How I Treat Patients With Diffuse Large B-Cell Lymphoma

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The disease we now call diffuse large B-cell lymphoma has gone by many names in the past. These have included reticulum cell sarcoma (1), diffuse histiocytic lymphoma (2), and, more recently, diffuse mixed lymphoma, diffuse large cell lymphoma, or immunoblastic lymphoma—terms from the Working Formulation (3). Early studies of therapy for patients with diffuse large B-cell lymphoma contained some patients with aggressive T-cell lymphoma as these were lumped together in the Working Formulation and some older classifications. The correct diagnosis today is diffuse large B-cell lymphoma as utilized in the WHO classification (4). (Table 1) However, we know that this is still a heterogenous group that includes lymphomas with a wide variety of morphological appearances (Table 2), protein expression patterns, and gene expression patterns. For example, patients with diffuse large B-cell lymphoma can be divided into at least three clinically relevant groups using gene expression profiling (5-7). These include the germinal center type, the activated B-cell type and mediastinal large B-cell lymphoma (Table 3). A few patients will not be easily classified in these catagories. (8) Mediastinal large B-cell lymphoma represents less than ten percent of all large B-cell lymphomas, occurs primarily in young women, and always presents with a mediastinal mass. The gene expression profile is similar to that seen in classical Hodgkin’s disease. (7, 9) The other two types of diffuse large B-cell lymphoma, and those not easily classified, have a median age at presentation in the sixties, a male predominance, and can present at essentially any site in the body. (8) They will be the major focus of this paper.
Lymphomas are the fifth most common systemic cancer with the most common subtype being diffuse large B-cell lymphoma followed by follicular lymphoma and Hodgkin’s lymphoma. Diffuse large B-cell lymphoma represents approximately 30% of all lymphomas and is the most common subtype throughout the world. This is in contrast to many other types of lymphoma which have striking geographic variation in frequency of occurrence.(10)

Diffuse large B-cell lymphoma can be seen after histological transformation of most other types of B-cell lymphoma. This is particularly frequent in patients with follicular lymphoma and is recognized clinically in up to 50% of patients. (11, 12) Although much less frequent, this transformation occurring in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma has the eponym Richter’s transformation.(13, 14) In general, patients with diffuse large B-cell lymphoma seen after histological transformation have a poorer response to therapy and prognosis than those with a de novo appearance—particularly if the patient was treated for the preceding lymphoma. This manuscript will focus on the treatment of patients with primary diffuse large B-cell lymphoma.

**Diagnosis**

The first step in treating any cancer is an accurate histological diagnosis. For non-Hodgkin’s lymphomas in general, and diffuse large B-cell lymphoma in particular, the initial diagnosis should be based on an adequate sample of tissue preferably obtained with an excisional biopsy of an abnormal lymph node or a generous incisional biopsy of an involved organ. In some cases, cutting needle biopsies can provide adequate tissue for diagnosis. However, the diagnosis of lymphoma based on fine needle aspirates should be discouraged. One of the most frustrating situations in the care of a patient with lymphoma arises when the diagnosis was based on inadequate material, the patient does not respond to therapy as expected, and to obtain another biopsy has become difficult or impossible.
The diagnosis of lymphoma and its subtype is best made by a hematopathologist with experience in diagnosing lymphomas. Expert hematopathologists using the WHO classification can make highly reproducible diagnoses for most subtypes of lymphoma (15). However, this depends upon adequate tissue and the availability of immunohistochemistry. (15) On occasion, cytogenetics or fluorescent in-situ hybridization (FISH) may help clarify a difficult diagnosis.

At the present time gene expression profiling is not part of routine clinical practice. This may be partly because of the technical difficulties in performing the arrays. The assignment of germinal center type versus non-germinal center type diffuse large B-cell lymphoma seems to be able to be reproduced by studying the expression of 3 proteins using immunohistochemistry. (16) Although the germinal center B-cell type and the activated B-cell type of diffuse large B-cell lymphoma do not have the same prognosis with anthracycline containing chemotherapy regimens (8), they are still treated in a similar way in the absence of studies showing superiority of specific regimens for each subtype. The poorer prognosis of patients with primary brain diffuse large B-cell lymphoma and the better outcome in pediatric patients might be partly explained by the predominance of activated B-cell type in the former (17, 18) and germinal center B-cell type in the latter (19, 20). The one time gene expression profiling may be important in current clinical practice is the distinction between diffuse large B-cell lymphoma and Burkitt’s lymphoma. A recent study showed that gene expression profiling might be able to make this distinction more accurately than other studies (21). This is important because patients with Burkitt’s lymphoma should be treated with different regimens than used for diffuse large B-cell lymphoma, and their survival is dramatically better when they receive appropriate regimens.
In my practice I am extremely reluctant to treat a patient for diffuse large B-cell lymphoma in the absence of an adequate biopsy reviewed by experienced hematopathologists. I prefer rebiopsy to guessing about the correct diagnosis.

