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THE TREATMENT OF NON-HODGKIN'S LYMPHOMAS

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SUMMARY

The non-Hodgkin's lymphomas are a heterogeneous group of diseases. Cell marker studies over the past 10-15 years have demonstrated that the majority of adult B cell lymphomas are of B lymphocyte origin while a minority are of T lymphocyte origin. They vary in their prognosis according to histologic and clinical features.

UNITERMS: *Lymphomas, non-Hodgkin's lymphomas, chemotherapy, radiotherapy.*

HISTOLOGY

The Rappaport classification, which was introduced in 1966[1], divides the non-Hodgkin's lymphomas into two major categories (Table 1). In the nodular lymphomas, the follicular architecture of the lymph node is preserved. In the diffuse lymphomas the follicular architecture is obliterated by infiltration with malignant cells. Within each category there are several cell types: well-differentiated lymphocytic, poorly differentiated lymphocytic, histiocytic and mixed lymphochtic and histiocytic. The "histiocytic" cell are large with large nuclei, vesicular chromatin and nucleoli. They resemble tissue macrophages, but marker studies have shown that the majority of cases are actually of B lymphocyte origin, some of T lymphocyte origin, and a small minority are of monocyte-macrophage origin. The well-differentiated lymphocytic cases are virtually always diffuse, and clinically and by cell marker analysis, are probably part of the spectrum of the same disease as chronic lymphocytic leukemia. The poorly differentiated lymphocytic types are comprised of tumors with small lymphocytes with cleaved nuclei. The mixed types have a mixture of small lymphocytes with cleaved nuclei and large cells. The lymphoblastic subtype occurs most commonly in young adults, often with large mediastinal masses and either initial or eventual leukemic involvement and meningeal metastasis. Cell maker studies have shown that this type is very closely related to acute lymphoblastic leukemia and is of T cell or non B, non T cell origin. In most cases the cells

TABLE 1 – Rappaport Classification[1]

Nodular
Lymphocytic, well differentiated
Lymphocytic, poorly differentiated
Mixed, lymphocytic and histiocytic
Histiocytic
Diffuse
Lymphocytic, well differentiated without plasmacytoid features
Lymphocytic, well differentiated with plasmacytoid features
Lymphocytic, poorly differentiated without plasmacytoid features
Lymphocytic, poorly differentiated with plasmacytoid features
Lymphoblastic, convoluted
Lymphoplastic, non-convoluted
Mixed, lymphocytic and histiocytic
Histiocytic without sclerosis
Histiocytic with sclerosis
Burkitt's tumor
Undifferentiated
Malignant lymphoma, unclassified
Composite lymphoma

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contain high levels of terminal deoxynucleotidyl transferase. The undifferentiated lymphomas are comprised of small primitive cells with non-cleaved nuclei. Often there are macrophages interspaced between the malignant cells which have phagocytized necrotic debris giving the so-called "starry sky" appearance. The latter morphology is typical for cases occurring in Africa, classically in young males with jaw tumors. This is the Burkitt's lymphoma which is associated with Epstein-Barr virus infection, and the translocations between chromosomes 8 and 14 or, more rarely, 8 and 22 or 2. The undifferentiated lymphomas have also been seen with increasing frequency in association with AIDS. The undifferentiated lymphomas are among the most rapidly growing malignancies in humans.

The separation of patients into nodular and diffuse categories has somewhat separated patients according to their prognosis. The survival of patients with nodular lymphomas has been longer than that of patients with diffuse histiologies with minimal treatment[2, 3, 4]. The survival of patients with nodular histologies with minimal treatment has differed in different centers. Jones from Stanford[2] reported median survivals of 8-9 years for the nodular poor-differentiated lymphocytic and nodular mixed varieties (NPDL, NML). The National Cancer Institute[3] and Memorial Hospital[4] found the median survival to be between 3 and 4 years. The differences are difficult to explain but may be due to differences in follow-up and in patient referral in the various centers. As described below, the different experiences of the different centers has influenced their current treatment philosophies.

