Anthracycline-based chemotherapy as primary treatment for intravascular lymphoma

On behalf of the International Extranodal Lymphoma Study Group (IELSG)

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Background: Optimal therapeutic management of intravascular lymphoma (IVL) lacks precise guidelines.

Patients and methods: The clinico-pathological features of 38 HIV-negative patients with IVL were reviewed to define efficacy of chemotherapy in these malignancies. Clinical characteristics of 22 patients treated with chemotherapy and of 16 untreated patients were compared in order to understand better the impact and causes of potential patient selection.

Results: Median age was 70 years (range 34–90), with a male/female ratio of 0.9; 23 (61%) patients had Eastern Cooperative Oncology Group performance status (ECOG-PS) >1; 21 (55%) had systemic symptoms. Cutaneous lesions and anemia were significantly more common among patients treated with chemotherapy; central nervous system (CNS) and renal involvement were significantly more common among untreated patients. Chemotherapy was associated with a response rate of 59% and a 3-year overall survival of 33±11%. Five of six patients with CNS involvement received chemotherapy: four of them died early; only one patient, treated with adriamycin, cyclophosphamide, vincristine, methotrexate, bleomycin and prednisolone (MACOP-B) followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT), was alive at 19 months. High-dose chemotherapy supported by ASCT was indicated at diagnosis in another patient (43 years of age, stage I), who was alive at 71 months, and at relapse after cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in two patients who died early after transplantation. PS ≤ 1, disease limited to the skin, stage I, and use of chemotherapy were independently associated with better outcome.

Conclusions: Anthracycline-based chemotherapy is the standard treatment for IVL. However, survival is disappointing, with a relevant impact of diagnostic delay and lethal complications. More intensive combinations, containing drugs with higher CNS bioavailability, are needed in cases with brain involvement, and the role of high-dose chemotherapy supported by ASCT should be further investigated in younger patients with unfavorable features.

Key words: angiotropic lymphoma, chemotherapy, CHOP regimen, CNS lymphoma, cutaneous lymphoma, intravascular lymphomatosis

Introduction

Correct therapeutic assessment is very difficult in rare malignancies, not only because of the intrinsic difficulty of performing prospective trials, but also because the reported
data are often fragmented and potentially biased. Angiotropic or intravascular lymphoma (IVL) is a classic example of these considerations since the relevant literature is almost exclusively made up of case reports, cumulative reviews and occasional case series that do not exceed 10–15 patients [1–3].

IVL is considered to be a rapidly aggressive and usually disseminated disease, characterized by exclusive or predominant growth of neoplastic cells within blood vessel lumina [4, 5]. IVL usually affects elderly patients, and is associated with poor performance status (PS), B symptoms, anemia, an elevated erythrocyte sedimentation rate (ESR) and elevated serum lactate dehydrogenase (LDH) levels. The brain and skin are the most frequently involved organs, while lymph nodes are usually spared. The optimal therapeutic strategy has not been identified. The heterogeneity of clinical symptoms and the lack of diagnostic algorithms may be responsible for a delayed diagnosis in many cases of IVL, hindering the timely delivery of treatment. Moreover, as IVL patients are usually aged and display poor PS, the use of intensive treatment per se may be troublesome. The published data suggest anthracycline-based chemotherapy as the best therapeutic choice considering the aggressive and disseminated nature of IVL. However, reported results with this strategy are conflicting, and the apparent clinical benefit may reflect selection bias rather than therapeutic efficacy. The analysis of a large, multicenter retrospective series is a useful strategy in order to clarify this issue.

This paper reports therapeutic management and outcome in the largest reported series of patients with IVL treated with anthracycline-based chemotherapy. An analysis of potential selection bias in the interpretation of therapeutic efficacy, by comparing treated and untreated patients’ characteristics, is also provided.

Patients and methods

Study group

Twenty-two centers affiliated with the International Extranodal Lymphoma Study Group (IELSG) provided demographic, clinical, pathological, therapeutic and survival data of HIV-negative patients with an in vivo or post-mortem pathological diagnosis of IVL. Clinical and laboratory characteristics considered for analysis were assessed around the time of pathological diagnosis. Histopathological categorization was performed according to the World Health Organization (WHO) classification criteria [6]. The study group consisted of 38 patients diagnosed from 1985 to 2003. Diagnosis was established in vivo in 30 patients and at autopsy in eight cases. Staging work-up included physical examination, complete biochemical profile, whole-body computed tomography (CT) scanning, and bone marrow aspirate and biopsy. Stage of disease was defined according to the Ann Arbor staging system. Some procedures, such as CT or magnetic resonance imaging (MRI) of the brain, CSF cytology examination, gastroscopy, abdominal ultrasound or hysteroscopy were indicated according to the presenting symptoms.