**Staging/Restaging**

As would be true for any type of cancer, after the diagnosis of diffuse large B-cell lymphoma a patient must be evaluated to determine sites of involvement by the lymphoma and the presence or absence of key prognostic factors to complete a staging evaluation. As currently used in practice today, the process of staging accomplishes several important tasks. These include allowing the choice of the most appropriate therapy, providing the most accurate possible prognosis for the patient and their family, and making clinical research and quality assessment possible by allowing patients to be stratified into prognostic groups. In potentially curable diseases such as diffuse large B-cell lymphoma this initial evaluation will be the basis for “restaging” that will be done after some or all of the patient’s treatment. This restaging will document the presence or absence of a complete response to treatment. Obviously, cure of the disease requires a complete response to therapy, but not all complete responders will be cured as our current tests cannot always find minimal residual lymphoma. Conversely, some patients with apparent incomplete responses due to residual masses on computed tomograms might be cured if the residual masses contain no active lymphoma. This problem is at least partially addressed by the use of functional imaging such as PET scans.

The initial evaluation of a patient with diffuse large B-cell lymphoma should include a careful history and physical examination, laboratory studies including hematological parameters, screening chemistry studies, and, specifically, a serum lactate dehydrogenase level. Imaging studies should include at least computed tomograms of the chest, abdomen and pelvis and a PET scan if available. An adequate bone marrow biopsy should be performed. Other laboratory studies, images, and biopsies might be appropriate in specific
patients. For example, I perform lumbar puncture to rule out meningeal involvement in patients presenting with testicular, epidural, or sinus involvement.

PET scanning is an increasingly important tool in the care of patients with diffuse large B-cell lymphoma. However, the best use of this technology is still in flux and basic issues such as what represents a negative PET scan post treatment does not have general agreement. Whether scans need to be done before treatment in a disease with a high likelihood of positivity such as diffuse large B-cell lymphoma has been debated,(23) The appropriate timing for follow up scans has also been a point for controversy. A recent consensus report on the use of PET scanning in lymphomas is a step towards trying to resolve these areas of uncertainty.(24)

Patients with diffuse large B-cell lymphoma are stratified into prognostic groups based on the International Prognostic Index (25) This system utilizes anatomic stage, performance status, the number of extranodal sites, serum lactate dehydrogenase level, and age to predict treatment outcome.(Table 4) The International Prognostic Index remains our most useful prognostic tool and should be applied to all patients with diffuse large B-cell lymphoma.(Table 5) However, the improvement in treatment response associated with the addition of the antibody rituximab to treatment regimens seems to have altered the survival of prognostic groups using the International Prognostic Index (Table 6) (26).

Restaging is a process of repeating all previously abnormal tests to see if the patient has achieved a remission. Although this is often done at the completion of a planned course of therapy, I perform restaging after four cycles of treatment for diffuse large B-cell lymphoma with the intention of treating patients two cycles past documented complete remission.(27) Thus, if the patient is in remission at four cycles, they receive a total of six. If they don’t achieve remission until after six cycles they would receive a total of eight cycles.
If they have not achieved a remission by six cycles, then I would switch to alternate therapies.

**Therapy**

The discussion of management of patients with diffuse large B-cell lymphoma can be conveniently divided into three groups. Those presenting with localized disease, those presenting with disseminated disease, and those patients who recur after an initial remission. In each group, patients who are elderly might not be managed in exactly the same way as young patients. Also, patients who have the disease involving specific organs might require special treatment approaches.

