The significance of a residual mediastinal mass following treatment for aggressive non-Hodgkin’s lymphomas


ABSTRACT: The chest radiographs of 252 patients with aggressive non-Hodgkin’s lymphoma, prospectively treated according to one of three protocols of combination chemotherapy, were reviewed to determine the incidence and prognostic significance of mediastinal abnormalities following treatment.

Residual mediastinal masses were defined as any abnormality, greater than 2 cm in diameter, that had initially responded to chemotherapy and then remained stable in size for at least three months after its maximal response, together with the disappearance of all other clinical and biological signs of active lymphoma.

At the end of treatment, 21 (8%) patients had some residual mediastinal abnormality. The predominant histological pattern was the diffuse large cell subtype (p<0.001). Disease-free survival and overall survival for these patients were similar to those observed among patients in complete remission without a persisting radiological mass after treatment.

We conclude that mediastinal residual masses after completion of treatment for aggressive lymphoma are frequent and do not indicate a poorer prognosis. Such patients can be observed clinically without any need for additional chemotherapy or radiotherapy,

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The mediastinum is a frequent site of involvement in patients with aggressive non-Hodgkin’s lymphomas (NHL). Large or bulky mediastinal involvement at presentation is thought to be of adverse prognostic significance and associated with a higher risk of relapse after treatment [1]. However, intensive chemotherapy has considerably modified the course of these aggressive diseases. Such regimens, as the C\textsubscript{3}H\textsubscript{2}OP protocol [2], have been associated with long-term survival rates in excess of 50%. More recently, with a median follow-up of 23 months, the LNH-84 protocol [3] has been associated with a 2yr survival rate of 67%.

The mediastinum may not return to normal after treatment. The introduction of newer and more sensitive radiographic technology, such as computed tomography (CT) and magnetic resonance imaging (MRI), has improved the detection of very small lesions. However, this increased precision may sacrifice specificity. The finding of a radiographically detectable residual mass when all other evidence of disease has disappeared is a common problem in NHL patients and may lead some physicians to biopsy the mediastinum or administer additional chemotherapy or radiation. Whilst they may effectively indicate persisting active disease for which additional treatment is required, alternatively, these residual mediastinal abnormalities may simply represent fibrotic residua; such findings are frequent after treatment of some solid tumours, such as testicular cancer [4].

This study analyses the experience in aggressive NHL patients of Hôpital Saint-Louis, who initially presented with a mediastinal mass. After completion of therapy, they were left with a radiologically detectable mass, whilst otherwise in a clinical complete response (CR). We sought to determine the prognostic significance of these residual mediastinal abnormalities.

Patients and methods

Patients

From January 1980 to December 1989, 252 patients with aggressive non-Hodgkin’s lymphoma were treated at Hôpital Saint-Louis in Paris (France). Eligibility criteria were the diagnosis of intermediate or high-grade non-Hodgkin’s lymphoma, according to the working formulation [5], stage I with tumour mass ≤ 10 cm or stages II to IV for intermediate grade NHL, all stages for high-grade NHL, no contraindication to doxorubicin and no previous chemotherapy or radiotherapy unless recent and
localized. No upper limit was given for age but patients
should not present abnormalities of major organs that
contraindicated high doses of doxorubicin or cyclophos-
phamide. All pathological diagnoses were reviewed and
confirmed by a specialized group of pathologists.

Of the 252 patients, 166 were male (66%) and 86 were
female (34%). Median age was 47 yrs. Initial staging
procedures included physical examination; complete
blood cell count and routine blood chemistry; posteroanterior and lateral chest roentgenograms, bone
marrow biopsy and cerebrospinal fluid examination;
thorax and abdominal CT was routinely used after 1984.
Other tests, e.g. endoscopy, bone scan, were performed
when clinically indicated. The histological subtypes were:

- follicular large cell: 12 patients (5%)
- diffuse small cleaved cell: 15 patients (6%)
- diffuse mixed: 54 patients (21%)
- diffuse large cell: 114 patients (45%)
- immunoblastic: 30 patients (12%)
- lymphoblastic: 15 patients (6%)
- small noncleaved cell: 12 patients (5%)

Clinical stage was decided at a multidisciplinary
lymphoma staging conference which included medical
oncologists, radiation therapists, radiologists, and
pathologists. The extent of disease was determined by
consensus.

