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A third generation regimen VACOP-B with or without adjuvant radiotherapy for aggressive localized non-Hodgkin's lymphoma - Report from the Italian Non-Hodgkin's Lymphoma Co-operative Study Group

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Abstract

The objective of this multicenter prospective study was to determine the clinical efficacy and toxicity of a polychemotherapeutic third generation regimen, VACOP-B, with or without radiotherapy as front-line therapy in aggressive localized non-Hodgkin's lymphoma. Ninety-three adult patients (47 males and 46 females, median age 45 years) with aggressive localized non-Hodgkin's lymphoma, 43 in stage I and 50 in stage II (non-bulky), were included in the study. Stage I patients received VACOP-B for 6 weeks plus involved field radiotherapy and stage II patients received 12 weeks VACOP-B plus involved field radiotherapy on residual masses. Eighty-six (92.5%) achieved complete remission and 4 (4.3%) partial remission. Three patients (3.2%) were primarily resistant. Ten-year probability of survival, progression-free survival and disease-free survival were 87.3, 79.9 and 83.9%, respectively. Eighty-four patients are surviving at a median observation time of 57 months (range: 6-126). Statistical analysis showed no difference between stages I and II in terms of response, ten-year probability of survival, progression-free survival or disease-free survival. Side effects and toxicity were negligible and were similar in the two patient groups. The results of this prospective study suggest that 6 weeks of VACOP-B treatment plus radiotherapy may be the therapy of choice in stage I aggressive non-Hodgkin's lymphoma. Twelve weeks of VACOP-B treatment with or without radiotherapy was shown to be effective and feasible for stage II. These observations need to be confirmed by a phase III study comparing first and third generation protocols in stage I-II aggressive non-Hodgkin's lymphoma.

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Introduction

In the 1960's and 70's radiotherapy was widely used for the treatment of localized non-Hodgkin's lymphoma (NHL) but results were unsatisfactory due to the high incidence of relapse and progression (1-5). Patients with localized, aggressive, non-bulky stage I and II NHL can be cured using first generation regimens containing doxorubicin, alone or in combination with involved field radiotherapy (6-8). In 1998, Miller et al. (7) published a randomized study comparing 3 cycles of classical first generation polychemotherapy containing doxorubicin (CHOP) plus involved field radiotherapy with 6-8 cycles of CHOP treatment for localized intermediate and high-grade NHL, without considering stage during randomization. The study cited suggested the advantage of combined therapy (CHOP plus radiotherapy) in terms of overall and progression-free survival. Further advantages included a decrease in both life-threatening toxic effects and heart failure due to cumulative doxorubicin toxicity (7,8). The CHOP regimen seems to represent a good treatment for early stage aggressive NHL. However, 6-8 cycles of CHOP treatment resulted in an increase in extra-hematological toxicity (7) without the potential advantages of disease eradication or avoiding the complications of radiotherapy (5,7,8). Left ventricular function can be significantly reduced in patients treated with 8 cycles of CHOP (7). Phase II studies seem to confirm the encouraging results obtained by combining chemotherapy and radiotherapy (9). Three cycles of doxorubicin-based chemotherapy and involved field radiotherapy seem to be a successful approach with respect to long-term outcome for most patients with early stage aggressive NHL (10). When compared to standard CHOP therapy, intensive second and third generation regimens seem to offer no advantage when used as front-line therapy in advanced diffuse and aggressive NHL (6,11,12). However, there are few reports of second or third generation regimens alone or combined with radiotherapy as front-line treatment for localized NHL (13,14).

VACOP-B is a third generation regimen consisting of etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin which was effective as front-line therapy for advanced and diffuse NHL (15,16). When compared with the CHOP protocol, toxicity was very low and treatment time was shorter in this subset of patients.

Thus, in October 1991, the Italian Non-Hodgkin's Lymphoma Co-operative Study Group (NHLCSG) began a controlled, prospective, non-randomized multicenter study to analyze the role of VACOP-B with or without radiotherapy in improving outcome and reducing chemotherapy-related toxicity in patients with aggressive localized NHL.