*Localized disease.*

Patients with Stage I (i.e. involvement of only one lymph node region or isolated organ involvement) fit into this category. However, selected patients with Stage II (i.e. two adjacent left node regions involved or organ involvement with involvement of regional lymph nodes) who could have their disease encompassed in one radiotherapy port might be approached in a similar manner. These patients were once treated with radiotherapy alone and a few were cured (28). The addition of adjuvant chemotherapy following the radiation improved treatment outcome (29) but an abbreviated course of chemotherapy followed by radiation became the most popular treatment.(30) A study done by the Southwest Oncology Group in the United States showed superiority of an abbreviated course of CHOP followed by radiation over a complete course of CHOP alone.(31) This became and has remained the standard treatment in the United States. A more recent Eastern Cooperative Oncology Group study suggested benefit of adjuvant radiation after 8 cycles of CHOP.(32) However, selected patients in whom radiation might be unusually problematic (e.g. young women in whom the treatment field would involve the breast or patients of any age in whom salivary gland treatment might lead to a dry mouth and loss of teeth) are often treated with a complete course of chemotherapy alone.
Studies from Europe have challenged this treatment approach. A GELA study in elderly patients compared four cycles of CHOP alone with four cycles of CHOP followed by radiotherapy.\(^{(33)}\) There was no advantage to the radiation and, in fact, a possible disadvantage in patients older than 70 years of age. In younger patients the same group compared an intensive chemotherapy regimen (ACVBP) to three cycles of CHOP followed by involved field radiotherapy.\(^{(34)}\) There was a significant advantage to the ACVBP arm. The MINT trial included some patients with minimal disease and compared a CHOP-like chemotherapy regimen to the same regimen with the addition of rituximab in young, good prognosis patients.\(^{(35)}\) For the most favorable patients (i.e. those without bulky disease) the results with a complete course of chemotherapy plus rituximab alone and no radiation led to a survival in excess of 90%. The Southwest Oncology Group in the United States reported a pilot study of an abbreviated course of CHOP plus the antibody rituximab followed by radiation and also showed progression free and overall survival in excess of 90%.\(^{(36)}\)

My personal approach to patients with localized diffuse large B-cell lymphoma involves the use of CHOP plus rituximab for four cycles. If the patient is in remission at that point, either involved field radiotherapy or two more cycles of the chemotherapy regimen would be administered based on the patient’s preferences and the site of the disease. I would generally not recommend radiation to young women in whom the breast would have to be irradiated and would offer drugs alone to patients in whom radiation to the salivary glands might lead to loss of their teeth. For the patient with very bulky (i.e. >10 cm mass) but localized lymphoma I would favor CHOP plus rituximab for six cycles followed by involved field irradiation.

Patients with localized disease involving certain organs need modifications of the general plan. Patients with testicular lymphoma have a predilection for spread to the opposite testis and to the central nervous system.\(^{(37)}\) Central
nervous system involvement can be meningeal or parenchymal. In addition, patients with testicular involvement, who are usually elderly men, have a higher than anticipated risk of late relapse. They would usually be treated with a complete course of chemotherapy such as CHOP plus rituximab accompanied by intrathecal treatment with methotrexate and/or cytarabine. After treatment these patients should have scrotal irradiation. Primary brain lymphoma is an increasing problem. While often accompanied by HIV infection, an increasing number of patients without HIV are developing the disease. Current treatment regimens are built around high dose methotrexate. The use of whole brain radiotherapy as part of the initial treatment is controversial and frequently associated with the development of dementia—particularly in elderly patients. Patients with epidural or sinus presentations and those with circulating tumor cells seem especially likely to develop meningeal metastasis. These patients should be treated with intrathecal methotrexate and/or cytarabine along with their initial chemotherapy regimen.

**Disseminated Disease**

The potential for cure using chemotherapy alone in patients with disseminated diffuse aggressive lymphoma was first reported in the early 1970s by Levitt et al (42) and DeVita et al. (43). In both studies some patients with documented complete remissions achieved long-term, disease-free survival. Shortly after these reports the CHOP regimen became popular in the United States and became the standard treatment regimen for patients with diffuse aggressive lymphoma. However, in the subsequent decade the development of new treatment regimens including M-BACOD, MACOP-B, and ProMACE/CytaBOM were reported to achieve results that seemed much better than had been observed with CHOP. These so-called “third generation” regimens appeared to represent an important advance in therapy until an intergroup trial carried out in the United States demonstrated no superiority over CHOP. This surprising result almost certainly was related to treating a better group of patients (i.e. probably younger, lower stage, with a lower IPI score) in
the studies of the new very intensive regimens and assuming that the results would apply to all patients with the disease. This example illustrates the importance of the randomized trial in documenting moderate improvements in therapy in this and any other disease.