There have been several newer histopathologic classifications suggested in recent years including the Lukes-Collins classification[5] and the Kiel classification[6]. These both emphasize cell morphology correlated with surface marker studies over follicular or diffuse pattern. Recently the Non-Hodgkin's Lymphoma Pathologic Classification Project compared the Rappaport, Lukes-Collins, Kiel, Dorfman, British National Lymphoma Investigation and WHO classifications. All were found to have prognostic utility[7], a finding that we have confirmed[8]. A new Working Formulation was proposed by this group which divides the Non-Hodgkin's Lymphoma into 3 prognostic groups: low grade, intermediate grade and high grade lymphomas (Table 2). These subdivisions also have prognostic utility.

The Lukes-Collins, Kiel and Working Formulation classifications have added a few new categories not well recognized previously. One of these is the lymphoplasmacytic lymphomas which were generally called diffuse well differentiated lymphocytic lymphoma with plasmacytic features in the Rappaport classification.

TABLE 2 – Working Formulation[7]

Low grade
A. Malignant lymphoma
Small lymphocytic
consistent with CLL
plasmacytoid
B. Malignant lymphoma, follicular
Predominantly small cleaved cell
diffuse areas
sclerosis
Intermediate grade
D. Malignant lymphoma, follicular
Predominantly large cell
diffuse areas
sclerosis
E. Malignant lymphoma, diffuse
Small cleaved cell
sclerosis
F. Malignant lymphoma, diffuse
Mixed, small and large cell
sclerosis
epithelioid cell component
G. Malignant lymphoma, diffuse
Large cell
cleaved cell
non-cleaved cell
sclerosis
High grade
H. Malignant lymphoma
Large cell, immunoblastic
plasmacytoid
clear cell
polymorphus
epithelioid cell component
I. Malignant lymphoma
Lymphoblastic
convoluted cell
non-convoluted cell
J. Malignant lymphoma
Small non-cleaved cell
Burkitt's
follicular areas
Miscellaneous
Composite
Mycosis fungoides
Histiocytic
Extramedullary plasmacytoma
Unclassifiable
Other

Lymphomatous lymph nodes from patients with the clinicopathologic diagnosis of Waldenstrom's macroglobulinemia generally have this histologic appearance. Although monoclonal serum proteins are seen most frequently among patients with this type of lymphoma, they are not found in most patients. There is a high incidence of bone marrow and splenic involvement. Also a high proportion of patients presenting in the oribit, gastrointestinal tract and lung have this variety of lymphoma. It is included among the low grade lymphomas.

Another contribution of the newer classifications is the recognition of various subtypes of large cell lymphoma, diffuse histiocytic lymphoma in the Rappaport classification. One subtype, the immunoblastic large cell lymphoma, was included among the high grade lymphomas in the Working Formulation, while the others were placed among those of intermediate grade. We have confirmed a worse prognosis for this subgroup for minimal treatment[8], although its prognostic importance for patients treated with current aggressive chemotherapy regimens is controversial.

STAGING

The Ann Arbor staging classification devised for Hodgkin's disease also has prognostic validity when applied, with some modifications, to the non-Hodgkin lymphomas [4, 9]. This classification divides the lymphomas into four stages: **Stage I** refers to disease in a single lymph node or lymph node group. **Stage II** refers to disease in two non-contiguous lymph node groups and/or spleen, either above or below the diaphragm. **Stage III** refers to disease in two or more lymph node groups and/or spleen on both sides of the diaphragm. **Stage IV** refers to disease in extranodal sites, usually lung, liver, bone or bone marrow, and more rarely other sites. Extranodal involvement by extension from lymph node disease to such sites as the lung, bone, pleura or skin may occur in Stages I-III and is not considered to increase the Stage to IV. Such disease is designated by a subscript E (IE, IIE, IIIE).

For each stage the absence of systemic symptoms is designated by the subscript "A," while the presence of unexplained fevers to 38°C or higher, night sweats and/or weight loss of greater than 10% over 6 months are designated by a "B" subscript. In general the prognosis worsens with higher stage, and, within each stage, the presence of B symptoms carries a worse prognosis than absence of such symptoms (A).