Design and Methods

Eligibility criteria and treatment

This was a prospective, non-randomized study, involving 8 NHLCSG centers, Italy. The study began in October 1991 and ended in December 2001. Study eligibility criteria were as follows: patient age from 16 to 60 years, patients with diffuse intermediate or high-grade malignancy NHL according to the Working Formulation Classification (17) (excluding lymphoblastic lymphoma and Burkitt's lymphoma); Ann Arbor System (18) stage I (including bulky disease), staging I-E non-bulky, stage II or non-bulky stage II-E disease; normal renal, pulmonary, cardiac, and hepatic function. Performance status (PS) was established according to the Eastern Cooperative Oncology Group system (19). Bulky disease was defined as a mediastinal mass >0.33 of the maximum intrathoracic diameter as determined by a chest X-ray or any other mass with a maximal diameter ≥10 cm. Previously treated

patients or those with a positive serology for human immunodeficiency virus and hepatitis B or C virus were excluded. All patients were ambulatory. Patients with a history of congestive heart disease, another cancer, or symptoms or findings compatible with central nervous system involvement by lymphoma were excluded. All participants gave written informed consent before treatment. The study protocol was approved by the institutional review board of each participating hospital. All cases were reviewed by a central committee to confirm the diagnosis.

After pretreatment evaluation, 93 patients were assigned to receive 6 cycles of VACOP-B followed by involved field radiotherapy (stage I, 43 patients) or 12 cycles of VACOP-B (stage II, 50 patients). Patients in stage II who still presented a residual mass were treated with involved field radiotherapy. The radiotherapy doses ranged from 4000 to 5000 cGy administered in 20 fractions over a period of 4 weeks. Most patients received 4,500 cGy. VACOP-B was given according to the original protocol (15). VACOP-B is a 12-week third generation protocol consisting of doxorubicin, 50 mg/m^2 *iv*, in the 1st, 3rd, 5th, 7th, 9th, and 11th weeks of treatment; cyclophosphamide, 350 mg/m^2 *iv*, in the 1st, 5th and 9th weeks; VP-16, 50 mg/m^2 *iv*, on day 1 and 100 mg/m^2 *po* on days 2-3 in the 3rd, 7th, and 11th weeks; bleomycin, 10 U/m^2 *iv*, and vincristine, 1.2 mg/m^2 *iv*, in the 2nd, 4th, 6th, 8th, 10th, and 12th weeks, and prednisone, 45 mg/m^2 per day *po*, in the 1st week and on alternate days until the end of treatment. Stage II patients who achieved complete remission after 12 cycles of VACOP-B were followed until the end of the study.

Disease status was defined on completion of treatment (chemotherapy alone or combined chemoradiotherapy). Patients in partial remission, non-responders, or relapsed patients received a second line conventional chemotherapy: 6 cycles of "CEMP" protocol repeated at 21-day intervals (cyclophosphamide, 650 mg/m^2 on day 1; VP-16, 150 mg/m^2 on day 1; mitoxanthrone, 12 mg/m^2 on day 1; methylprednisone, 60 mg daily given orally on day 1 to 5) (20) or 6 cycles of the traditional CHOP protocol (6). Patients who had not obtained complete remission after two conventional chemotherapy series underwent an intensified phase including cyclophosphamide at the dosage of 7 g/m^2 to reduce tumor burden and to collect peripheral blood progenitor cells for subsequent autologous stem cell transplant (21).

Staging and response criteria

Staging included routine blood chemistry tests, complete blood cell counts and differentials, ECG, and chest X-ray. Extent of disease was confirmed by physical examination, bilateral iliac crest bone marrow biopsies, and computed tomography (CT) of the chest, abdomen, and pelvis. Magnetic resonance imaging (MRI) and radionuclide scans were performed when required. Laparotomy and/or laparoscopy to confirm clinical and instrumental stage were not performed.

Complete re-staging was performed at the end of treatment. This included two posterior iliac crest biopsies, CT of chest, abdomen, and pelvis, MRI scan and radionuclide scan when required. Re-staging was performed every three months during the first year after completion of therapy, every 6 months in the second year, and annually thereafter. In addition, patients were carefully followed and all necessary tests were performed when clinically required.

Complete remission was defined as the complete disappearance of the disease and normalization of all laboratory values for at least 4 weeks. Patients with persistent CT abnormalities but >75% regression of the initial tumor were defined as being in unconfirmed complete remission if in complete remission in all other parameters (22). Partial remission was defined as a >50% to 75%

reduction of all measurable lesions. Non-response was defined as a less than 50% reduction in tumor mass, and progressive disease as an increase of at least 25% in the size of disease or the appearance of new lesions.