We defined a stable residual mass as any mediastinal
abnormality >2 cm in diameter on the posteroanterior or
lateral chest X-ray or CT scan of the thorax, that had
initially responded to combination chemotherapy, and
had then remained stable in size for at least 3 months
after reaching its maximal response, together with the
disappearance of all other clinical and biological signs
of active lymphoma. All patients were regularly
re-evaluated clinically and radiographically (with chest X-
ray performed every month and CT scan every 3 months,
from 1984).

All radiographs were reviewed by one researcher (J.F.).
At presentation, the size of the mediastinum on a
posteroanterior chest radiograph was measured at its
widest diameter. The transhthoracic diameter was meas-
ured at its widest point, just above the domes of the
diaphragm. The ratio of these two numbers was used in
classifying the mediastinal width as <33% or ≥33% of
the transhthoracic diameter. Measurements of mediastinal
width were then made on each serial film. The width of
the stable residual mass was defined as the product of
multiplying the two largest diameters of the mass,
measured on the chest X-rays or on the CT scan.

Table 1. — Comparative induction courses of the three
treatment protocols used

<table>
<thead>
<tr>
<th>Drugs</th>
<th>C2HOP</th>
<th>LNH-84</th>
<th>LNH-87</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin mg·m²</td>
<td>90</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Cyclophosphamide mg·m²</td>
<td>1800</td>
<td>1200</td>
<td>1200</td>
</tr>
<tr>
<td>Vindesine mg·m²</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Bleomycin mg</td>
<td>0</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Prednisone mg·m²</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

A consolidation phase of sequential chemotherapy began
one month after the last induction course. Only patients
treated with the C2HOP protocol received radiotherapy at
the end of chemotherapy treatment if a CR was not
achieved or a residual mass observed.

Statistical methods

The date when the trial observations ceased was
October 1st, 1990. Disease-free survival was calculated
from the date of randomization to the date of progression
or death. Survival analysis was estimated by the method
of KAPLAN and MEIER [6], Log-Rank and generalized
Wilcoxon tests [7] were used to establish the significance
of unadjusted differences in survival for each variable.
These results were obtained using the BMDP package
(Statistical Software, Los Angeles, CA, USA).

Results

Of the 252 patients with aggressive lymphoma
treated at Hôpital Saint-Louis, 58 (23%) had mediastinal
masses at presentation. At the end of treatment, 21
(8%) had some residual mediastinal abnormality.
Five had been treated with the C2HOP protocol, 10 with
the LNH-84 protocol and six with the LNH-87 protocol.
There was no significant difference in the initial staging
of these patients, whatever the year of diagnosis and
treatment. Table 2 displays the initial characteristics of
these 21 patients. The predominant histological pattern
was the diffuse large cell subtype (p<0.001). The area of
the mediastinal residual mass ranged from 4–63 cm² with
a mean of 23 cm².

Fifteen patients did not relapse; the mediastinal
widening remained stable without any significant
difference between the different histological subtypes.
The same applied to four patients among them who had
received mediastinal radiotherapy.

Six of the patients with a residual mediastinal mass
relapsed (29%). The histological subtype was always of
the diffuse large cell pattern. All of these patients
received salvage chemotherapy. Two of them presented as
relapse in the mediastinum and, subsequently, the disease
rapidly disseminated and these two patients died 9 and 16
months after initial diagnosis. The other four did not
appear to relapse at the site of the initial mediastinal
mass but nearby, as judged by CT scan. One of the four,
initially treated in 1983, had previously received
mediastinal radiotherapy at the end of the induction
chemotherapy. Only one of these patients died of
lymphoma (19 months after diagnosis); unfortunately, a
fourth death was by suicide in a patient with a stable
second CR.
Table 2. — Initial characteristics of the 21 patients with a residual mediastinal mass

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs</td>
<td>19-58</td>
</tr>
<tr>
<td>Median</td>
<td>35</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
</tr>
<tr>
<td>Clinical Staging:</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>13</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
</tr>
<tr>
<td>B symptoms</td>
<td>6/15</td>
</tr>
<tr>
<td>LDH &gt; 1.25 x normal</td>
<td>16</td>
</tr>
<tr>
<td>Mediastinal bulky &gt; 33%</td>
<td>16</td>
</tr>
<tr>
<td>Histological subtypes:</td>
<td></td>
</tr>
<tr>
<td>diffuse large cell</td>
<td>17</td>
</tr>
<tr>
<td>lymphoblastic</td>
<td>3</td>
</tr>
<tr>
<td>diffuse mixed</td>
<td>1</td>
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<td></td>
</tr>
<tr>
<td>C&amp;H, OP</td>
<td>5</td>
</tr>
<tr>
<td>LNH 84</td>
<td>10</td>
</tr>
<tr>
<td>LNH 87</td>
<td>6</td>
</tr>
</tbody>
</table>

LDH: lactate dehydrogenase. B symptoms: night sweats, weight loss > 10%, fever > 38°C.

