/sqm and thereafter 10 mg/sqm).

Results. Clinical characteristics of the two groups were not significantly different. One $HBsAg^+$ patient died of hepatic necrosis in the VICOP-B arm, and severe (WHO grade > 2) toxicities occurred in 7 patients treated with VACOP-B and in 5 treated with VICOP-B; the only significant difference was for mucositis (p=0.02). Complete remission (CR) was obtained in 79% of patients receiving VACOP-B and in 56% (idarubicin 8 mg/sqm) and 75% (idarubicin 10 mg/sqm) of those in the VICOP-B group (p=n.s.). Prognostic factors that negatively affected CR were advanced stage in VACOP, bone marrow infiltration in both schedules. At a median follow-up of two years, overall survival (67% VACOP and 61% VICOP) and disease-free survival (65% and 67%, respectively) were not significantly different.

Interpretation and Conclusions. Idarubicin is slightly less toxic than doxorubicin; at a dose of 10 mg/sqm the former is easily tolerated and shows the same efficacy as doxorubicin in the treatment of DLCL.

Key words: malignant lymphoma, chemotherapy, anthracyclines

The treatment of diffuse large cell lymphomas (DLCL) has been a well-developed field of clinical research since 1976 when the CHOP regimen[1] was shown to obtain a high proportion of complete remission (CR) in these lymphomas and cure about 30-35% of patients.[2]

Third generation regimens started in 1983 with ProMACE-MOPP,[3] MACOP-B,[4] M-BACOD.[5] The results achieved with these combinations seemed to be better than CHOP when evaluated in a single institution, but in a study conducted in North America in which CHOP was randomized with m-BACOD, ProMACE-CyTABOM and MACOP-B, this advantage was not evident.[6] A total of 899 patients entered this study and the same CR rate and the same survival curve were obtained with all four regimens; furthermore, toxicity was higher with the more recent schedules.

In the Italian Multiregional NHL Study Group (IMRNHLSG) we have been using the MACOP-B scheme[7,8] since 1986, obtaining a CR in 71% of patients and DFS of 50% at 40 months. We observed a 5% rate of toxic deaths mainly due to mucositis and infections. in an attempt to reduce this number we have employed VACOP-B since 1990, a schedule proposed by O'Reilly *et al*.[9] in which methotrexate was substituted by etoposide, because it is less toxic but is described as having cytotoxic effects on neoplastic cells. Idarubicin was added to the therapeutic armamentarium some years ago and is widely used in acute myelogenous leukemia (AML) and acute promyelocytic leukemia (APL),[10,11] but it is seldom utilized in NHL, especially in association with other drugs. Interestingly, idaru-

Correspondence: Dott. Marilena Bertini, Divisione di Ematologia, Azienda Ospedaliera S. Giovanni Battista, corso Bramante 88, 10100 Turin, Italy.
Received January 7, 1997; accepted April 8, 1997.

bicin and its metabolite idarubicinol use different mechanisms to escape MDR effusion pumps, and idarubicinol can cross the blood-brain barrier.[12]

To evaluate the efficacy of idarubicin in DLCL, we randomly assigned the patients under our observation to treatment with the VACOP-B or VICOP-B scheme, in which doxorubicin was substituted by idarubicin. The aims of our study were to confirm that VACOP-B is less toxic than MACOP-B and to evaluate whether VICOP-B is less toxic than and has the same effectiveness as VACOP-B.

Patients and Methods

One hundred and four patients with de novo advanced stage DLCL were enrolled in a cooperative study conducted by the *Italian Multiregional NHL Study Group* (IMRNHLSG) between January 1992 to December 1994; these patients were observed through June 1996 or until death.