Patients who received consolidation radiotherapy were assessed for response on completion of therapy. The toxicity of conventional chemotherapy was evaluated according to World Health Organization (WHO) criteria.

Statistical analysis

This was an open-label phase II study. The primary end-point was tumor response. Overall survival, progression-free survival (progression-free survival) and disease-free survival (disease-free survival) were assessed as secondary end-points.

It is assumed that the combination therapy will be of no further interest for patients with stage I-II NHL if the true tumor response rate is less than 60% (H_0). The alternate hypothesis (H_1) assumes that a true response rate of 75% or more would be of considerable interest in patients with the disease. The study took place in two stages: the first stage included 34 patients. If less than 21 responses had been seen, the trials would have been terminated. Otherwise, accrual was to continue up to a total of 95 patients with a 5% alpha-error and a power of 90%. If more than 64 responses were observed we would conclude that the combination therapy was promising for further study.

Patients were enrolled by telephone from the Central Office (University of Genoa, Istituto dei Tumori, Italy). Analysis was based on disease status on December 15th, 2002. Overall survival was measured from the date of enrollment to the date of death or last follow-up evaluation. Progression-free survival was applied to all patients and was calculated from the date of enrollment to the date of relapse, progression, death or last follow-up evaluation. Disease-free survival was only applied to patients who achieved complete remission. Duration was calculated from the date of complete remission assessment to the date of relapse or last confirmation of complete remission status. Actuarial curves were estimated according to the Kaplan and Meier (23) method. The statistical significance of the difference between groups was determined by the log-rank test. The relationship between parameters and outcome was examined by univariate and multivariate analysis according to Cox's hazards regression model (24). Survival analysis according to a number of prognostic factors included in the step-wise Cox analysis was as follows: PS (0 *vs* 1), stage (I *vs* II), and lactate dehydrogenase (LDH) (normal *vs* abnormal). We also carried out a retrospective analysis of patients according to the International Non-Hodgkin's Lymphoma Prognostic Factors Project (International Prognostic Index, IPI) (25) stage modified by Miller et al. (7) and adjusted for age ≤60 years. The adverse factors considered were stage II, increase of LDH level, and a PS > 1. Age over 60 years was removed from the analysis according to the original IPI indication. Statistical tests for comparison of main objectives were regarded as significant if the two-sided P value was less than 0.05. The χ^2 test or the Fisher exact test was used to compare toxicity according to group.

Results

Patient characteristics

Ninety-three patients with a median age of 45 years (range 17-60) entered the study. Forty-seven patients were males and 46 were females; 43 were in stage I and 50 were in stage II; 79 patients had a PS = 0 and 14 patients a PS = 1. Seven patients in stage I and 15 patients in stage II showed mediastinal involvement. Two stage I patients had

mediastinal bulky disease. Extranodal involvement was present in 8 stage I-E patients (sinus, 4; breast, 2; bladder, 1; bone, 1) and in 5 stage II-E patients (sinus, 4; thyroid, 1). All patients received VACOP-B with or without radiotherapy according to the protocol. There were no patients with a PS > 1. The distribution of patients according to the IPI stage, modified by Miller et al. (7) and adjusted for age ≤60 years, only included patients with no more than 2 negative prognostic factors. Histology features and other patient characteristics at diagnosis are reported in Table 1.

Response to treatment and survival

All patients were available for response. At the end of therapy, 86 of 93 patients (92.4%) were in complete remission or in unconfirmed complete remission (3 patients), 4 in partial remission (4.3%) and 3 (3.2%) were non-responders.

After 6 cycles of VACOP-B, 37 stage I patients entered complete remission + unconfirmed complete remission (1 patient) (86%), 2 achieved partial remission and 4 were non-responders. After involved field radiotherapy, 41 stage I patients were in complete remission (95%) and 2 were non-responders (5%). These last 2 patients died 7 and 16 months after diagnosis because of progression in spite of a polychemoterapeutic salvage regimen containing cisplatinum and Citarabin (DHAP) (26) in one case and high-dose therapy in the other. Eleven stage I patients (26%) had received treatment following a diagnostic biopsy without visible tumor masses. Four patients refused to undergo involved field radiotherapy.