After the disappointing results with the “third generation” chemotherapy regimens in the United States, there was a lull in developing new regimens and CHOP was the standard therapy. However, research continued—particularly in countries other than the U.S.—and a number of new treatment approaches have been developed. Currently, the search for the optimal chemotherapy regimen for treating diffuse large B-cell lymphoma continues.

The GELA developed the ACVBP regimen (i.e. which involves very intensive chemotherapy for four courses followed by an intensive consolidation) which was shown to be superior to CHOP in subgroups of patients.(49) In Germany national trials found that the addition of etoposide to CHOP improved results in young patients(50) while CHOP administered at 14 rather than 21 day intervals seemed to improve the results in elderly patients.(51) An infusional chemotherapy regimen developed at the United States National Cancer Institute referred to as EPOCH had very encouraging results.(52) This regimen plus rituximab is currently in a randomized trial in the United States.

However, the study that changed practice throughout the world was performed by the GELA and compared CHOP versus the same regimen plus the antibody rituximab in elderly patients.(53, 54) A highly significant advantage in response rate, failure free survival, and overall survival was seen with the addition of the antibody. In the United States a trial comparing CHOP +/- rituximab administered in a different schedule and with or without maintenance rituximab generally confirmed the GELA results with a significant advantage for receiving rituximab either during induction or maintenance, but no advantage to getting both.(55) An international study called the MINT trial compared
chemotherapy with CHOP or a “CHOP-like” regimen with or without rituximab in younger, good prognosis patients (i.e. both the GELA and the America Intergroup trials were done in patients over 60 years of age). (35) The MINT trial demonstrated a significant advantage in response, failure-free survival, and overall survival with the addition of the antibody. The German High Grade Lymphoma Study Group studied the utility of six versus eight cycles of CHOP at 14 day intervals with or without rituximab in elderly patients with diffuse large B-cell lymphoma. Again, this demonstrated the importance of rituximab, but also hinted that eight cycles of treatment might be deleterious in very elderly patients.(56) Finally, investigators from the Cancer Institute in British Columbia had the opportunity to do a population based study of the impact of adding rituximab to CHOP.(57) Because cancer drugs are paid for by the government in British Columbia and the addition of rituximab to CHOP was approved at a particular point in time, they used that point in time as the variable to see if approval of the drug improved treatment outcome. This was despite the fact that a few patients before the date of approval received the drug and not all patients did after the date of approval. However, with only approval of the drug and its general availability as a variable, survival for diffuse large B-cell lymphoma in British Columbia went up about 20%. (57) (Figure 1)

The addition of rituximab to CHOP or other chemotherapy regimens has been a major improvement in our ability to treat patients with diffuse large B-cell lymphoma. An important question has been whether or not all patients need the rituximab. Studies from France and the American National Cancer Institute suggested that the improvement with rituximab was largely seen in patients with tumors overexpressing the Bcl-2 protein(58, 59) although not all groups found the same results.(60) This might relate to the Bcl-2 protein expression having prognostic significance in the activated B-cell type but not the germinal center B-cell type of diffuse large B-cell lymphoma.(61) A recent report from the French group using the method of competing risks suggested that benefit was seen in
both Bcl-2 positive and Bcl-2 negative lymphomas, but that the benefit was more striking in those patients whose tumors were Bcl-2 positive.(62)

Autologous hematopoietic stem cell transplantation has been shown to be an effective therapy for patients with diffuse large B-cell lymphoma who relapsed from complete remission and whose lymphoma still responded to standard dose salvage chemotherapy.(63) In a randomized trial comparing DHAP plus radiotherapy to autologous hematopoietic stem cell transplantation, patients who underwent transplant had a superior disease-free and overall survival (64). Benefit from transplantation was seen in patients with an International Prognostic Index score of $\geq 1$. (65)

Because of this encouraging data, a large number of studies have tested the value of incorporating autologous hematopoietic stem cell transplantation into the primary therapy of patients with diffuse large B-cell lymphoma. (66-76) These studies were not all comparable with some testing transplantation early in the course of therapy with an abbreviated standard treatment regimen, some have used novel treatment regimens, some have studied complete and partial responders, some but not all have incorporated only high risk patients, and some have tested transplant as an adjuvant treatment following complete remission. Although the interpretation of this data remains a point for controversy, the conclusion that I draw is that transplantation is only likely to benefit high risk patients who achieve a complete remission after a complete course of a standard chemotherapy regimen. The results from a randomized trial from France when the analysis was restricted to patients with an age adjusted IPI score of two or three, is presented in Figure 2 (70) along with the progression-free survival curve for 53 high risk patients transplanted in first complete remission following a complete course of anthracycline based chemotherapy treated at the University of Nebraska Medical Center. One important issue to consider is that the definition of high risk may change as new treatment approaches are developed. For example, a recent report from the University of British Columbia in
Vancouver suggested that the results by IPI score have “shifted” with the addition of rituximab. (Table 6) (26)