Therapeutic management

Twenty-two patients were treated with chemotherapy which was anthracycline-based in 19 cases; 16 patients did not receive chemotherapy (eight with in vivo diagnosis and eight autopic cases). A comparison of the clinical characteristics between these two subgroups is reported in Table 1. Therapeutic management is summarized in Table 2.

Statistical considerations

Distribution of variables between patients who either received or did not receive chemotherapy was investigated using the Fisher’s exact test for categorical variables. Survival curves were generated by the Kaplan–Meier method. Overall survival (OS) was calculated from the date of pathological diagnosis to death or to the last date of follow up, while event-free survival (EFS) was calculated from the first day of treatment to relapse, progression or death, or to the last date of follow-up. The association of survival with clinical and therapeutic variables was evaluated using the log-rank test. The independent prognostic value of variables was analyzed using the Cox model. Backward stepwise regression was performed to identify the most powerful predictors of survival. All the probability values were two-sided, with values of $P<0.05$ considered significant. Analyses were carried out using the statistical package Statistica 4.0 for Windows (Statsoft; Tulsa, OK, USA).

Results

Patient characteristics

Thirty-eight patients had a median age of 70 years (range 34–90), with a male/female ratio of 0.9. Clinical presentation was extremely heterogeneous, with a remarkable deterioration in PS in many cases (≥1 in 36 cases; 95%). The median time from onset of symptoms to histological diagnosis was 1.06 months (range 0.3–24.8) for patients treated with chemotherapy, 3.78 months (range 0.2–25) for patients with in vivo diagnosis but treated without chemotherapy and 3.14 months (range 2–6) for cases diagnosed at autopsy ($P=0.0005$). No significant differences in age, gender, PS, stage of disease or frequency of elevated serum LDH levels between patients treated with chemotherapy and untreated patients were observed (Table 1). Conversely, cutaneous lesions (55% versus 19%; $P=0.04$) and anemia (77% versus 44%; $P=0.04$) were more common among patients treated with chemotherapy; whereas CNS (23% versus 63%; $P=0.02$), renal involvement (5% versus 31%; $P=0.05$) and cardio-pulmonary infiltration (5% versus 31%; $P=0.05$) were less common (Table 1). Ten patients (seven in the group treated with chemotherapy and three in the other group) had disease limited to the skin (‘cutaneous form’).

Twenty-one patients (55%) had systemic symptoms, mainly fever, which were more common in patients treated with chemotherapy (68% versus 38%; $P=0.09$). Concomitant involvement of liver, spleen and marrow was observed in eight patients (21%). Overall, bone marrow biopsies were positive in 12 cases (32%). No difference in the frequency of involvement of these organs between both studied subgroups was observed. With the exception of anemia, no differences in laboratory findings between patients treated with chemotherapy and patients who did not receive systemic treatment were observed (Table 1). Anemia was the most frequent cytopenia. Leukopenia or thrombocytopenia did not occur without anemia. Eight of 11 (73%) patients with thrombocytopenia had concomitant bone marrow infiltration and hepatosplenic involvement. Of all the patients with marrow infiltration, one had anemia and eight
of them also had thrombocytopenia; nine of 13 patients with hepatic and/or splenic involvement had anemia or thrombocytopenia. When analysis of the patients’ characteristics was limited to patients who did not receive chemotherapy, as expected, the sole significant difference between patients with in vivo diagnosis and autopsy cases was more disseminated disease in the latter subgroup.

Patients treated with chemotherapy

Twenty-two patients were treated with primary chemotherapy (anthracycline-based in 19 patients). Ten patients achieved complete remission (CR) and three a partial response (PR), with an overall response rate of 59%; seven patients experienced progressive disease (PD) and two died of toxicity (TD). Among the responders, seven subsequently experienced relapse, which invariably involved extranodal organs and, mostly, the primary site of disease.