The criteria for inclusion were: a histologic diagnosis of diffuse non-Hodgkin's lymphoma of large-cleaved, large noncleaved or immunoblastic types according to the Working Formulation;[13] age between 13 and 65 years; performance status (PS) less than 3 on the *Eastern Cooperative Oncology Group* (ECOG) scale, and no past or present medical history of severe cardiac, renal or hepatic disease. Patients were required to have advanced stage III or IV disease according to Ann Arbor criteria.[14] Stage II patients were included only if they had B symptoms, bulky disease or extensive E lesions not reasonably encompassed by a radiotherapy treatment field. Patients with primary gastrointestinal lymphoma and non contiguous abdominal lymph nodes (i.e. retroperitoneal) involved by the tumor were classified as having stage IV disease only if they had either biopsy proven or unequivocal radiological findings of non contiguous extranodal disease. In keeping with our previous study,[8] we administered VACOP-B or VICOP-B only to patients at low or intermediate risk or older than 55 years. Those in a high risk group or younger than 55 years were treated with a more aggressive schedule followed by ABMT or PBPC support.[15] Patients with AIDS or ones who were human immunodeficiency virus positive were not included in the study.

Staging included routine blood chemistry tests, blood cell counts and differentials, ECG, chest x-ray, computed tomography (CT) of the chest, abdomen and pelvis; bilateral bone marrow biopsy was carried out in all patients. Percutaneous liver biopsy, a gastrointestinal series with endoscopy, lumbar puncture and CSF examination, and brain CT scan were performed only when there was clinical concern that liver, GI tract or CNS involvement was present.

The patients were randomized to receive VACOP-B or VICOP-B chemotherapy. The VACOP-B regimen was given according to the original scheme proposed by O'Reilly *et al*.:[9] doxorubicin 50 mg/sqm during weeks 1, 3, 5, 7, 9, 11; cyclophosphamide 350 mg/sqm during weeks 1, 5, 9; etoposide 75 mg/sqm for two consecutive days in weeks 3, 7, 11; vincristine 1.4 mg/sqm and bleomycin 15 mg/sqm during weeks 2, 4, 6, 8, 10, 12; prednisone 45 mg/sqm p.o. for 15 days then every other day. In the VICOP-B scheme doxorubicin was substituted by idarubicin at a dose of 8 mg/sq and after June 1994 this was raised to 10 mg/sqm in 8 patients. Dose reduction guidelines were the same for both schedules and, as in the original study,[4] dosages of doxorubicin and cyclophosphamide were reduced if necessary on the basis of blood counts obtained on the day that chemotherapy was due. The use of growth factors was not planned.

Patients with bone marrow (BM) or sinus involvement were given CNS prophylaxis consisting of six doses of intrathecal cytarabine 30 mg/sqm plus prednisolone 25 mg/sqm given twice a week during the treatment program, starting after the bone marrow or sinuses were cleared of disease. Tumor volume was assessed in two ways: 1) by the presence or absence of bulky disease in a single location, defined as a mass > 10 cm in one diameter or more than one third of the chest diameter in the mediastinum; 2) by determining tumor burden (TB) as low or high according to the number of extranodal sites and the number of extensive nodal areas as proposed by MDAH in 1986.[16] An extensive nodal area was defined as a T3 to T4 tumor according to the tumor-node metastasis (TNM) classification (*American Joint Committee of Cancer Staging*) for Waldeyer's ring; for neck and axilla, a nodal mass > 10 cm; any mediastinal mass, and for the abdomen, any palpable mass, organ displacement, periaortic and pelvic nodal involvement, or nodal mass > 10 cm. TB was considered high in cases of more than two extensive nodal areas, more than three extranodal sites, or the association of one extensive nodal area with two extranodal sites. An international prognostic index score (IPI) was assigned according to the Shipp criteria.[17]

All patients were evaluated for pretreatment characteristics possibly predictive of CR, DFS and OS. Factor analysis included age, performance status, constitutional symptoms, histologic subtype, disease stage, BM involvement, bulky disease status, lactate dehydrogenase (LDH) level, TB and IPI.

One month after the completion of treatment patients were fully restaged. Restaging tests included blood chemistries and CT scans of the chest, abdomen and pelvis in all patients and repetition of any previously abnormal staging sites, including appropriate biopsies. The same restaging tests were performed at 6, 12, 24 months off therapy. Patients with no evidence of active disease for a minimum of 4 weeks were judged as having a CR. Patients with a residual radiological mass and no signs or symptoms of active disease (i.e. B symptoms or elevated LDH level) with subsequent stabilization for at least 3 months after treatment, were judged to have CR. A partial remission (PR) was defined as a 50% or greater decrease in the sum of the products of the maximum perpendicular diameters of all measured lesions lasting for at least 4 weeks. Failure was defined as anything less than a PR. Patients in CR at the end of treatment received no further therapy. Patients with a PR or failure received different combinations of radiation and salvage chemotherapy.