My treatment approach for patients with disseminated diffuse large B-cell lymphoma who are not participating in a clinical trial is to initiate CHOP plus rituximab after starting the patient on allopurinol as tumor lysis syndrome can be seen in this disease. Patients receive concomitant intrathecal methotrexate if the testis, sinus, or epidural area were involved at presentation. After four cycles of treatment I reevaluate the patient with history and physical examination, laboratory studies, and images including PET scan. If the patient has achieved a complete remission I give two more cycles of therapy and discontinue treatment. If the patient presented with a very bulky (i.e. >10 centimeter) mass at any site, I would consider adjuvant radiotherapy to that site if it could be administered safely. If the patient was 60 years of age or less and had a high serum lactate dehydrogenase level, poor performance status, multiple extranodal sites of disease, and Ann Arbor Stage III or IV (i.e. or at least two of these findings), I would discuss adjuvant autologous hematopoietic stem cell transplantation in complete remission as an option. I don’t believe there is any evidence to support maintenance therapy in patients with this disease.

Follow Up

After a patient has completed planned therapy and is in complete remission, there is still a significant chance for recurrence. Most patients who are going to relapse will do so in the first two of three years, but we have seen patients relapse more than 13 years after completing therapy. Follow up is aimed at identifying relapse, but also managing the complications that might develop related to the treatment and to helping the patient deal with the diagnosis and their concerns about possible relapse. I see patients at two monthly intervals for the first year, three monthly intervals for the second year, four monthly intervals for the third year, twice a year for the fourth and fifth years,
and then annually indefinitely. While this follow up pattern is arbitrary, I believe that seeing the patient more often early after treatment is useful to the patient.

Follow up visits include interval history, careful physical examination, and laboratory studies including a complete blood count, chemistry screen, and serum lactate dehydrogenase. Once a complete remission is documented I would do no more images in the absence of some abnormality hinting at relapse or at the patient’s request. I know it is standard care in much of the U.S. to do routine images in complete remission, but this approach cannot be supported with data. There is no convincing evidence that routine images in remission accomplish their goal of improving survival by finding early relapse although this could be tested in a prospective trial. While there is at best minimal evidence that routine images in remission could improve survival,(77) it is certain that they are expensive. Whether these studies make a patient less anxious because a negative test is reassuring, or make them more anxious by reminding them that they should be afraid of relapsing, is a point that could be argued. However, given the specificity and sensitivity of the tests, and the chances of relapse at any particular point in time, it can be shown that abnormal findings on routine images are much more likely (i.e. >80% of the time) to represent false positives and lead to inappropriate further evaluation, or, even worse, instituting inappropriate therapy.(78)

A major mistake to avoid in following patients with diffuse large B-cell lymphoma in complete remission is to initiate therapy for apparent relapse without a biopsy. While most patients with new lymphadenopathy will have recurrent lymphoma, it is certainly not true for all. Table 7 lists the diagnoses that my colleagues and I have found on biopsy in patients with “obvious” recurrent lymphoma. Patients who have never been diagnosed with lymphoma would not be treated without a biopsy, and neither should patients who are being followed in documented complete remission.
Salvage Therapy

Unfortunately, some patients with diffuse large B-cell lymphoma will not respond to their initial treatment, not achieve an initial complete remission or relapse from remission. True primarily refractory patients occasionally benefit from alternate chemotherapy regimens, but, in general, have very poor outlook. Partial responders sometimes will further benefit from an alternate chemotherapy regimen and might undergo autologous hematopoietic stem cell transplantation. Some of these patients will be long-term, disease-free survivors. Patients who relapse from complete remission, and are younger than 60-65 years of age are usually offered hematopoietic stem cell transplantation and a significant subset of these patients can be cured.(63, 64) If the patient responds to an alternate chemotherapy regimen and achieves a complete remission, approximately 50% of patients will be long-term, disease-free survivors, with a smaller proportion surviving free of disease after a partial response. Salvage chemotherapy regimens today often include a platinum containing agent, but it is unclear that one regimen is distinctly superior to others. Patients who relapse after an autologous hematopoietic stem cell transplant can occasionally be rescued with allogeneic hematopoietic stem cell transplantation.(79-81) Some patients relapsing after autologous transplant seem unusually responsive to rituximab and can have prolonged survival. I have seen a small number of patients have prolonged survival using rituximab and alpha interferon.(82) For patients with localized relapse involved field radiotherapy can be utilized, but durable responses are the exception rather than the rule.

