

Therapy for Stage I Aggressive Non-Hodgkin's Lymphoma

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Although radiotherapy was considered sufficient for stage I and limited stage II aggressive non-Hodgkin's lymphoma in the past, new data from randomized studies have shown that intensified chemotherapy or combined modality therapy (multiagent chemotherapy followed by involved field radiotherapy) can result in complete remission in 75-90% of the cases, with 5-year overall survival ranging between 82% and 89%. However, not all patients benefit from this management. Patients above 60 years of age, with high lactate dehydrogenase concentration, poor performance, or extranodal disease localized in the testis or central nervous system have a much worse outcome. Therefore, typical extranodal character of this disease (40-57% of the patients show a primary extranodal localization) needs to be recognized and therapy adapted to these subcategories.

Key words: *central nervous system; combined modality therapy; lymphoma, mucosa-associated lymphoid tissue; lymphoma, non-Hodgkin; skin; testis*

During the last decades, the management of stage I aggressive non-Hodgkin's lymphoma has been changed. Data from clinical studies have resulted in a better insight of this subgroup of non-Hodgkin's lymphoma patients. Not all patients have a good prognosis, which appears to depend on the presence or absence of specific risk factors, and especially on the localization of the lymphoma. Evidently, aggressive non-Hodgkin's lymphoma – regardless of stage – cannot be considered as a single entity to be treated with only one treatment modality. This holds true also for stage I disease. There are new concepts of stage I aggressive non-Hodgkin's lymphoma, for which adapted and more intensive therapy is needed.

Nodal vs Extranodal Stage I Non-Hodgkin's Lymphoma

Stage is an important prognostic factor in patients with aggressive non-Hodgkin's lymphoma, and as such included in International Prognostic Index (IPI) (1). Patients with stage I or limited stage II disease have a much better outcome than patients with stage III and IV disease (1). Not only stage, but also the site of the lymphoma is important for prognosis. Stage I non-Hodgkin's lymphomas are very often located outside the classical nodal regions (in some series even up to 57%) and thus designated as extranodal (2). In a population-based registry, excluding cutaneous T cell lymphomas, it seemed that 21% of the nodal stage I non-Hodgkin's lymphomas involved the Waldeyer's ring (2), and 47% of the extranodal aggressive non-Hodgkin's lymphoma cases involved the stomach or intestine. For the remaining cases,

lymphoma localizations were recorded in ear, nose and throat regions, bone, connective tissue, skin, testis, brain, thyroid gland, female breast, spinal cord, and bladder (2). The large majority (93%) of these aggressive stages I extranodal non-Hodgkin's lymphomas were large diffuse B cell lymphoma and often, if in the stomach, of mucosa-associated lymphoid tissue (MALT) type.

Whereas several extranodal stage I non-Hodgkin's lymphomas, such as involvement of the skin, have an excellent prognosis, for others (involvement of central nervous system) the prognosis is still dismal. This means that a general outline for the therapy of stage I aggressive non-Hodgkin's lymphoma cannot be easily given.

Therapy Modalities: Radiotherapy, Chemotherapy or Combined Modality

During the 1960s and 1970s, radiotherapy was considered the sole and best therapy for localized aggressive non-Hodgkin's lymphoma. However, since many patients often had relapses of the disease, chemotherapy was applied, either alone or as a combined modality therapy. Still, even in the 1980s, many groups considered radiotherapy alone sufficient and continued to treat patients with stage I disease with radiotherapy only. Randomized studies comparing radiotherapy alone with chemotherapy or combined modality therapy were not available. However, in a retrospective analysis comparing combined modality with radiotherapy alone, van der Maazen et al (3) convincingly showed that combined modality resulted in a much better progression-free and overall

survival. In this retrospective analysis of 296 patients treated in the Netherlands between 1980 and 1994, the actuarial 10-year rates for progression-free survival and overall survival were 83% and 70%, respectively, for the patients treated with the combined modality treatment, and 47% and 43%, respectively, for the patients treated with radiotherapy alone. This means that patients relapsing after radiotherapy alone cannot be salvaged by second line chemotherapy.

