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Perspectives and Commentaries

Role of Chemotherapy for Localized Non-Hodgkin's Lymphoma?

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TRADITIONALLY, patients with stages I and II non-Hodgkin's lymphomas (NHL) have received treatment with radiotherapy alone with variable results [1, 2]. Careful selection of patients using intensive staging techniques, including laparotomy, have improved these results [3, 4]. However, for some patients with diffuse lymphomas, these results still remain unsatisfactory. Nodular and diffuse non-Hodgkin's lymphomas (NHL) have different behavior [5] and response to radiation therapy [6]. Therefore, in this review, the treatment of localized low-grade malignant lymphomas will be considered separately from that of the intermediate and high grades.

The low grade malignant lymphomas

Jones *et al.* showed that a subset of NHL had a favorable prognosis and, in addition, that patients with a limited disease fared better than those with advanced disease [1]. The working formulation published in 1982 has now clearly defined this population which includes the diffuse small lymphocytic lymphomas, the follicular small cleaved cell and follicular mixed small cleaved and large cell lymphomas [7].

A relatively small proportion of patients with these low grade lymphomas present with early-stage (I–II) disease, comprising only 6–21% of all patients undergoing staging laparotomy [7, 8, 9]. Without complete pathologic staging, the nodular lymphomas are often understaged. Goffinet *et al.* [8] reported a series of 20 (31%) patients who were reassigned to stage III and IV following bone marrow biopsy and laparotomy. This observation clearly explains the improved disease-free survival (DFS) observed in laparotomy-staged patients with limited disease (I and II) [10, 11].

In the Stanford series, the most important prognostic factor in a multivariate analysis was age: the subpopulation of patients under 40 years old had a freedom from relapse (FFR) in excess of 80% at 10 years. Patients with stage I disease had better survival than patients with stage II, although in that series, it was due to a difference in the number of intercurrent deaths. The presence of extranodal disease and the number of sites involved were not statistically significant prognosistic factors.

Bulky disease did not significantly affect either survival or FFR [10]; this is in contrast to diffuse histiocytic lymphoma (DHL) where bulky disease is a negative prognostic factor [16]. In addition, the prognosis of patients with a strictly nodular architectural pattern was not different from that in those with combined nodular and diffuse features [10].

Low-grade lymphomas are generally highly responsive to radiotherapy. For example, Fuks and Kaplan reported satisfactory local control rates of about 90% when doses in excess of 40 Gy were utilized [6]. The same authors reported that for early stages, 76% of the patients had contiguous sites of involvement at presentation and that 33% relapsed in contiguous sites [6]. Radiotherapy has been, and still remains, the standard treatment, although the extent of the treatment fields has not been uniform [2, 11, 13, 14]. Two large series of nodular lymphomas investigated that question:

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Table 1. Treatment of stage I and II low-grade malignant lymphomas

Authors (Ref.)	No. of patients	Stages	Treatment	FFR (%) 5-yr	FFR (%) 10-yr	Survival (%) 5-yr	Survival (%) 10-yr
Paryani [10]‡	124	PS–I	IF, EF, TLI	65	54	98	68
		PS–II	IF, EF, TLI	60	54	70	68
Gosporadowicz [15]	190	PSI–II	IF	50	53	60	58
Chen [2]	25	CSI–II	IF, EF	83	—	100	—
Monfardini [13]‡	26	PSI–II	IF	55	—	62	—
		PSI–II	IF + 6 CVP	65	—	93	—
Landberg (14)‡	12	CSI–II	EF ± 9 CVP	66†	—	91*	—
Carde [11]‡	28	PS + CSI	EF ± 12 CVP	87	—	100	—
	20	PS + CSII	EF + CVP/TLI + CVP	35	—	70	—
Toonkel [17]	14	PSI–II	IF ± CHOP	75†	—	87*	—

FFR: Freedom from relapse. PS: Pathologic stage. CS: Clinical stage. IF: Involved field radiotherapy. EF: Extended field. TLI: Total lymphoid irradiation. CVP: Cyclophosphamide, vincristine, prednisone. CHOP: Cyclophosphamide, adriamycin, oncovin®, prednisone. *2-yr survival. †2-yr FFR. ‡Randomized trials.

one has been conducted by Paryani *et al.* at Stanford, in 124 patients with stage I–I_E and II–II_E lymphomas randomized to receive one of 3 treatments: either total lymph node irradiation (TLI) involved field (IF) or extended field (EF) radiotherapy [10]. Ten-year survival and FFR in all the 3 arms were greater than 50% and the actuarial curves of FFR showed a plateau after 5 years suggesting that half of these patient may be cured [10]. Gospodarowicz reported similar results in 190 patients treated with IF irradiation [15]. Considering the pattern of relapse [6], Paryani's study suggests that the initial treatment of all lymph node regions might be more appropriate than a restricted field by decreasing the likelihood of relapse in initially not-involved node sites. However, this prospective trial failed to show a statistically significant difference in survival between the 3 groups [10].