There have been some modifications of the Ann Arbor classification for the non-Hodgkin's lymphomas. Stage IE refers to a solitary extranodal presentation of non-Hodgkin lymphoma. This includes GI tract, most commonly stomach, skin, bone, thyroid gland and breast. Such solitary extranodal presentations are extremely rare in Hodgkin's disease. For gastric lymphomas, Musshoff[10] has separated stage IIE into 2 subgroups. Stage IIE_1 refers to involvement of the gastric and regional perigastric lymph nodes. Staging IIE_2 refers to gastric involvement with distant abdominal node involvement, usually nodes in the celiac axis. Stage IIE_1 has a similar prognosis to stage IE, while stage IIE_2 has a similar prognosis to stage III.

Certain nodal sites are more common in non-Hodgkin's lymphoma than Hodgkin's disease. Waldeyer's ring involvement is seen in 5%-10% of patients with non-Hodgkin's lymphomas and is extremely rare in Hodgkin's disease. There is an association of Waldeyer's ring and GI tract involvement, usually in the stomach or small bowel. Mesenteric node involvement is quite common in the non-Hodgkin's lymphomas, but it is seen at presentation in Hodgkin's disease in less than 5% of the patients. Bone marrow involvement at presentation may be seen in from 15% to 40% of patients with non-Hodgkin's lymphoma.

Bone marrow biopsy is generally more sensitive than bone marrow aspiration, since focal involvement may be detected on biopsy but missed on aspiration. In the well differentiated lymphocytic lymphoma/chronic lymphocytic leukemia and in lymphoblastic lymphoma, bone marrow aspiration may be more sensitive than biopsy. Bilateral posterior iliac crest bone marrow aspirations and biopsies may increase the yield by approximately 10% over unilateral aspirations and biopsies. Flow cytometry may detect a clonal excess of kappa or lambda light chains on the surface of lymphocytes in peripheral blood or bone marrow which are not morphologically involved with lymphoma[11]. If the light chain is of the same type as those on the surface or tumor cells from other tissue, there may be lymphoma cells in the marrow or peripheral blood which cannot be detected morphologically. However, the clinical implications of these findings are still not completely clear.

The differences in the sites typically involved at presentation between Hodgkin's disease and non-Hodgkin's lymphomas has a number of implications for staging. Computerized tomography of the abdomen should be performed routinely in non-Hodgkin's lymphoma patients to

look for mesenteric as well as retroperitoneal node involvement. Lymphangiography is employed as secondary procedure to look for involved nodes in the retroperitoneum when the computerized tomogram is normal. As with Hodgkin's disease, an abnormal filling pattern in the nodes with lymphangiogram contrast may suggest nodal involvement by lymphoma even if the nodes are of normal size. Because of the association, mentioned above, of Waldeyer's ring involvement and GI tract involvement, patients with Waldeyer's ring involvement shoud have an upper GI series performed with a small bowel follow-through. Laparoscopically-directed liver biopsy is recommended, as in Hodgkin's disease, when liver biopsy is indicated.

Staging laparotomy with splenectomy, liver biopsy and retroperitoneal and mesenteric lymph node biopsies is not recommended routinely, since between 85%-95% of patients will have disease beyond stage I or IE with clinical staging. Staging laparotomy is only considered in relatively young stage I or IE patients where a positive finding would lead to systemic treatment with chemotherapy rather than localized radiotherapy.

TREATMENT

Stage I and IE: There are several ways in which these patients may be approached, and there is not sufficient data to recommend one approach over another. With regional treatment, radiotherapy (RT) with or without surgery, approximately 30%-50% of patients can be expected to recur, generally outside the RT portals[12]. The local control rate with doses of RT of 4400 rads or greater is 80-90%[13], and we have seen few in-field relapses above a dose of 3500 rads. Our results have been similar for nodular and diffuse histologies and for nodal and extranodal presentations. For 17 pathologically staged I or IE patients, the group at the University of Chicago reported a 72% disease-free survival and a 70% overall survival at 10 years with extended field RT[14]. As in our own experience, the majority of PS II or IIE patients relapsed following RT only.

Our regional approach has included partial gastric resection in addition to abdominal RT for patients with limited gastric IE or IIE_1 disease. This approach has decreased the incidence of catastrophic bleeding and perforation[10]. Total gastrectomy shoud not be performed because of the nutritional morbidity of the procedure. Limited resection can also be useful in the management of localized colonic or rectal lymphoma. Lymphomas involving the small bowel are often more extensive making resection of large portions of the small bowel impractical because of short and long-term morbidity.