The Future

The future for treating patients with diffuse large B-cell lymphoma is likely to be exciting. Advances in functional imaging will change staging and restaging, and may make other tests obsolete. Further understanding of the genetic subtypes and the associated patterns of protein expression is likely to lead to individualized therapy based on knowing that lymphomas expressing certain proteins (i.e. associated with activation of specific metabolic pathways) are
particularly likely to respond to specific agents. Among the first hints at this approach are the apparent disproportionate benefit of patients with the activated B-cell type of diffuse large B-cell lymphoma from treatment with rituximab (83) and the rare patient with a durable response to a salvage regimen after failing CHOP plus rituximab. We already cure a significant proportion of patients with diffuse large B-cell lymphoma. Almost certainly this proportion will continue to rise.
Table 1. WHO histological classification of lymphoid neoplasms (4)

- Precursor B-cell and T-cell neoplasms

  Precursor B lymphoblastic leukaemia/lymphoblastic lymphoma (precursor B-cell acute lymphoblastic leukaemia)

  Precursor T lymphoblastic leukaemia/lymphoblastic lymphoma (precursor T-cell acute lymphoblastic leukaemia)

- Mature B-cell neoplasms

  Chronic lymphocytic leukaemia/small lymphocytic lymphoma
  B-cell prolymphocytic leukaemia
  Lymphoplasmacytic lymphoma
  Splenic marginal zone lymphoma
  Hairy cell leukaemia
  Plasma cell myleoma
  Monoclonal gammopathy of undetermined significance (MGUS)
  Solitary plasmacytoma of bone
  Extrasosseous plasmacytoma
  Primary amyloidosis
  Heavy chain diseases
  Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)
  Nodal marginal zone B-cell lymphoma
  Follicular lymphoma
  Mantle cell lymphoma
  Diffuse large B-cell lymphoma
  Mediastinal (thymic) large B-cell lymphoma
  Intravascular large B-cell lymphoma
  Primary effusion lymphoma
  Burkitt lymphoma/leukaemia

- Mature T-cell and NK-cell neoplasms

  Leukaemic/disemminated
  T-cell prolymphocytic leukaemia
  T-cell large granular lymphocytic leukaemia
  Aggressive NK cell leukemia
  Adult T-cell leukaemia/lymphoma

  Cutaneous
  Mycosis fungoides
  Sezary syndrome
  Primary cutaneous anaplastic large cell lymphoma
  Lymphomatoidpapulosis
Other extranodal
  Extranodal NK/T cell lymphoma, nasal type
  Enteropathy-type T-cell lymphoma
  Hepatosplenic T-cell lymphoma
  Subcutaneous panniculitis-like T-cell lymphoma

Nodal
  Angioimmunoblastic T-cell lymphoma
  Peripheral T-cell lymphoma, unspecified
  Anaplastic large cell lymphoma

Neoplasm of uncertain lineage and stage of differentiation
  Blastic NK cell lymphoma
Table 2. Morphological subtypes of diffuse lymphocytic B-cell lymphoma

- Centroblastic
- Immunoblastic
- Anaplastic
- Plasmablastic
- Intravascular
- Multi-lobulated
- T-cell rich
- Lymphomatoid granulomatosis type
- Primary effusion
Table 3. Clinically relevant molecular subtypes of diffuse large B-cell lymphoma (8, 61, 84)