Five of six patients with CNS involvement detected during staging were treated with chemotherapy. Three of them received CHOP chemotherapy and one was treated with the cyclophosphamide, vincristine and prednisone (CVP) regimen, none achieved CR, and all died within 4 months of diagnosis. The fifth patient with CNS involvement and treated with chemotherapy was a 52-year-old woman, with multiorgan disease other than CNS involvement, who was treated with the MACOP-B regimen followed by high-dose chemotherapy supported by autologous stem cell transplantation (ASCT). She is alive and relapse-free at 19 months from diagnosis. Another patient (43 years of age), with a single endometrial lesion, was treated with the CHOP regimen followed by consolidative high-dose chemotherapy supported by ASCT; she is alive and relapse-free 71 months from diagnosis. Three patients treated without anthracyclines (CVP regimen) experienced disease progression within 9 months of diagnosis: two died a few weeks after relapse, while the third experienced spontaneous regression of a cutaneous relapse, and is alive with no evidence of disease 10 years from diagnosis. In the whole cohort, all failures but one occurred within the first year of follow up. The median time to treatment failure for 22 patients treated with primary chemotherapy was 8 months (range 1–71), with a 3-year EFS of 27%.

Six of 14 patients who experienced PD or relapse received salvage therapy: conventional chemotherapy in four cases (two PD, two PR) and high-dose chemotherapy supported by ASCT in two cases (TD, PD). The survival duration from relapse was 7, 8, 9+, and 19 months, and 2 and 18 months, respectively. All but one patient who did not receive salvage therapy died within 4 weeks of relapse.

Eight patients treated with primary chemotherapy were alive (seven disease-free) at a median follow up of 35 months.

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Chemotherapy group, n (%) (n = 22)</th>
<th>No chemotherapy group, n (%) (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>69 (39–86)</td>
<td>71 (34–90)</td>
<td>0.82</td>
</tr>
<tr>
<td>Male sex</td>
<td>11 (50)</td>
<td>7 (44)</td>
<td>0.75</td>
</tr>
<tr>
<td>ECOG PS ≥ 3</td>
<td>10 (45)</td>
<td>11 (69)</td>
<td>0.19</td>
</tr>
<tr>
<td>Other malignanciesa</td>
<td>2 (9)</td>
<td>4 (25)</td>
<td>0.21</td>
</tr>
<tr>
<td>Stage-I disease (Ann Arbor)</td>
<td>6 (27)</td>
<td>6 (38)</td>
<td>0.72</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>15 (68)</td>
<td>6 (38)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cutaneous lesions</td>
<td>12 (55)</td>
<td>3 (19)</td>
<td>0.04</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>5 (23)</td>
<td>10 (63)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hepatosplenic involvement</td>
<td>8 (36)</td>
<td>5 (38)</td>
<td>1.00</td>
</tr>
<tr>
<td>Bone marrow infiltration</td>
<td>8 (36)</td>
<td>4 (25)</td>
<td>0.50</td>
</tr>
<tr>
<td>Cardio-pulmonary involvement</td>
<td>1 (5)</td>
<td>5 (25)</td>
<td>0.05</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>1 (5)</td>
<td>5 (31)</td>
<td>0.05</td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (77)</td>
<td>7 (44)</td>
<td>0.04</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8 (36)</td>
<td>3 (19)</td>
<td>0.29</td>
</tr>
<tr>
<td>Increased serum LDH levelb</td>
<td>18/20 (90)</td>
<td>7/9 (78)</td>
<td>0.56</td>
</tr>
<tr>
<td>Increased erythrocyte sedimentation rate</td>
<td>12 (55)</td>
<td>4 (25)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>5 (23)</td>
<td>1 (9)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

aThe other malignancy was diagnosed prior to IVL in five cases (gastric MALT lymphoma, diffuse large B-cell lymphoma of the parotid, prostate cancer, breast cancer, colon cancer) and concomitant to IVL in one case (renal cancer).

bNumber of positive cases on assessed patients (20 treated with chemotherapy and nine untreated).

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status.
Among the surviving patients, three had IVL limited to the skin at diagnosis and two had stage I disease. Patients who did not receive chemotherapy In spite of an in vivo diagnosis of IVL, eight patients did not receive chemotherapy. Three of them were young women (<50 years of age) displaying IVL limited to the skin: two (with single lesions) were treated with surgical resection or radiotherapy and were alive and relapse-free at 7 and 14 years from diagnosis; the third patient (multiple cutaneous lesions) was treated with corticosteroids and was lost to follow up after 1 month. A 78-year-old man was not treated due to concomitant renal cancer; he died from other causes while progression-free at 24 months from diagnosis. A 73-year-old man experienced early CNS dissemination and died before the start of any treatment. Three patients referred to surgical resection of uterine, renal and gallbladder masses with diagnostic purpose and did not receive cytotoxic treatment due to fatal post-surgical complications: renal failure in two women (74 and 90 years of age) and pulmonary thromboembolism in a 63-year-old man. Overall, only three women with disease limited to the skin survived without chemotherapy, with a 3-year OS of 29% for the subgroup of patients with in vivo diagnosis who did not receive chemotherapy. No significant difference between treated and untreated patients with in vivo diagnosis was observed (Figure 1).