At Memorial Hospital we currently have a clinical trial which randomizes patients to 6 months of adjuvant chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone or observation (CHOP-see Table 3). The dose of cyclophosphamide was lowered to 600 mg/m² from 50 mg/m² and the dose of doxorubicin to 40 mg/m² from 50 mg/m² in the adjuvant protocol from the standard doses in CHOP. It is hoped that adjuvant chemotherapy might cure a portion of the 50% of patients destined to relapse following regional treatment, most of whom probably have occult systemic disease. Some support for the adjuvant approach can be

TABLE 3 – CHOP for large cell lymphoma

cyclophosphamide	750 mg/m² IV	day 1
doxorubicin	50 mg/m² IV	day 1
vincristine	1.4 mg/m² (max 2 mg IV)	day 1
prednisone	100 mg p.o.	days 1-5
Repeat every 3–4 weeks X 8 cycles		
Attenuation of doses:		
WBC *(per mm³)*	Platelet count *(per mm³)*	*Doses*
⩾ 4000	⩾ 150,000	Full Dose
3000-3999	100,000-149,000	100% vincristine and prednisone 50% cyclophosphamide and adriamycin
2000-2999	5,000- 99,000	100% vincristine and prednisone 25% cyclophosphamide and adriamycin
⩾2000	⩾ 50,000	Hold

found in 3 European studies randomizing patients to adjuvant chemotherapy following RT[15, 16, 17]. All of these show an advantage for chemotherapy, but this is mostly among the stage II patients who should all probably be treated systemically with chemotherapy. It will take more patients and longer follow-up to determine whether or not adjuvant chemotherapy will be successful in curing an increased number of stage I patients as compared with those receiving regional treatment only.

Finally, promising early results have also been reported for the use of combination chemotherapy alone for stage I large cell lymphoma[18] using cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). The number of patients is too small and the follow-up too short to warrant any definitive conclusions about this approach.

STAGE II, III AND IV DIFFUSE NON-HODKIN'S LYMPHOMA

Major advances in the treatment of large cell lymphoma were the reports of DeVita et al[19] and Berd et al[20] of the achievement of long-term survival in patients treated with combination chemotherapy. DeVita et al used cyclophosphamide, vincristine, procarbazine and prednisone (C-MOPP) (Table 4) and achieved long-term unmaintained remissions and survival in approximately 40% of patients. The group at Yale and later the group at the University of Chicago[21] employed a combination of cyclophosphamide, vincristine, intermediate-dose methotrexate with leucovorin and cytosine arabinoside (COMLA). Forty to 50% of patients achieved a CR, and, overall, there were approximately 35% long-term survivors. The Southwest Oncology Group pioneered the use of cyclophosphamide, doxorubicin, vincristine and prednisone (Table 3) with or without bleomycin. These studies resulted in CR rates of approximately 50%. In common with the other programs mentioned above, the long-term survival rate has been approximately 30%. Most relapses from CR in all of these studies tended to occur within the first 3 years, but late relapses out to 6-7 years have been seen[20, 22]. It is not clear that bleomycin added to the CHOP regimen increased its efficacy.

Our results at Memorial Hospital were similar to those mentioned above for similar regimens[23]. We have recognized that certain prognostic features particularly predict a poor outcome. Patient with bulky mediastinal presentations of large cell lymphoma have generally done poorly with the type of regimen mentioned above. Bulky abdominal disease and multiple extranodal sites of involvement have also been associated with a poor prognosis although not as strongly as mediastinal presentation. The most important prognostic factor in large cell lymphoma with respect to both CR percentage and survival has been initial elevations of serum lactic acid dehydrogenase (LDH). There has been an inverse relationship of survival with the amount of elevation[23].

Recently several groups[24-27] have reported an improvement in survival for patients with large cell lymphoma of from 30%-40% to 50%-60%.