Thus, seventeen of these 21 patients (81%) are alive, after a median follow-up of 36 months. Overall survival (fig. 1) as well as disease-free survival (fig. 2) for these 21 patients were similar to those observed among patients in complete remission without a persistent radiological mass after treatment.

Fig. 1 — Overall survival for the 166 patients in complete response (CR) according to the presence of persistent radiological mediastinal mass (RM) after chemotherapy. ———: with RM; ———: without RM.

Fig. 2 — Disease-free survival for the 166 patients in complete response (CR) according to the presence of persistent radiological mediastinal mass (RM) after chemotherapy. ———: with RM; ———: without RM.

Discussion

Mediastinal involvement is common in NHL and although response to induction therapy is usually rapid, residual mediastinal abnormalities are frequently observed on the post-treatment chest radiograph, which raises the possibility of persistent disease. The significance of this residual mass remains a challenge for the evaluation of these patients with a high expectation of cure, and raises the question of salvage therapy (e.g. autologous bone marrow transplantation and/or radiotherapy).

The same phenomenon is already known to occur after chemotherapy for testicular carcinoma. Here, the common practice is to resect residual pulmonary or intrabdominal masses following chemotherapy. Such a policy in patients achieving an excellent, but less than complete, response found residual carcinoma in 15 out of 41 patients [8]. The remaining patients had only necrosis-fibrosis, or mature teratoma.

A similar issue has been illustrated for the malignant lymphomas, especially in patients treated for Hodgkin's disease (HD). Jochelson et al. [9] retrospectively analyzed the chest roentgenograms of 65 patients treated for HD with initial mediastinal adenopathy [9]. On completion of treatment, 57 (88%) of the 65 patients had some residual mediastinal abnormality. However, these patients did not have a higher incidence of recurrence. The study by Radford et al. [10] addresses the issue of residual mediastinal masses in 110 patients.
treated for advanced HD with chemotherapy and/or radiotherapy. Residual mediastinal abnormalities occurred in 64% of patients at the completion of treatment. The presence of a mediastinal abnormality following treatment did not predict relapse. Recently, Orlandi et al. [11] reviewed the chest radiograms of 102 patients with HD presenting with mediastinal involvement at diagnosis. Thirty nine cases (38%) showed residual mediastinal widening at the end of therapy. The isolated intrathoracic relapse rate was 11% for patients without residual mass as compared to 20.5% for those with residual widening (p=0.3).

Few data are available concerning residual masses after chemotherapy for aggressive NHL. Vematsu et al. [12] treated four patients with extensive mediastinal NHL. After completion of treatment, follow-up CT showed a residual mediastinal mass in all four patients, who have remained alive and well for more than 19 to 45 months without any supplemental treatment.

These data are in complete accordance with ours, since we did not find any negative prognostic significance for residual mediastinal masses observed among 21 patients heavily treated for aggressive lymphoma. Nevertheless, some patients relapse in the site of the residual mass, which means that active disease was persisting. Therefore, it is important to identify patients whose residual masses have a high likelihood of relapse. An accurate estimate of residual viable tumour would facilitate the use of appropriate second-line therapy [13].

Computed tomography of the thorax has had a remarkable impact on the determination of extent of disease in lymphoma. After completion of treatment, it can demonstrate better than chest radiography the persistence of residual mediastinal abnormalities. However, it is generally considered to be unable to distinguish between fibrous tissue and viable neoplasm [14], except when it shows their cystic nature [15]. The use of MRI could be complementary to the CT scan and increase the specificity of the clinical diagnosis. Finally, gallium scanning could be the best test for the identification of viable residual disease in lymphoma patients, but requires further evaluation [16-18].

We conclude that mediastinal residual masses after completion of treatment for aggressive lymphoma are frequent and do not suggest a negative prognostic significance. According to a strict application of our criteria for stable disease, a patient in clinical CR with a stable residual mediastinal mass can be observed radiologically, thus avoiding a diagnostic thoracotomy.

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References