Several studies have investigated the addition of chemotherapy (CT) to radiotherapy (RT). Monfardini in Milan reported a randomized study of IF RT vs. IF RT followed by 6 courses of CVP [13] in 26 patients (PS I–II nodular). The 5-year survival was 62% for the 11 patients treated by RT alone and 95% for 15 treated by RT + CVP. The 5-year FFR, respectively 55 and 65%, was not significantly different. However, it should be stressed that in the Stanford study [10], using IF radiation therapy only, the 5-year survival was considerably higher (83%) compared to 62% in Milan. Landberg *et al.* [14], in a randomized study comparing EF RT vs. EF RT followed by 9 courses of CVP, reported 4/7 relapses after RT and 0/5 after RT + CVP. Survivals in both arms were not signficantly different [14]. In another non-randomized study of 14 patients with I–II nodular lymphomas, 2/11 relapsed after IF RT and 1/3 relapsed after IF RT plus 12 courses of CHOP with or without bleomycin (BLM). These paradoxical results may be attributable to the inclusion of cases with a less favorable prognosis in the group treated by RT + CT. Also, these numbers are too small to be meaningful [17]. In the EORTC trial conducted by Carde *et al.*, adjuvant CVP to either ER–RT or TLI failed to show any benefit in survival [11].

These studies are summarized in Table 1. None shows a clear benefit for adjuvant CT (CVP in all but one study) after RT in terms of survival or FFR. Patients with stage I–II and favorable histology NHL, have a good long-term prognosis, ranging from 60 to 100% 5-year survival, and although TLI shows a trend for increased DFS (mostly under 40 years old), IF RT, in carefully staged patients, remains the recommended therapy.

High or intermediate grade lymphomas

Most of the studies have been conducted in diffuse histiocytic lymphomas (DHL, according to Rappaport). However, nodular histiocytic lymphomas have also a poor survival [7, 10], justifying their classsification as intermediate grade lymphomas [7]. Two of the high grade lymphomas, lymphoblastic and small non-cleaved cell, are particularly aggressive and must be considered separately. Before the introduction of combination CT, RT was the standard treatment but results were often unsatisfactory [1, 2].

Three series of laparotomy-staged I diffuse NHL treated with RT reported a 5-year FFR of

Table 2. Treatment of stage I diffuse non-Hodgkin's lymphomas

Authors (Ref.)	No. of patients	Stages	Treatment	5-yr FFR (%)	5-yr Survival (%)
Jones [1]	13	CS–I	EF	50*	65†
Chen [2]	20	CS–I	IF, EF	55*	78†
Levitt [3]	9	PS–I	EF	100	100
Sweet [4]	14	PS–I	IF, EF, TLI	100	100
Hoppe [9]‡	18	PS–I	EF, TLI	73	90
Carde [11]‡	35	CS + PS–I	EF ± 12 CVP	55	75
Cabanillas [20]	11	CS–I	CT	90	100
Miller [19]	8	CS–I	CT	88	100
Bajetta [22]‡	20	CS–I	CT + IF + CT	92	92

FFR: Freedom from relapse. PS: Pathologic stage. CS: Clinical stage. IF: Involved field radiotherapy. EF: Extended field. TLI: Total lymphoid irradiation. CVP: Cyclophosphamide, vincristine, prednisone. CT: Chemotherapy (adriamycin-containing regimens). *2-yr FFR. †2-yr survival. ‡Randomized trials.

Table 3. Treatment of stage II diffuse non-Hodgkin's lymphomas

Authors (Ref.)	No. of Patients	Stage	Treatment	5-yr FFR (%)	5-yr survival (%)
Jones [1]	35	CS–II	EF	35*	40†
Chen [2]	33	CS–II	IF, EF	30*	52†
Sweet [4]	14	PS–II	IF, EF, TLI	43	50
Hoppe [9]‡	14	PS–II	EF, TLI	43	56
Carde [11]‡	15	CS + PS–II	EF + CVP/TL + CVP	10	10
Cabanillas [20]	28	CS–II	CT	72	63
Miller [19]	20	CS–II	CT	60	80
Bajetta [22]‡	42	CS–II	CT + IF + CT	74	75

FFR: Freedom from relapse. PS: Pathologic stage. CS: Clinical stage. IF: Involved field. EF: Extended field. TLI: Total lymphoid irradiation. CVP: Cyclophosphamide, vincristine, prednisone. CT: Adriamycin-containing chemotherapy regimens. *2-yr FFR. †2-yr survival. ‡Randomized trials.

90–100% and a 5-year survival of 73–100% (Table 2). Those results have to be considered with caution in view of the small number of patients; [3, 4, 9] however, it seems likely that improved staging and radiotherapy techniques have resulted in an increased survival and FFR in patients with stage I diffuse NHL treated by radiotherapy alone.