TABLE 4 – MOPP and C-MOPP[19]

Day 1 and 8	HN_2 (mustargen) 6 mg/m^2 (cyclophosphamide 650 mg/m^2 IV could be given instead, if nausea and vomiting are intolerable). Vincristine 1.4 mg/m^2 IV (maximum 2 mg).
Days 1–14:	Procarbazine 100 mg/m^2 p.o. (maximum 150 mg). Prednisone 40 mg/m^2 p.o. (cycle 1 and 4).
Repeat X 6 cycles	

Attenuation of doses:

WBC	*Platelets*	*Doses*
⩾ 4000	150,000	Full Doses
3000-3900	100,000-149,000	100% VCR, Prednisone 50% HN_2, PRO
2000-2900	50,000-100,000	100% VCR, Prednisone 25% HN_2, PRO
1500-1999		50% VCR, 25% HN_2, PRO
< 1500	50,000	Hold therapy re-evaluate in 1 week

One of the simplest of these regimens is m-BACOD as reported by Skarin et al[24] from the Dana Farber Cancer Center. High dose methotrexate was added to CHOP and bleomycin. The initial dose of methotrexate was 3 gm per meter squared IV followed by Leucovorin rescue[24], but similar results have apparently been achieved with an intermediate dose of methotrexate of 200 mg per meter squared IV followed by Leucovorin with less toxicity[28]. (m-BACOD-Table5).

Recently, excellent early results have been reported with an intensive weekly schedule of cyclophosphamide, doxorubicin, vincristine, bleomycin, prednisone and intermediate dose methotrexate for 12 weeks by Klimo and Connors[27]. (MACOP-B, see Table 6). Eight-four percent of patients achieved a CR and 76% of patients are surviving at a median follow-up of 2 years.

It is possible that the improved results re-

TABLE 5 – m-BACOD for large cell lymphoma[24]

doxorubicin	45 mg/m^2 IV	day 1
cyclophosphamide	600 mg/m^2 IV	day 1
vincristine	1 mg/m^2 IV	day 1
bleomycin	4 mg/m^2 IV	day 1
methotrexate	200 mg/m^2 IV	day 8,15
leucovorin	25 mg p.o. q6hrs X 6 doses at 24 hours after methotrexate	
dexamethasone	6 mg/m^2 p.o.	day 1–5

Repeat every 22 days X 10 cycles.

Attenuation of doses: WBC (per mm^3)		PLT count (per mm^3)	Dose
> 3500		> 100,000	100%
2000-3500	or	50,000-100,000	50% cyclophosphamide, doxorubicin
< 200	or	< 50,000	Hold X 1 week

TABLE 6 – MACOP-B for large Cell lymphoma[27]

	1	2	3	4	5	6	7	8	9	10	11	12
Adria	50/m^2	x	50/m^2	x	50/m^2	x	50/m^2	x	50/m^2	x	50/m^2	x
Cytoxan	350/m^2	x	350/m^2	x	350/m^2	x	350/m^2	x	350/m^2	x	350/m^2	x
MTX+FA	x	400/m^2	x	x	x	400/m^2	x	x	x	400/m^2	x	x
Vincr.	x	2mg	x	2mg	x	2mg	x	2mg	x	2mg	x	2mg
Bleo	x	x	x	10/m^2	x	x	x	10/m^2	x	x	x	10/m^2
Pred.	75 mg/day continuously →	→	→	→	→	→	→	→	→	→	→	TAPER
Septra	2 b.i.d. daily continuously →	→	→	→	→	→	→	→	→	→	→	→

Prednisone tapering schedule: 60mg/day x 2, then – 5 mg/day till 0.

MTX: 100/m^2 i.v. push THEN 300/m^2 over 4 hours, THEN leucovorin rescue at 24 hours from the beginning of infusion - 15 mg.q.6.h. p.o. (or i.v.)x 6 doses

Attenuation of doses of adriamycin and cyclophosphamide would be based upon neutrophil counts derived within 24 hours of the next drug dose as shown in the table below:

If neutrophil count is:	over 1000/cmm	100 – 1000/cmm	under 100
then give:	100%	65%	0

cently reported for large cell lymphoma with more intensive chemotherapy regimens may be partly due to selection of patients with favorable prognostic features in some of the series. Our group has had promising results in large cell lymphoma patients with unfavorable prognostic features with the use of supralethal TBI and high dose cyclophosphamide followed by autologous bone marrow rescue in cases without initial bone marrow involvement[29]. This procedure has also had some success as a "salvage" regimen in relapsed patients. Whether or not autologous bone marrow transplantation is superior to current intensive "conventional" chemotherapy for the large cell lymphoma patients with an unfavorable prognosis is currently under investigation in a randomized trial at Memorial Hospital.