All the patients who started on treatment were considered evaluable. As in our previous report survival includes all patients and an event is defined as the death of a patient due to any cause. Survival duration was measured from the beginning of treatment to the date of death or last living follow-up. DFS applies only to patients who achieved a CR: its duration was calculated from the time of CR assessment to the date of relapse or the last follow-up free of disease. Univariate analysis for CR was performed. Survival and DFS curves were plotted according to the method of Kaplan and Meier.[18] Statistical significance among curves was determined by the Breslow generalized Wilcoxon test. All calculations were made with the BMDP program (1985) developed at the Health Science Computing Facility, University of California at Los Angeles (NHI), Special Research Resources, USA.

Results

From January 1992 to December 1994 we treated 52 patients with VACOP-B and 52 with VICOP-B in a random manner. The clinical characteristics of these 104 patients are listed in Table 1. The median age was 51 years (16-65); 27 patients treated with VACOP-B were males, while 34 males received VICOP-B. There were no other differences between the two groups (histology, LDH level, PS, symptoms, stage, E lesions, presence of bulky disease, BM involvement).

Response to treatment

CR was obtained in 79% of the patients treated with VACOP-B, in 56% (idarubicin 8 mg/sqm) and 75% (idarubicin 10 mg/sqm) of those receiving VICOP-B (p = n.s.). PR were 14% in the VACOP

Table 1. Clinical characteristics of the 104 DLCL patients studied.

	VACOP		VICOP	
Patients	52		52	
Age				
median (years)	51		52	
< 60 years	42	(81)	35	(67)
Sex				
male	27	(52)	34	(65)
female	25	(48)	18	(35)
Histologic subtype	27	(52)	24	(46)
G	17	(33)	25	(48)
H	8	(15)	3	(6)
K1				
ECOG performance status				
0	26	(50)	22	(42)
1	19	(36.5)	15	(30)
2	4	(8)	9	(17)
3+4	3	(6)	6	(11)
Stage				
II	19	(51)	18	(49)
III	12	(50)	12	(50)
IV	20	(48)	22	(52)
*LDH level**				
normal	21	(43)	21	(40)
above normal	28	(57)	31	(60)
Bulky disease				
no	29	(56)	24	(46)
yes	23	(44)	28	(54)
I.P.I.				
1	14	(29)	12	(23)
2	24	(49)	17	(33)
3	6	(12)	17	(33)
4	5	(10)	6	(11)

**LDH level was not determined in 3 patients.*

and 18% in the VICOP groups, and treatment failures were, respectively, 7% and 20%. Of the sixteen patients in PR, 11 were converted to CR with chemotherapy and 5 died of lymphoma. Of the fourteen NR patients, 13 died of lymphoma and 1 is alive and well after intensive chemotherapy and reinfusion of his PBPC. Among the prognostic factors in the VACOP-B group, advanced stage and BM infiltration negatively affected the achievement of remission in univariate analysis, whereas in the VICOP-B group patients with BM infiltration and high tumor burden had less favorable outcomes (Table 2). At a median follow-up of 28 months from the initiation of treatment, overall survival was 67% for patients treated with VACOP and 61% for those given VICOP; the difference was not statistically significant. DFS at a median follow-up of 28 months was 65% and 67%, respectively.

Toxicity

The general toxicity was quite low for both regimens (Table 3). Only one case of toxic death from hepatitis was reported in a patient who was HBsAg positive.

Table 2. Prognostic factors for CR.