<table>
<thead>
<tr>
<th></th>
<th>Germinal Center B-cell</th>
<th>Activated B-cell</th>
<th>Mediastinal</th>
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<tr>
<td>Median age (years)</td>
<td>58</td>
<td>66</td>
<td>35</td>
</tr>
<tr>
<td>Age &gt;60 years (%)</td>
<td>52</td>
<td>66</td>
<td>9</td>
</tr>
<tr>
<td>Female (%)</td>
<td>50</td>
<td>40</td>
<td>70</td>
</tr>
<tr>
<td>Female &lt;35 years (%)</td>
<td>3</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>5-year survival (#%)</td>
<td>59</td>
<td>30</td>
<td>64</td>
</tr>
<tr>
<td>Full Index</td>
<td>Age Adjusted</td>
<td></td>
<td></td>
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<tr>
<td>------------</td>
<td>-------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognostic Factors (APLES)</td>
<td>Prognostic Factors (PLS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Age &gt;60 years</td>
<td>- Performance status &gt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Performance status ≥ 2</td>
<td>- LDH &gt;1 x normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- LDH &gt;1 x normal</td>
<td>- Stage III or IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Extranodal sites ≥ 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Stage III or IV</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Risk Category</td>
<td>Factors</td>
<td>Risk Category</td>
<td>Factor</td>
</tr>
<tr>
<td>Low</td>
<td>0 or 1</td>
<td>Low</td>
<td>0</td>
</tr>
<tr>
<td>Low-intermediate</td>
<td>2</td>
<td>Low-intermediate</td>
<td>1</td>
</tr>
<tr>
<td>High-intermediate</td>
<td>3</td>
<td>High-intermediate</td>
<td>2</td>
</tr>
<tr>
<td>High</td>
<td>4 or 5</td>
<td>High</td>
<td>3</td>
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Table 5. Outcome for patients with diffuse aggressive lymphoma after
anthracycline containing chemotherapy International Index  (25)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th># Risk Factors</th>
<th>% Cases</th>
<th>CR Rate</th>
<th>RFS of CRs 5 yr</th>
<th>Survival 5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0,1</td>
<td>35%</td>
<td>87%</td>
<td>70%</td>
<td>72%</td>
</tr>
<tr>
<td>Low-intermediate</td>
<td>2</td>
<td>27%</td>
<td>67%</td>
<td>50%</td>
<td>50%</td>
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<tr>
<td>High-intermediate</td>
<td>2</td>
<td>22%</td>
<td>55%</td>
<td>48%</td>
<td>43%</td>
</tr>
<tr>
<td>High</td>
<td>4,5</td>
<td>16%</td>
<td>44%</td>
<td>40%</td>
<td>26%</td>
</tr>
</tbody>
</table>
Table 6. Results with a revised IPI when CHOP-R is given for diffuse large B-cell lymphoma (26)

<table>
<thead>
<tr>
<th>Group</th>
<th># Factors</th>
<th>% Patients</th>
<th>% 4-Year Overall Survival</th>
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<tbody>
<tr>
<td>Standard IPI</td>
<td>0,1</td>
<td>28</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>27</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>21</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>4,5</td>
<td>24</td>
<td>58</td>
</tr>
<tr>
<td>Revised IPI</td>
<td>0</td>
<td>10</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>45</td>
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<td></td>
<td>3,4,5</td>
<td>45</td>
<td>58</td>
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</tbody>
</table>
Table 7. Diagnoses from biopsies in “obviously” relapsed patients.

- Follicular hyperplasia
- Thymic rebound
- A different lymphoma
- Carcinoma
- Desmoid tumor
- Glioblastoma
- Non-specific inflammatory process
- Tuberculosis
- Fungal infection
- Sarcoidosis
Legends

Figure 1. The progression-free survival of patients treated in British Columbia before or after the approval of rituximab for general use. A few patients before the date of approval received rituximab and some patients did not receive the drug after the date of approval. However, all are included.

Figure 2 a. The disease-free survival of patients who had two or three adverse risk factors in the age adjusted International Prognostic Index, responded to ACVBP and were randomly allocated to allotransplant or consolidation with further chemotherapy.

Figure 2 b. Progression-free survival for 56 high risk patients undergoing autotransplant at the University of Nebraska Medical Center in first remission after an anthracycline containing chemotherapy regimen.
References:


Figure 1.
The Impact of Adding Rituximab To CHOP in British Columbia

Percent Survival

Post-Ritux

Pre-Ritux

Log rank p =0.0009

Progression-Free Survival (y)
Fig 2a. Estimated disease-free survival according to randomized consolidation procedure for the high/intermediate- and high-risk patients.

- ASCT
- Chemotherapy

$P = 0.02$
Figure 2b. Diffuse large cell lymphoma undergoing autologous HSCT in first complete remission.
How I treat patients with diffuse large B-Cell lymphoma

James Olen Armitage