For the treatment of stage II or II_E disease the rationale for RT is less clear (Table 3). Survival at 2 years after completion of radiotherapy is reported to be only 40–60% and DFS 30–35% for clinically-staged (CS) patients [1, 2, 14]. The results are better in surgically staged patients [12], however, in two series [4, 13] only 45% of PS II patients treated by RT were free of disease at 2 years.

All these results are probably overestimates due to patient selection factors. Indeed, in some series, patients were excluded because of progressive disease during RT: Bonadonna [13] and Landberg [14] reported that 10% of patients developed progressive disease during RT and therefore were excluded. In Stanford [16], 15 of 27 patients intended for TLI failed during the initial local therapy thus preventing administration of complete TLI. Moreover, laparotomy-staged patients may represent a more favorable subgroup with respect to age, functional status and intercurrent disease. Finally, in contrast to nodular lymphomas, and Hodgkin's disease, there is no clear cut RT dose–response relationship in DHL [6]; for example, the failure rate of achieving local tumor control in DHL was 34% at 40–42 Gy and 38% at 50–60 Gy. These considerations lead us to believe that RT may be curative in only a small portion of patients with DHL after extensive staging.

In an attempt to improve the results of RT for localized disease, several centers have undertaken trials of RT followed by CT. The results presented in Table 4 suggest that RT +CT might be better than with RT alone [11, 12, 13, 14], however, the study conducted at Stanford failed to demonstrate a benefit from adjuvant CT [12]. Two reasons may explain these disappointing observations: (a) most patients did not begin CT until 3–4 months after diagnosis; poor results are probably related

Table 4. Combined treatment for stage I–II diffuse non-Hodgkin's lymphomas

Authors (Ref.)	No. of patients	Stage	Treatment	5-yr FFR (%)	5-yr survival (%)
Monfardini [13]‡	68	PS I–II	IF/IF + 6 CVP	45/70§	60
Landberg [14]‡	48	CS I–II	EF ± 9 CVP	41*	90†
Glatstein [12]‡	48	PS I–II	TLI ± CT	50	70
Toonkel [17]	39	PS I–II	IF ± CT	65*	85†

FFR: Freedom from relapse. PS: Pathologic Stage. CS: Clinical stage. IF: Involved field. EF: Extended field. TLI: Total lymphoid irradiation. CVP: Cyclophosphamide, vincristine, prednisone. CT: Adriamycin-containing chemotherapy regimens. *2-yr FFR. †2-yr survival. ‡Randomized trials. §P less than 0.007.

to the delay in initiating systemic treatment for a disease with a high growth rate and a known propensity for early hematogenous spread; (b) the chemotherapy regimen used in most of these trials (CVP) is less effective than adriamycin (ADR)-containing combinations [18]. It appears likely that adjuvant CT, if employed, should utilize the most effective regimens and be started early.

Two series addressed the important question of initial chemotherapy alone. Miller *et al.* treated 28 patients with CS I and II disease with ADR-containing regimens only [19]. A total of 100% achieved complete remission, 80% were alive at 5-year and 75% had remained disease-free. These results were confirmed by the investigators at the MD Anderson Hospital and Tumor Institute [20]. The complete remission rate was 90% in 39 evaluable patients. At 10 years, 10/11 patients with CSI and 21/28 patients with CSII remained disease-free with a total disease-free survival of 75%. The early systemic CT has clearly improved the prognosis of patients with clinical stage II DHL and probably obviates the need for extensive staging. In a third series published in this journal, 26 patients with CS II B NHL were treated with a combination of BLM, adriamycin, cyclophosphamide, vincristine and prednisone (BACOP) achieving 81% of CR. The median duration of CR has not been reached but the median follow-up is only one year [21].

The role of adjuvant RT remains to be defined. There are 3 non-controlled studies addressing the issue of adding RT to ADR-containing chemotherapy: CT sandwiched around a course of irradiation [22] and CT followed by adjuvant RT [9, 19]. In one of these studies [19], 17 patients were treated with CT and adjuvant RT only to sites of bulky disease. All these patients remained free of disease, the median follow-up being 4 year. A few patients who were over 65 years received a less intensive therapy with good results: 2 courses of CHOP followed by local irradiation (40–50 Gy) with good results. These data, in older patients, suggest that clinically undetected disease may be eliminated with relatively few courses of combination CT but the minimal number remains to be defined.

The average results of the 3 trials exploring the role of adjuvant RT are very good with 80–93% survival at 4 years for CS I patients and 68–75% survival at 4 years for CS II patients [9, 19, 22]. Miller *et al.* found no difference in survival and DFS between CT and CT followed by RT [19]; however, a prospective randomized trial is required to definitely define the role of adjuvant radiation therapy.

In conclusion, the treatment strategy for localized intermediate and high-grade lymphoma has evolved considerably during the past decade. In view of an increasing number of second malignancies associated with CT, it is important to identify those patients who may require only RT. For patients with stage I disease, possible complications of CT must be balanced against the risks of surgical staging, which is required if RT alone is contemplated. Patients with stage II (CS or PS) do benefit from initial CT; the role of adjuvant RT remains to be established.

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