After 12 courses of VACOP-B, 40 stage II patients achieved complete remission + unconfirmed complete remission (2 patients) (80%), 8 entered partial remission and 2 patients were non-responders. Ten patients received involved field radiotherapy. At the end of treatment 45 patients were in complete remission (90%), 4 in partial remission and 1 patient was a non-responder. Four patients of this last group showed a stable persistence of minimal residual masses (≤1.5 cm) after radiotherapy, and required extensive re-staging including an MRI scan and radionuclide scan. They were judged to be in complete remission three months after radiotherapy. Salvage therapy in the 4 partial remission patients and in 1 non-responder

Table 1. Characteristics of the patients before treatment.

Characteristics	No.	%
Age (years)		
Median	45	
Range	17-60	
Sex		
Male	47/93	50.5
Female	46/93	49.5
Performance status		
0	79/93	84.9
1	14/93	15.1
Histology		
Diffuse mixed	13/93	14.0
Diffuse large-cell	56/93	60.2
Large-cell immunoblastic	13/93	14.0
Other		
Anaplastic/Ki-1	6/93	6.4
Unclassifiable	5/93	5.4
Stage		
I	41/93	44.1
I bulky >10 cm	2/93	2.1
II	50/93	53.8
Symptoms		
A	87/93	93.5
B	4/93	4.3
NA	2/93	2.2
Immunophenotype		
B	83/93	89.2
T	6/93	6.5
Null	4/93	4.3
Lactate dehydrogenase		
Normal	78/93	83.9
Increased	15/93	16.1
Number of risk factors*		
0	36/93	38.7
1	49/93	52.7
2	8/93	8.6

NA = not available. *Adverse risk factors were defined as a stage II, increased lactate dehydrogenase, and a performance status of 2 (IPI stage modified by Miller et al. (7) and adjusted for age).

patient consisted of the DHAP regimen for 2 patients and high-dose therapy for 3 patients. Two patients in partial remission achieved complete remission after DHAP and 3 died because of progressive disease 7, 9 and 9 months after diagnosis, respectively.

Two of 41 (51%) stage I patients relapsed 3 and 6 months after complete remission. After conventional therapy both achieved a second complete remission. Eight of 45 (18%) stage II patients relapsed within a median time of 14 months (range: 6-43 months) after complete remission, 4 at a different site and 4 at the initial site of disease (3 of these had previously received involved field radiotherapy). These patients received DHAP (4 patients), CHOP plus radiotherapy (1 patient), and DHAP plus high-dose therapy (3 patients). Four patients achieved a second complete remission, while 4 died from progressive disease within a median time of 9 months after relapse.

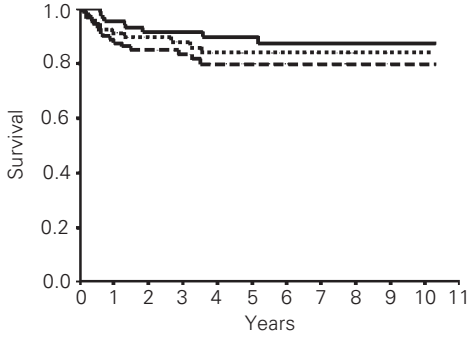

Figure 1. Overall survival (continuous black line), disease-free survival (dotted line) and progression-free survival (broken line) for 93 non-Hodgkin's lymphoma patients treated with VACOP-B with or without radiotherapy.