In 1998, Miller et al (4) published an important randomized trial performed by the South West Oncology Group (SWOG). The patients with aggressive non-Hodgkin's lymphoma, stage I or limited stage II, who were included in the SWOG trial, received either 8 CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) cycles (n = 201) or 3 CHOP cycles with rather high doses of radiotherapy (40-55 Gy) (n = 200). After a follow-up of 4.4 years, it seemed that the patients treated by the combined modality therapy had a significantly better progression-free and overall survival (Table 1). Pooled data from these 401 patients according to the stage-adapted IPI risk factors, showed that a large majority of these patients harbored none or only 1 risk factor. They had a progression-free survival at 5 years of 77% (range 72-83%), and an overall survival of 82% (range 77-87%). On the other hand, a few patients with 2 or more risk factors had a 5-year progression-free survival ranging from 60% (2 factors) to 34% (3 factors), and a 5-year overall survival ranging from 71% (2 factors) to 48% (3 factors). The cause of death was mostly non-Hodgkin's lymphoma, with remarkably late relapses.

Table 1. Summary of the therapy applied and the stage of the disease, risk factors, and remission in patients with non-Hodgkin's lymphoma (NHL) included in Miller et al's study (4)^a

Parameters	Patients (%) with NHL who received	
	8 CHOP cycles alone (n = 201)	3 CHOP cycles + RT (n = 200)
Stage I	67	68
Stage II	33	32
Risk factors: ^b		
0-1	71	74
2	22	19
3	7	7
4	<1	<1
% CR	73	75
5-year PFS	64	77
5-year OS	72	82

^aAbbreviations: CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone; RT – radiotherapy; CR – complete remission; PFS – progression-free survival; OS – overall survival.

^bAccording to the "stage-adapted International Prognostic Index": age > 60 years, stage II, elevated lactate dehydrogenase, and performance according to the World Health Organization ≥ 2.

At the 8th International Conference on Malignant Lymphoma 2002, in Lugano, Italy, the French Groupe d'Etude des Lymphomes de l'Adulte (GELA) presented the LNH 93-1 study (5). This was the second very large randomized study which included patients with stage I or stage II disease. In contrast to Miller's study, this cohort was selected on the basis of the absence of any adverse factor. Therefore, all patients were below the age of 60 years (median age 47 years), had normal serum LDH concentrations, and a

good performance, with 10% of them having bulky disease and 10% non-Hodgkin's lymphoma of a T cell type. Fifty percent had extranodal disease (Waldeyer's ring was considered extranodal). The treatment consisted of 3 CHOP cycles and 30-40 Gy involved-field radiotherapy, and was compared with the GELA gold standard regimen: 3 ACVBP cycles (doxorubicin 75 mg/m² and cyclophosphamide 1.2 g/m² on day 1; vindesine 2 mg/m² and bleomycin 10 mg/m² on days 1 and 5; prednisone 60 mg/m² on days 1 to 5), with doxorubicin and cyclophosphamide of a 150%-200% higher dose intensity, followed by sequential consolidation (methotrexate, ifosfamide, etoposide, and cytarabine). This means that the best arm of the Miller study (4) was compared with a very intensive chemotherapy regimen without radiotherapy. The intensity of the GELA regimen was reflected by the fact that in 30-56% of the patients, usage of the growth factor granulocytic-colony stimulating factor (G-CSF) was required. Out of 631 patients randomized, 592 patients were eligible for analysis (Table 2). In general, complete remission percentages were much higher than in the American study, but this can easily be explained by the selection of very favorable subgroup of patients. It seemed that the intensive GELA regimen had a better outcome (both event-free survival and overall survival). As expected, the percentage of locoregional relapses was lower in the CHOP plus radiotherapy arm.

Table 2. Summary of the therapy, stage of the disease, remission, and survival in patients with non-Hodgkin's lymphoma (NHL) included in Reves et al's study, GELA LNH 93-1 (5)^a

Parameters	Patients (%) with NHL who received		p
	ACVBP + high dose consolidation (n = 295)	3 CHOP + RT (n = 295)	
stage I	67	67	
G-CSF usage	30-56	2-3	
% CR	93	92	
5-year EFS	82	74	0.004
5-year OS	89	85	0.030
Relapse			
delay from diagnosis (months)	17	11	
locoregional	40	20	

^aAbbreviations: GELA – Groupe d'Etude des Lymphomes de l'Adulte; LNH – lymphoma non-Hodgkin; ACVBP – doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone; RT – radiotherapy; G-CSF – granulocytic-colony stimulating factor; CR – complete remission; EFS – event-free survival; OS – overall survival.