**Predictors of survival**

Multivariate analysis performed on the entire series and adjusted for age (continuous variable), ECOG-PS (0–1 versus ≥2), clinical presentation (disease limited to the skin or ‘cutaneous form’ versus others), stage (I versus IV), B symptoms (no versus yes), serum LDH level (normal versus increased), anemia (no versus yes) and use of chemotherapy (no versus yes) showed a significant and independent association between the use of chemotherapy and survival [odds ratio (OR), 0.24 [95% confidence interval (CI) 0.09–0.59]; \( P = 0.005 \)], PS <1 [OR, 0.23 (95% CI 0.08–0.63); \( P = 0.008 \)], ‘cutaneous form’ [OR, 0.28 (95% CI 0.08–0.91); \( P = 0.05 \)] and stage I disease [OR, 0.28 (95% CI 0.09–0.81); \( P = 0.02 \)] were also independently associated with a better OS. When a multivariate analysis limited to patients with in vivo diagnosis was performed, the association between the use of chemotherapy and survival was approaching significance [OR, 0.18 (95% CI = 0.02–1.04); \( P = 0.06 \)], while the predictive role of the other three variables remained unchanged (data confirmed by backward stepwise regression).

**Discussion**

The analysis of therapeutic strategies and outcome from the present series of patients with IVL suggests that all patients with IVL should be considered as having disseminated disease, and, accordingly, treated with combination chemotherapy. A possible exception might be represented by cases with single small cutaneous lesions, which have some probability of cure with local treatment. The inclusion of anthracycline as part of chemotherapy combinations appears critical because the use of other regimens without these drugs has been associated with disappointing outcome [7, 8]. In our series, each of the three patients treated with CVP regimen relapsed within 9 months, and two of them died within a few weeks of relapse.
Conversely, anthracycline-based chemotherapy was associated with a 59% response rate and a 3-year OS rate of 32 ± 11%. Several cases of objective response after CHOP or CHOP-like chemotherapy have been previously reported [9–11]; however, follow-up in these case reports was short and, in many other cases, this strategy has been followed by inexorable progression [12–15]. There were fewer than 50 patients with IVL treated with anthracycline-based chemotherapy and assessable for outcome reported in the literature (published in English). Half of them relapsed and died within 18 months of diagnosis and one third of relapses involved the CNS [14, 16]. In one third of cases, the follow up of survivors was >1 year; nearly 10% of cases were alive and disease-free with a follow up of >3 years [1, 9, 17, 18].

In spite of some encouraging anecdotal evidence [1, 17, 19], the vast majority of reported patients with CNS involvement treated with anthracycline-based chemotherapy relapsed and died within 9 months of chemotherapy [20, 21]. In our series, five patients with CNS involvement were treated with a CVP, CHOP or MACOP-B regimen. Despite initial responses, three patients relapsed and died within 4 months of diagnosis and one died of septic complications; only the patient treated with MACOP-B followed by high-dose chemotherapy supported by ASCT is alive and disease-free at 19 months. Thus, a more intensive combination is needed in cases with CNS involvement, and consistent with previous reports [1, 22, 23], drugs with higher bioavailability in the CNS, such as methotrexate or cytarabine, should be included.

The use of high-dose chemotherapy supported by ASCT, an important strategy to intensify treatment against NHL, may improve current outcomes. However, this strategy appears feasible only in a small proportion of patients with IVL, considering that their median age is 70 years and PS is usually poor. Worldwide experience with this treatment modality in IVL is extremely limited, with some encouraging results both as first- and second-line treatment [18, 24, 25]; however, it is possible that some unsuccessfully treated IVL patients have not been reported. In our series, four patients were treated with high-dose chemotherapy supported by ASCT as consolidation treatment after anthracycline-based chemotherapy (CHOP and MACOP-B regimens) in two cases. They are both alive and relapse-free at 19 and 71 months from diagnosis. In the other two cases, this strategy was used as salvage therapy for systemic relapses that occurred after CHOP chemotherapy; no responses were observed, both patients died early after transplantation. Thus, the role of early consolidation with high-dose chemotherapy supported by ASCT appears to be a promising approach and deserves to be investigated further in young patients with unfavorable features.