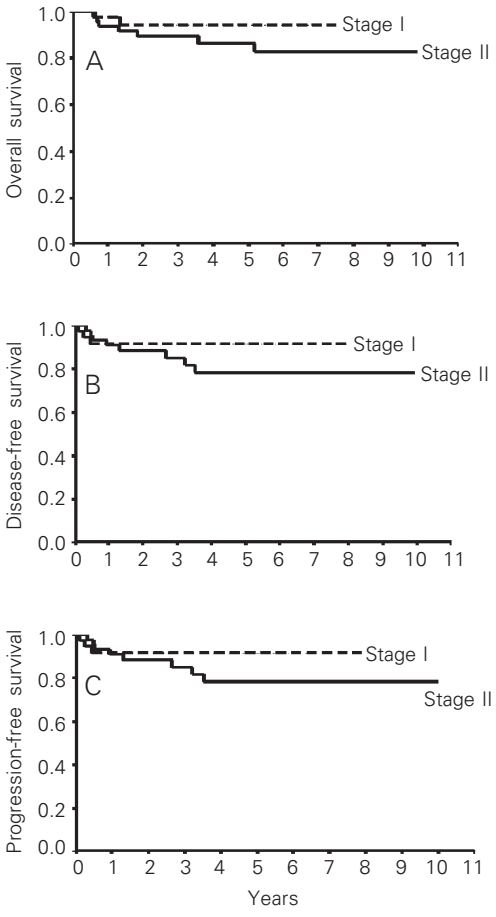

Figure 2. Overall survival (A), disease-free survival (B) and progression-free survival (C) for non-Hodgkin's lymphoma patients in stages I and II treated with VACOP-B with or without radiotherapy and staged as described elsewhere (18).

On July 7, 2003, 84 of 93 patients were still alive. The median follow-up observation time for these patients was 57 months (range: 6-126 months). The ten-year survival estimate for patients was 87.3% (SEM 4.2%). The ten-year probability of disease-free survival and of progression-free survival was 83.9% (SEM 4.6%) and 79.9% (SEM 4.6%), respectively (Figure 1).

The overall survival rates at 8 years were 94.5% (SEM 3.8%) for stage I patients and 82.8% (SEM 6.1%) for stage II patients ($P = 0.2$; Figure 2). The probability of disease-free survival and of progression-free survival was similar in both groups of patients with a trend in favor of stage I patients (Figure 2). Univariate analysis for PS and disease-free survival did not show any difference in relation to prognostic factors. Univariate analysis for progression-free survival showed PS as an adverse factor predicting a poor outcome ($P = 0.02$).

The ten-year estimates of overall survival according to the IPI stage, modified by Miller et al. and adjusted for age ≤60 years, were 96.1% (SEM 3.8%) for patients with zero risk factors (36 patients), 85.3% (SEM 5.8%) for patients with 1 risk factor (49 patients), and 57.1% (SEM 24.9%) for patients with 2 risk factors (8 patients) ($P = 0.07$). Pairwise comparison showed a significant difference between patients without

negative factors and patients with 2 negative factors (P = 0.01).

Toxicity

The toxicity was similar in the two patient groups (Table 2), the first (stage I) treated with 6 courses of VACOP-B plus involved field radiotherapy and the second (stage II) treated with 12 courses of VACOP-B with or without involved field radiotherapy. Table 2 summarizes grade 3-4 toxicity of the two treatments. We observed a trend at the limit of statistical significance in terms of anemia and mucositis in favor of patients receiving less chemotherapy. Six patients (6.5%) experienced brief episodes of fever of unknown origin during granulocytopenia, and 3 patients (3.2%) suffered short-lived grade 1-2 bronchitis. Cardiac grade 1 toxicity was observed in two of 93 patients (2.2%). Nine patients required a delay in drug administration (median: 7 days). Growth factors were not used.

No treatment-related mortality was observed. No patients developed a secondary tumor.

Discussion

The aim of the present study was to define the efficacy and toxicity of a third generation regimen, VACOP-B, as front-line therapy for aggressive and localized NHL. With this study we were able to demonstrate that VACOP-B offers a high percentage of stable complete remissions with a low relapse rate and low toxicity. On completion of therapy, the complete remission rates in stage I and II were 95 and 90%, respectively. These results compare favorably to those obtained by Miller et al. (7) who reported a complete remission rate of 82% in patients receiving 3 cycles of CHOP plus radiotherapy and a complete remission rate of 80% in patients treated with 6-8 cycles of CHOP chemotherapy alone.

Current practice is to treat this category of patients with CHOP chemotherapy or other regimens containing doxorubicin. Combining or alternating chemotherapy and radiotherapy presents significantly superior results to those obtained with radiotherapy alone (2-5,7-10) and represents the most common treatment method for these patients. Radiotherapy alone yielded 5-year survival rates ranging from 56 to 100% for patients with stage I disease and from 0 to 55% for patients in stage II (1-5). Studies using chemotherapy with and without radiotherapy reported 5-year survival rates ranging from about 70% to about 80%, with no statistically significant difference between stage I and stage II disease (7-10). Our results show a 6-year survival probability of 94.5% for stage I patients and 82.8% for stage II (P = 0.2). These results correlate well with previously published data reporting a similar complete remission, survival and disease-free survival probability using third generation regimens (13,14), with very low treatment-related toxicity.