The treatment of patients with diffuse poorly differentiated lymphocytic lymphoma and diffuse mixed lymphocytic-histiocytic lymphoma is still not satisfactory. With conventional combination chemotherapy the percentage of remissions has been high, but they have been of shorter duration than those of patients with large cell lymphoma[30]. Whether or not an increase in durable CRs will be obtained with more intensive chemotherapy regimens is not known.

Lymphoblastic lymphoma is closely related to acute lymphoblastic leukemia by clinical behavior and by cell marker analysis, as mentioned above. At Memorial Hospital approximately 40-50% of these patients have achieved long-term survival using the same intensive approach that has been employed with the same results in adult acute lymphoblastic leukemia[31]. This approach involves a standard ALL-type induction with vincristine and prednisone with added pulses of cyclophosphamide and doxorubicin, an intensive, highly myelosuppressive consolidation and 2 1/2 years of a rotating schedule of drugs given on an out patient basis. Prophylactic intrathecal methotrexate is used throughout induction, consolidation and maintenance. The meningeal relapse rate has been low, and it seems that continuous prophylactic intrathecal chemotherapy combined with intensive systemic chemotherapy has made the use of prophylactic CNS irradiation, with its associated morbidity, unnecessary. The results achieved with this approach are among the best reported (figure 1). Cures have also been achieved with this approach for patients with undifferentiated lymphomas.

Diffuse well-differentiated lymphocytic lymphoma is probably part of a spectrum of the same disease as chronic lymphocytic leukemia (CLL), as mentioned above. With minimal treatment these patients had a median survival of 76 months in the Memorial Hospital experience[4], a survival which is similar to that of patients with CLL. There is no evidence that combination chemotherapy prolongs survival in these patients. Good palliative results have been reported with low dose total body irradiation and with alkylating agents, often combined with prednisone. A randomized trial is in progress at Memorial Hospital comparing cyclophosphamide and prednisone alone and in combination with low dose TBI. The following is a convenient schedule for administering chlorambucil and prednisone: Chlorambucil 30 mg per meter squared p.o. over 1-2 days with prednisone 30 mg per meter squared p.o. daily for 4 days. This dose can be repeated every 2-3 weeks until remission is achieved or until myelosuppression occurs. I have often continued treatment after remission has been achieved to give a total treatment period of approximately 1 year even after remission has been achieved. Despite the use of a large dose of chlorambucil at once, nausea and vomiting do not occur or are minimal and are controllable with antiemetics. Obviously, a risk exists for the development of acute leukemia with the long-term use of alkylating agents in this disease, so treatment is generally started only if the clinical situation warrants it.

NODULAR OR FOLLICULAR LYMPHOMAS: STAGES II, III AND IV

The treatment of these lymphomas is controversial and is not entirely satisfactory. As with the diffuse poorly differentiated lymphocytic and the diffuse lymphocytic-histiocytic lymphomas, remissions are achievable in approximately 60% of patients with nodular poorly-differentiated lymphocytic and nodular mixed lymphomas (NPDL, NML) with combination chemotherapy. The National Cancer Institute has reported that the CRs in the NHL and NML groups may be more durable than those for the NPDL group[32, 33]. The variability of the manner in which pathologists classify patients as to whether they have NML or NPDL has made it difficult to confirm these reports.

Another major difficulty in the interpretation of treatment results for the nodular lymphomas has been the difference in natural history reported at various centers as discussed above. The Stanford group has reported median survivals of