	VACOP		VICOP	
Patients	52		52	
Age				
> 60 years	81%	ns	66%	ns
< 60 years	80%		41%	
Sex				
male	74%	ns	62%	ns
female	88%		50%	
Histologic subtype (WF)				
G	93%		58%	
H	71%	ns	52%	ns
K1	63%		100%	
ECOG performance status				
0	81%		59%	
1	84%	ns	67%	ns
2	75%		44%	
3+4	67%		50%	
Stage				
II	95%		60%	
III	83%	p=0.02	67%	ns
IV	65%		50%	
*LDH level**				
normal	76%	ns	67%	ns
above normal	82%		52%	
Bulky disease				
no	79%	ns	67%	ns
yes	78%		50%	
I.P.I.				
1	57%		67%	
2	46%	ns	47%	ns
3	33%		41%	
4	40%		50%	
BM				
infiltrated	85%	p=0.04	65%	
p=0.02				
not infiltrated	50%		22%	
TB				
low	83%	ns	68%	
p=0.05				
high	77%		39%	

**LDH level was not determined in 3 patients.*

Severe mucositis (WHO grade 3 and 4) occurred in 4 patients receiving VACOP-B and in none in the VICOP-B group, and the difference between the two regimens was significant (p = 0.02). Cardiotoxicity was very mild in both schedules and G.I. toxicity (nausea and vomiting) was irrelevant (2 patients with grade 2 nausea in each group). Peripheral neurotoxicity (grade 3 constipation) was observed in one patient receiving VACOP-B and in 2 receiving VICOP-B. Two patients showed grade 3 and one grade 4 hepatotoxicity in the VICOP-B group.

Three cases of severe infection were observed: one of grade 4 in the VACOP-B arm; one $HBsAg^+$ patient died fifteen days after completion of VICOP-B chemotherapy of acute hepatitis reactiva-

Table 3. Toxicity.

		No VACOP	*VICOP*
Patients		52	52
mucositis WHO grade	0	34	43
	1	10	6
	2	4	3
	3	3	0
	4	1	0
cardiac	0	52	49
	1	0	1
	2	0	2
hepatic	0	50	46
	1	1	1
	2	1	1
	3	0	2
	4	0	1
infections	0	41	43
	1	3	4
	2	5	4
	3	2	1
	4	1	0
	5	0	1
nadir neutrophils			
	< 0.5x10⁹/L	6	4
	< 1.0x10⁹/L	8	11
nadir platelets			
	< 20x10⁹/L	0	0
	< 50x10⁹/L	0	3
nadir Hb			
	< 8 g/dL	4	8
	< 9 g/dL	15	9

LDH level was not determined in 3 patients.

tion. One case of pneumothorax, one of deep venous thrombosis and one of pulmonary embolism were seen among the patients treated with the VACOP-B regimen.

Hematological toxicity was also mild (Table 3) and neutropenia less than 0.5×10^9/L was recorded only in 12% of those treated with VACOP and 8% of patients treated with VICOP. No patient received growth factors. Thrombocytopenia less than 50×10^9/L was never recorded. Mild anemia was observed in 39% and 29% of patients respectively; severe anemia was recorded in 8% of patients in the VACOP-B arm and in 17% of those in the VICOP-B group.

The most important difference in toxicity between the MACOP-B combination of our previous study and the present VACOP/VICOP-B regimen involved mucositis (WHO grade 3 and 4: 33% vs 4%; p = 0.03).

Discussion

The IMRNHLSG started to administer the MACOP-B regimen in 1986,[7,8] and found that this treatment was very useful in patients belonging to the low-risk group[17] (90% CR, 81% DFS and 72% OS), also provided good results in intermediate-risk cases (71% CR, 76% DFS and 67% OS) but yielded poor results in high-risk patients (50% CR, 44% DFS and 28% OS).[19]

In 1992 the IMRNHLSG undertook a study based on intensified chemotherapy (MACOP-B) followed by myeloablative therapy and autologous stem cell transplantation (ASCT) as first-line treatment in high-risk diffuse large cell lymphoma in patients aged less than 55 years.[15] For patients in the low