Any new study involving stage I patients should especially focus on patients with 2 or more risk factors, which is the category that can profit from further improvement. Because most stage I patients exhibit favorable risk factors, the numbers of patients with 2 or more risk factors is very low. Such a study will require an Intergroup status. Unfortunately, an attempt made by the European Organization of Research and Treatment of Cancer (EORTC) Lymphoma Group to initiate such an Intergroup trial incorporating rituximab and maintenance therapy was not received with enough enthusiasm by other groups to go on. This means that – based upon *published* data – the best therapy thus far that can be offered to stage I patients should consist of 3 CHOP-like courses followed by

radiotherapy, realizing that for patients with 2 or more risk factors a better therapy is still indicated.

Amount of Radiotherapy in Combined Modality Regimens

It is not known how much radiotherapy needs to be given as involved field dose to stage I patients. Whereas 40 Gy is considered standard (6), SWOG group (4) applied 40-55 Gy, which has certainly resulted in short-term and late-term toxicity. Only a single retrospective analysis is available where patients in complete remission after 4 cycles of CHOP received either 26 or 40 Gy. No significant differences were found, although a trend suggested better outcome for those who received 40 Gy (7).

Specific Categories

As mentioned before, patients with extranodal stage I disease belong to different categories with a different outcome.

Stage I Testis Non-Hodgkin's Lymphoma

Separate treatment policy is advocated for this category, because these patients tend to have relapses in the other testis and in the central nervous system (8). Therefore, all patients should receive at least 6 cycles of CHOP-like therapy, every time combined with methotrexate administered intrathecally. Moreover, after the end of chemotherapy, the whole scrotum should be irradiated to prevent relapse in the other testis. Evidently, the patient should afterwards be treated with hormonal substitution. During the Lugano International Conference on Malignant Lymphoma 2002, the Working Party on extranodal lymphomas concluded that it would not be possible to perform any study (e.g., investigating the number of CHOP cycles needed) because the incidence of this lymphoma is so low.

Stage I Central Nervous System Non-Hodgkin's Lymphoma

Patients with primary non-Hodgkin's lymphoma not related to acquired immunodeficiency syndrome (AIDS) have an exceptionally poor prognosis. Until recently, patients both received dexamethasone and underwent whole brain radiotherapy with an overdose delivered to the lesion. In spite of high percentages of complete responses, most if not all patients relapsed and the 5-year overall survival usually did not exceed 3-4%. Increasing the dose of radiotherapy did not result in a better outcome (9). During the last decade, several trials have tried to improve this by adding intensive chemotherapy consisting of drugs that penetrate the blood-brain barrier. The most impressive results were obtained by Blay et al (10) who showed with "C5R" protocol a projected survival of 70% at 2 years and 56% at 5 years. Out of 25 patients, 3 died due to toxicity. Similarly, Poortmans et al (11) recently presented for the EORTC the first results from a phase II study consisting of 2 MBVP (methotrexate, BCNU, teniposide, and methylprednisone) cycles followed by 40 Gy whole brain radiotherapy. The results from the first 42 patients showed a 2-year overall survival of 69%. Five patients died, which was proba-

bly therapy-related. From these data, it seems that the overall survival can be improved, but at the costs of a 10% lethal toxicity. Moreover, with more surviving patients, there is a serious risk that this therapy might be followed by severe late toxicity to central nervous system, probably related to the combination of radiotherapy and chemotherapy (10,12,13). Hopefully, further improvement can be obtained by performing a phase III trial studying various doses (none, low or standard) of radiotherapy after induction chemotherapy. Such a trial can only be performed in an intergroup setting, and the first steps for the development of such a group have already been taken.

Stage I Cutaneous Non-Hodgkin's Lymphoma

In contrast to the above mentioned extranodal non-Hodgkin's lymphoma with an extremely poor prognosis, the reverse is true for primary cutaneous non-Hodgkin's lymphoma of a large B cell type (14,15). In this regard, the sole important prognostic factor is related to the localization of this lymphoma: head and trunk vs non-Hodgkin's lymphoma on the leg. These lymphomas are usually irradiated, and not treated by CHOP-like chemotherapy. This is justified by the excellent prognosis (>95% overall survival at 5 years) after radiotherapy only for the "non-leg" primary B cell lymphomas. However, the leg localizations have worse prognosis (5-year survival of 50%) and probably should receive additional chemotherapy and/or rituximab. Due to the rarity, randomized studies will most probably not be possible.

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