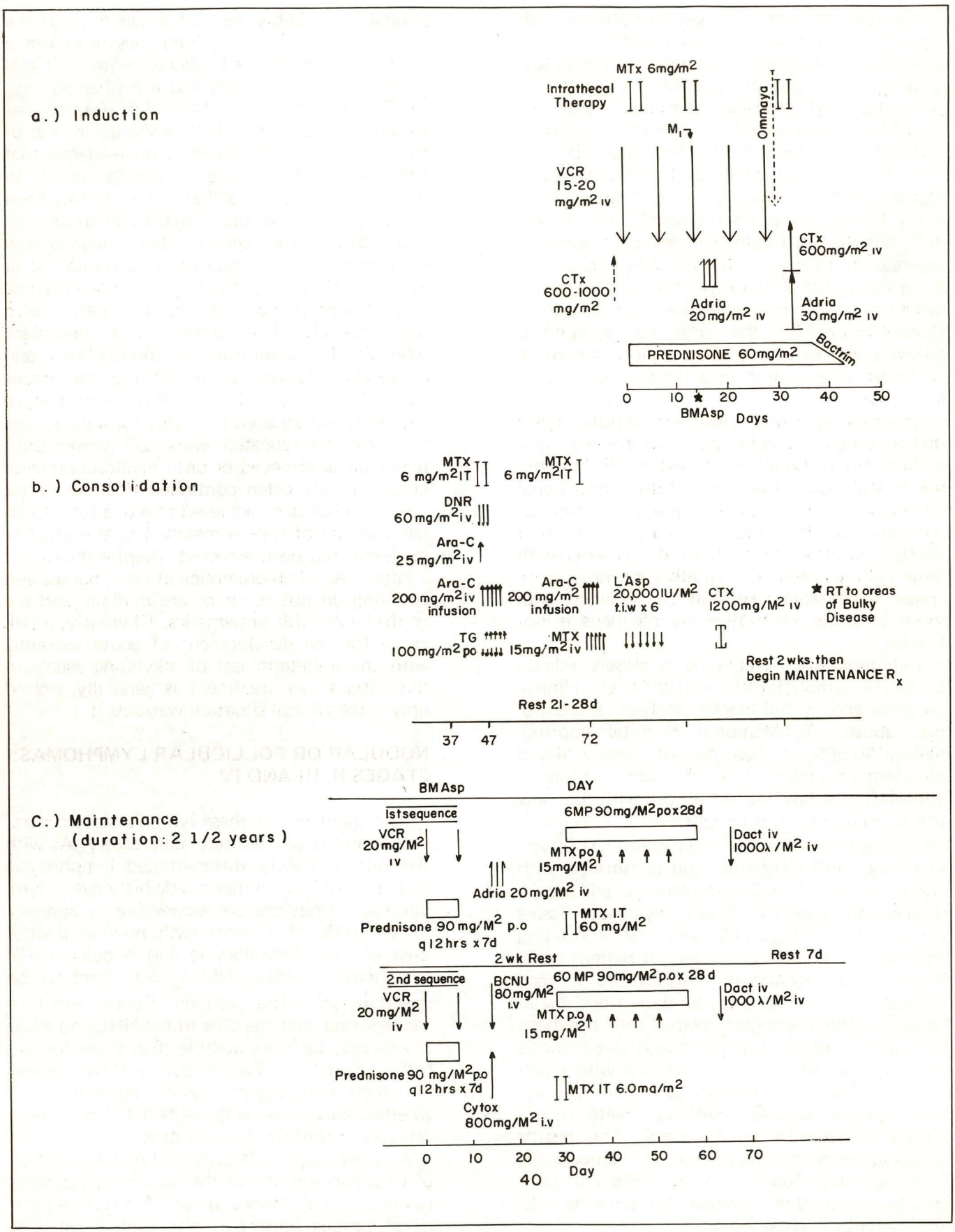

FIGURE 1 — L-17M Protocol for lymphoblastic lymphoma[31]

8-10 years for the NPDL and NML groups with some spontaneous remissions[2, 34]. The groups at Memorial Hospital and the National Cancer Institute have reported median survivals of only 3-4 years from the conservative treatment era. Using TNI or low-dose TBI either alone or in combination with single alkylating agents, or cyclophosphamide, vincristine and prednisone (CVP), the Stanford group was unable to demonstrate an improvement in survival[35]. The one exception was a selected group of stage III patients who had an excellent survival following TNI[36]. This has led the Stanford group to adopt a "watch and wait" approach for asymptomatic patients with nodular lymphomas, since they feel their survival would be long without treatment and that treatment will not prolong it[34, 37]. Selected asymptomatic patients treated only when complications occurred had the same survival as symptomatic patients treated with the above modalities. It could be argued that this study shows advantage for treatment, since the survival of symptomatic patients was probably prolonged to that of asymptomatic patients by treatment.