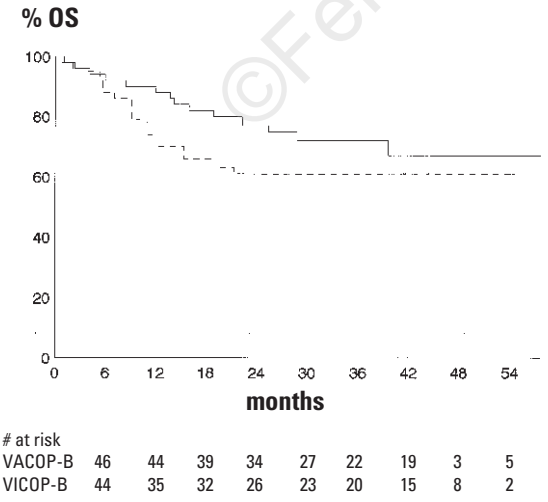

Figure 1. Overall survival of 102 patients; solid line, VACOP-B; dashed line, VICOP-B.

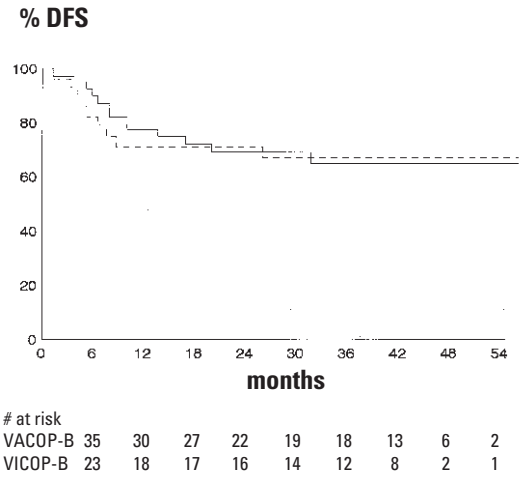

Figure 2. DFS of 71 patients achieving CR: solid line, VACOP-B; dashed line: VICOP-B.

and intermediate risk groups or older than 55 years we chose a less toxic regimen, VACOP-B, which had been used with the same results and less toxicity than MACOP-B by the Vancouver group.[9]

During this period new anthracyclines have been developed and proposed as effective substitutes for doxorubicin. Thus, epirubicin has been successfully employed in a CHOP-like combination called CEOP.[20] Zinzani *et al*.[21] employed idarubicin in a CHOP-like combination known as CIOP, showing that this new anthracycline was less toxic than doxorubicin and equally effective. These authors also found an equivalent therapeutic effect and slightly reduced clinical toxicity in the CIOP group.

We decided to test the efficacy of idarubicin in place of doxorubicin in VACOP-B. In the present study the results of the two regimens were similar (CR, DFS and OS) and did not differ from those obtained by our cooperative group with MACOP-B. Mucosal toxicity is milder in the VACOP-B/VICOP-B study ($p = 0.03$). Cardiac toxicity was very mild in both groups; only 3 patients in the VICOP-B group experienced grade 1 cardiotoxicity.

Analyzing the results of VACOP-B/VICOP-B we observed no statistical differences between the two schedules, but VICOP-B fared less favorably; the CR rate was 63% vs 79% and OS was 56% vs 73%, but DFS was the same. The clinical characteristics of the patients randomized to the VICOP-B group casually happened to be more negative than those of the patients who received VACOP-B: according to the IPI score, 44% of the patients in the VICOP-B group had an intermediate-high risk or high risk score vs. 22% in the VACOP-B arm.

Eight out of 51 patients in the VICOP group were given idarubicin at 10 mg/sqm based on recent data in AML that demonstrated that the effectiveness and myelotoxicity of idarubicin compared to those of doxorubicin.[22] Moreover, in our study the few patients who received idarubicin at 10 mg/sqm obtained a better CR rate (75% vs 56%, p = ns).

In conclusion, our results confirm that idarubicin is an effective, safe and manageable antineoplastic agent which combines high antitumor activity with a very acceptable level of toxicity. The weekly VACOP-B/VICOP-B regimen is more manageable than MACOP-B because it is less toxic. It is a good schedule for low or intermediate-low risk group DLCL patients.