Since IVL is usually a disseminated malignancy, the role of radiation therapy appears of secondary importance. Nonetheless, radiotherapy may be considered the exclusive treatment in elderly patients with single cutaneous lesions. Its use as consolidation therapy after chemotherapy has been reported in cases with CNS involvement [3, 26] or bulky extranodal disease [9, 27], but its true efficacy cannot be determined from these reports. Other therapeutic strategies have been used anecdotaly, including interferon [28], plasmapheresis [3, 29] and a case of cutaneous IVL successfully treated with rituximab [30].

The clinical benefit offered by chemotherapy could potentially reflect a selection bias. In the present series, the comparison between patients treated with chemotherapy and patients who did not receive this therapy might contribute to a better understanding of the real reasons for patient selection and its prognostic impact on this rare malignancy. First of all, our data seem to suggest that patient selection is not due to age, PS or disease extent. Well-known prognostic factors for aggressive lymphomas, such as age, PS, stage of disease and serum LDH level, displayed a similar distribution between the studied subgroups. Actually, patient selection in our series could be attributed to a higher rate of post-surgical complications, a different clinical presentation profile and the lack of diagnostic suspicion of IVL. In fact, only two patients experienced fatal complications in the group of patients treated with chemotherapy, while, in the other group, three of eight patients with in vivo diagnosis died of post-surgical complications ($\chi^2, P=0.03$). It should also be noted that the duration of the period between symptom onset and diagnosis was three times shorter in patients treated with chemotherapy compared with the rest. This could be explained either by more rapidly progressive disease or, more probably, by diagnostic delay. Since IVL is an aggressive and disseminated disease, diagnostic delay is usually associated with rapid and progressive impairment of multiorgan function and PS, which hampers the use of adequate chemotherapy. Furthermore, in our series, there was a significantly different distribution of sites of disease between subgroups of patients divided according to the use of chemotherapy. Importantly, cutaneous lesions were significantly more common in patients treated with chemotherapy with respect to the rest. As suggested by multivariate analysis, cutaneous presentation is independently associated with better survival and allows a more rapid histological diagnosis when considering its earlier detection and easier access. On the other hand, CNS involvement, which is associated with worse prognosis, was significantly more common in patients who did not receive chemotherapy. Intriguingly, fever, anemia and a raised ESR were significantly more common in the group of patients treated with chemotherapy. Even if these observations remain unexplained, it could be hypothesized that, in some cases, these features may have lead to the performance of a bone marrow biopsy, which allowed an earlier histopathological diagnosis and timely treatment.

Response assessment after initial chemotherapy can be troublesome in IVL patients because measurable disease (i.e. lymphadenopathy and tumor masses) is often lacking. In the present series, patients treated with chemotherapy had measurable cutaneous lesions in 12 cases, hepatosplenic nodules in two, bone marrow infiltration in two, CNS lesions in two, pulmonary nodules in one and lymphadenopathy in one. In two patients, no measurable disease remained after surgical biopsy; one of them died of toxicity during chemotherapy, the other
In conclusion, clinical benefit of anthracycline-based chemotherapy is conditioned by selection in IVL patients. Lethal complications and diagnostic delay, resulting from variable clinical presentation and rapidly progressive disease, are the most important causes of patient selection. Notwithstanding, anthracycline-based chemotherapy remains the cornerstone of IVL treatment, producing a moderate rate of durable remissions, mostly in patients with disease limited to the skin, good PS and small tumor burden. Early consolidation with high-dose chemotherapy and ASCT should be considered in patients <60 years of age with unfavorable features. For patients with CNS involvement, the CHOP regimen is a sub-optimal treatment and it seems likely that drugs used in other aggressive primary CNS lymphomas, such as methotrexate and cytarabine, should be included. The role of rituximab, an effective anti-CD20 monoclonal antibody against B-cell lymphomas, should also be investigated in IVL patients. Management of patients with the ‘cutaneous form’ of IVL remains a matter of debate considering that some cases show excellent prognosis even if treated without chemotherapy, while others experience early relapse after intensive therapy. Biological studies could help us to distinguish different risk groups in patients with the ‘cutaneous form’ of IVL, which need distinct therapeutic approaches.

In brief, survival of IVL patients is still disappointing and further efforts to improve our knowledge of this malignancy are needed; they will result in a higher proportion of early diagnoses and better control of complications, with consequent delivery of adequate and timely treatment.

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Preliminary results have been published in part in abstract form [31] and as an oral presentation at the Eighth International Conference on Malignant Lymphoma, Lugano, Switzerland, 2002 [32]. In addition, a poster presentation was given at the 44th Annual Meeting of the American Society of Hematology, Philadelphia, USA, 2002.

References