Others have found that achievement of a CR has prolonged survival for patients with nodular lymphomas[38]. Our results with the combination of thioTEPA, vincristine, chlorambucil and prednisone followed sequentially by cyclophosphamide, doxorubicin, melphalan and prednisone (NHL-4 protocol) has improved survival early on as compared with our previous results with minimal treatment[39]. Although how many of these CRs will ultimately be durable is not yet certain, there certainly are some patients in remission remaining off treatment for a number of years. Of course historic comparisons are difficult because treatment results might improve with time due to an overall improvement in medical care and a change in patient population with time rather than to specific effects of treatment. The National Cancer Institute is currently conducting a randomized trial of "watching and waiting" vs aggressive initial chemotherapy (D. Longo, personal communication). Such randomized trials of an intensive chemotherapy approach vs a conservative approach are clearly needed.

Until these problems are resolved, the current recommendation for stage II, III and IV nodular lymphomas might be the following. For elderly patients who are asymptomatic a "watch and wait" and ultimately conservative approach with single alkylating agents such as chlorambucil or cyclophosphamide or mild combination chemotherapy such as with cyclophosphamide, vincristine and prednisone (CVP) seems reasonable. Symptomatic elderly patients might be treated conservatively at time of diagnosis. Symptomatic younger patients should definitely be treated at time of diagnosis. Consideration could be given to one of the more aggressive combinations employed for large cell lymphoma, since it is possible that improving the likelihood for CR and the quality of CR might improve chances for disease-free survival. Such treatment might also be considered either initially or after a period of observation for young asymptomatic patients, since the natural history of their disease is uncertain.

COMBINED MODALITY TREATMENT FOR NON-HODGKIN'S LYMPHOMAS

Addition of adjunctive RT for localized, particularly bulky, initial disease has been advocated, since these may be areas at particular risk as sites of relapse following combination chemotherapy. Whether or not such radiotherapy will improve results needs to be addressed in large-scale randomized trials.

TREATMENT OF MENINGEAL DISEASE

The role of prophylactic intrathecal methotrexate to prevent meningeal recurrence is unclear. Long-term survival is achievable with intrathecal or intraventricular treatment with or without whole brain irradiation in perphaps one fourth of patients presenting with meningeal disease[40]. Patients who develop meningeal disease during their course virtually always die of their disease, although autopsies have showed control of meningeal disease following treatment in one half[40].

Our recommendation is for biweekly intrathecal methotrexate, 6 mg per meter squared, to be administered until the cerebrospinal fluid cytology becomes negative. Thereafter it is administered at gradually increasing intervals. A decision to eventually stop treatment has to be made only on an individualized basis after prolonged treatment. Patients with cranial nerve palsies should immediately be started on high dose dexamethasone to reduce edema and whole brain RT to a dose of 3500 rads in addition to intrathecal treatment. It is important to start as soon as possible to try to reverse the neurological deficits. For patients in whom active systemic treatment is planned and fror whom reasonably long term survival is possible, placement of an Ommaya reservoir for direct intraventricular

treatment is recommended. The pharmacokinetics of CSF methotrexate is improved over intrathecal administration, and there is some suggestion that clinical results may be improved also[40].

CONCLUSION

Radiotherapy achieves excellent local control of non-Hodgkin's lymphomas. Approximately 50% of stage I and IE patients and a selected group of stage II and III patients have achieved long-term unmaintained remissions and are probably cured with RT. Total nodal irradiation has been the method employed most successfully for stage II and III patients. The role of adjuvant RT along with combination chemotherapy remains to be clarified. Intensive combination chemotherapy has also achieved long-term unmaintained remissions in between 30 and 70 percent of patients with stage II, III and IV large cell, undifferentiated and lymphoblastic lymphomas. Further work is needed to further improve results for these patients and for patients with other types of non-Hodgkin's lymphoma.

RESUMO

Os linfomas não-Hodgkin são um grupo heterogêneo de doenças. Estudos com marcadores celulares nos últimos 15 anos demonstraram que a maioria dos linfomas de células B no adulto são originários dos linfócitos B, enquanto que a minoria tem a sua origem nos linfócitos T.

UNITERMOS: *Linfomas, linfomas não-Hodgkin, quimioterapia, radioterapia.*

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