The problem with using radiotherapy alone seems to be represented by the high relapse rate after treatment. As previously reported in a randomized study (5), this is more than 50%. The problem with using conventional chemotherapy alone seems to be represented by the hematological and ex-

Table 2. Toxicity in 93 patients according to disease stage.

Grade (WHO)	Stage I		Stage II	
	3	4	3	4
Anemia			3	
Granulocytopenia	4	1	3	1
Fever of unknown origin			1	
Peripheral neurotoxicity			1	
Alopecia	12	3	19	3
Mucositis	1			
Nausea/vomiting			1	
Constipation			1	

Stage I = 43 patients; stage II = 50 patients. Non-Hodgkin's lymphoma was staged as described elsewhere (18).

tra-hematological toxicity (7). We could use 50% of conventional chemotherapy courses followed by involved field radiotherapy, as suggested by others (7-10), to achieve the best results while avoiding treatment-related toxicity. Adjuvant radiotherapy should be a necessary component of the treatment program when localized residual disease still remains at the end of chemotherapy. Miller et al. (7) showed in a randomized study that radiotherapy is useful not only in reducing the number of CHOP cycles with a consequent reduction in cardiac doxorubicin-related toxicity, but also in improving overall outcome.

Our study design was partially consistent with these considerations. Stage I patients received 6 cycles of VACOP-B plus adjuvant involved field radiotherapy at the site of initial disease. Stage II patients received VACOP-B for 12 cycles plus involved field radiotherapy at the site of residual disease. Adjuvant radiotherapy improved the complete remission rate in about 10% of both groups of patients. Grades 3 and 4 granulocytopenia occurred in about 10% of patients but infections were negligible and short-lived, and growth factors were not required. Extra-hematological toxicity was very low, apart from alopecia which was seen in the majority of patients. No patients died because of treatment. Two patients presented grade 1 cardiac toxicity. Miller et al. (7) reported life-threatening toxicity in 40% of patients treated with 8 cycles of CHOP and in 30% of patients treated with 3 cycles of CHOP plus radiotherapy. The same authors reported a "disconcerting" finding of myocardial toxicity associated with 8 cycles of CHOP chemotherapy. Shenkier et al. (10) treated patients with 3 cycles of CHOP or CHOP-like regimens plus involved field radiotherapy and reported a complete remission rate of 97%. After treatment, 2 patients died of sepsis, 1 patient of myocardial infarction, and about 20% of new malignancies were observed at a median time of 51 months after the diagnosis of aggressive lymphoma. In the present series, no patient developed a secondary tumor. The reasons for these differences in terms of toxicity and secondary tumors are probably due to the low age of our patients (younger than 60 years). If we compare this with the two studies discussed above we see that the first study included about 50% of patients older than 60 years while in the second study patients had a median age of 64 years. The comparison of toxic effects between 6 and 12 weeks of VACOP-B with or without radiotherapy according to the trial design showed no statistical difference apart from mucositis which was more evident in patients receiving 12 weeks of VACOP-B. However, according to our observation, 12 weeks of VACOP-B followed by involved field radiotherapy seem to represent a good choice of treatment for stage II patients in terms of efficacy and low toxicity.

In our series, univariate analysis showed a poor outcome in patients with a PS = 1 (WHO). We were not able to stratify our patients into 4 groups according to the IPI stage modified by Miller et al. (7) and adjusted for age ≤60 years because no patient showed a PS > 1. However, patients with 2 negative factors showed a poorer outcome in terms of survival than those with no negative factors at diagnosis. In recent years new treatment strategies have been employed ranging from anti-CD20 (rituximab) to anthracycline chemotherapy regimens, particularly in elderly patients (27,28) in order to improve survival in large cell lymphomas.

In conclusion, the third generation VACOP-B regimen with or without radiotherapy in patients younger than 60 years of age presenting localized disease was shown to be effective and feasible, and was characterized by very low toxicity. However, a randomized trial comparing a first generation regimen (CHOP or similar) with or without radiotherapy and a third generation regi-

men (VACOP-B) with or without radiotherapy is required to confirm our observations. It would also be useful to study a reduced chemotherapy regimen (6-week VACOP-B) plus radiotherapy in patients with stage II to evaluate the possibility of an even shorter duration of treatment, thereby reducing toxicity without compromising efficacy.

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