References

1. McKelyey EM, Gottieb JA, Wilson HE, et al. Hydroxyldaunomycin (adriamycin) combination chemotherapy in malignant lymphoma. Cancer 1976; 38:1484-93.
2. Coltman AC jr. CHOP is curative in thirty per cent of patients with large cell lymphoma: a twelve-year Southwest Oncology Group follow up. In: Skarin AT, ed. Update on treatment for diffuse large cell lymphoma. New York:Park Row, 1986. p. 71-7.
3. Fisher RI, De Vita VT jr, Hubbard SM, et al. Diffuse aggressive lymphoma: increased survival after alternating flexible sequences of ProMACE and MOPP chemotherapy. Ann Intern Med 1983; 98:304-9.
4. Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of advanced diffuse large cell lymphoma. Ann Intern Med 1985; 102:596-602.
5. 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.
6. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non Hodgkin's lymphoma. N Engl J Med 1993; 328:1002-6.
7. Vitolo U, Bertini M, Tarella C, et al. MACOP-B treatment for advanced stage diffuse large cell lymphoma. A multicenter Italian study. Eur J Cancer Clin Oncol 1989; 25:1441-9.
8. Vitolo U, Bertini M, Brusamolino E, et al. MACOP-B treatment in DLCL: identification of prognostic groups in an Italian multicenter study. J Clin Oncol 1992; 10, 2:219-27.
9. O'Reilly SE, Hoskins P, Klimo P, et al. MACOP-B and VACOP-B in diffuse large lymphoma and MOPP/ABV in Hodkin's disease. Ann Oncol 1991; 22(suppl 1):17-23.
10. Bassan R, Lerede T, Rambaldi A, Buelli M, Viero P, Barbui T. The use of anthracyclines in adult acute lymphoblastic leukemia. Haematologica 1995; 80:280-91.
11. Bassan R, Barbui T. Remission induction therapy for adults with acute myelogenous leukemia: towards the ICE age? Haematologica 1995; 80:82-90.
12. Smith DB, Margison JM, Lucas SB, et al. Clinical pharmacology of oral and intravenous 4-demethoxydaunorubicin. Cancer Chemother Pharmacol 1987; 19:138-42.
13. The non Hodgkin's Lymphoma Classification Project. National Cancer Institute sponsored study of classification of NHL. Summary and description of a working formulation for clinical usage. Cancer 1982; 49:2135-212.
14. Carbone PP, Kaplan HS, Mushoff K, et al. Report of the commitee on Hodgkin's disease staging classification. Cancer Res 1971; 31:1860-1.
15. Vitolo U, Cortellazzo S, Liberati AM, et al. Intensified chemotherapy followed by myeloablative therapy and autologous stem cell transplanation (ASCT) as first line therapy in high risk diffuse large cell lymphoma (DLCL). Blood 1995; 86:(suppl 1)458.
16. Jagannath S, Velasquez WS, Tucker SL, et al. Tumor burden assessment and its implications for a poor prognostic model in advanced diffuse large cell lymphoma. J Clin Oncol 1986; 4:859-65.
17. Shipp M. A predective model for aggressive non Hogkin's lymphoma. The international non Hodgkin's lymphoma prognostic factors project. N Engl J Med 1993; 329:987.
18. Kaplan EL, Meier P. Non-parametric estimation from incomplete information. J Am Stat Assoc 1958; 53:457-81.
19. Freilone R, Vitolo U, Brusamolino E, et al. Late relapse and toxicities in advanced stage diffuse large cell lymphoma (DLCL) treated with MACOP-B: an eight year follow-up analysis. Ann Oncol 1996; 7:(suppl 2) 58.
20. Lambertenghi Deliliers G, Butti C, Baldini L, et al. A cooperative study of epirubicin with cyclophosphamide, vincristine and prednisone (CEOP) in non-Hodgkin's lymphoma. Haematologica 1995; 80:318-24.
21. Zinzani PL, Martelli M, Storti S, et al. Phase III Comparative Trial using CHOP vs CIOP in the treatment of advanced intermediate-grade non Hodgkin's lymhoma. Leuk Lymphoma 1995; 19:329-35.
22. Keating MJ. The expanding role of idarabucin in hematologic malignancies. Satellite Simposium "Emerging Trends in the management of hematological Malignancies" during the second Meeting of the EHA, Paris, 1996, May 29.