Progress in the non-Hodgkin's lymphomas

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Benefits of the International Prognostic Factor Index

For many years, the treatment of aggressive non-Hodgkin's lymphoma appeared to be improving. Second and third generation chemotherapy regimens that introduced new agents or intensified therapy appeared better than first generation treatments such as CHOP [1]. However, a large intergroup study that compared CHOP to newer regimens such as m-BACOD, MACOP-B, and ProMACE-CytaBOM showed that these new treatments were no better [2]. One explanation for this surprising and sobering result is that treatments didn't improve, but rather, investigators were increasingly skilled at selecting patients who were likely to do better. Thus, as the ability to select more favourable patients increased, so too did the apparent efficacy of each subsequent generation of chemotherapy.

The International Prognostic Factors Index was a joint attempt to identify prognostic factors that could be agreed upon and used universally [3]. This project involved 16 institutions and cooperative groups in the United States, Canada, and Europe. Information was collected on adult patients with aggressive lymphoma who received doxorubicin-based combination chemotherapy between 1982 and 1987. The primary goals in this analysis were to identify independent factors that predicted overall and relapse-free survival. Information on 2031 patients was collected and analysed. Five risk factors that predicted diminished overall survival included age > 60, stage III-IV disease, abnormal serum lactate dehydrogenase (LDH) levels, non-ambulatory performance status, and more than one extranodal site of disease. The 5-year overall survival ranged from 72% among patients with no or one risk factor to 26% among patients with four or five. The study also identified three risk factors that predicted for decreased overall survival among patients 60 years of age or younger. These factors included stage III-IV disease, non-ambulatory performance status, and elevated serum LDH levels. In a similar fashion, four risk groups were identified with 5-year overall survival rates ranging from 83% among patients with no adverse risk factors to 32% among patients with all three poor prognostic indicators.

One of the major benefits of the international index is the ability to identify poor prognostic groups of patients that might be targeted in innovative studies. The index has been particularly useful in the development of clinical strategies utilizing high dose therapy with stem cell or bone marrow support. For example, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) conducted a large randomised study involving 464 patients with aggressive non-Hodgkin's lymphoma [4]. Patients achieving a complete response were randomised to consolidation with either additional standard chemotherapy or high dose therapy with autologous bone marrow transplantation. Among all patients, there was no difference in 3-year disease-free or overall survival. However, in a retrospective analysis using the age-adjusted international index, those patients with two or three adverse risk factors who received high dose therapy consolidation had an improved 5-year survival (65% vs 52%). The information gained in this subgroup analysis using the international index provided support for a subsequent prospective study by GELA that included only patients with at least two adverse risk factors [5]. Patients were randomised to receive standard anthracycline-based chemotherapy or an abbreviated course of chemotherapy followed by autologous stem cell support. Surprisingly, the group who received high dose therapy had inferior overall survival (61% vs 73%) compared to those who received standard therapy. The international index is currently being used in the selection and design of several randomised studies testing high dose therapy against standard chemotherapy in the Eastern Cooperative Oncology Group (ECOG) and the Southwest Oncology Group.

A second benefit of the international index is the ability to interpret results of studies that might not have used the index prospectively. For example, Gianni and colleagues compared standard MACOP-B chemotherapy to high-dose sequential therapy in a randomised study of 98 patients with aggressive B-cell lymphoma [6]. Event-free survival and overall survival were better among patients who received initial treatment with high-dose sequential therapy. The relatively small number of patients in this study might have introduced an imbalance in the distribution of favourable patients. However, further analysis using the age-adjusted international index showed that a greater number of patients in the high-dose arm had unfavourable features (94% vs 74%). Thus the improvement in outcome is particularly noteworthy given the greater number of patients with high-risk features in the experimental arm.

A third major benefit of the international index is the applicability to other subtypes of non-Hodgkin's lymphoma. For example, Lopez-Guillermo and colleagues showed that 125 patients with low-grade lymphoma could be separated into four risk groups with different 10-year survival ranging from 74% to 0% [7]. Ansell and colleagues found a similar utility of the index among 78 patients with peripheral T-cell
lymphoma [8]. Five-year survival among low risk patients was 80% compared to 10% among patients with high-risk features.

In summary, the international prognostic index has provided a widely accepted set of criteria that allows the identification of patients with favourable or unfavourable outcomes with standard chemotherapy. It has provided a common base for interpreting results of studies with regard to patient characteristics, and has broad applicability to other subtypes of non-Hodgkin’s lymphoma.

Anti-CD20 antibody therapy

The vast majority of low grade B-cell lymphomas express the CD20 antigen on the cell surface. This antigen has provided the target for a number of monoclonal antibody therapies that include the naked antibody or antibody conjugated with toxins or radioactive isotopes. IDEC-C2B8, or Rituximab, is a chimeric anti-CD20 monoclonal antibody that contains human IgG1 and k constant regions with murine variable regions. Rituximab is the first monoclonal antibody approved for use by the US Food and Drug Administration and has received treatment indication for patients with recurrent low grade B-cell lymphoma. Maloney and colleagues reported results in 37 patients treated in a multicentre phase II study [9]. All had relapsed low grade lymphoma with a median of two chemotherapy treatments. Antibody treatment consisted of four weekly infusions at a dose of 375 mg/m². Side effects were mild and consisted of infusion-related fevers, chills, respiratory symptoms, and occasional hypotension. Depletion of peripheral B-cells occurred quickly and recovered beginning about 6 months after treatment. However, an increased rate of infections was not observed. The overall response rate was 46%. Responses were observed as early as 1 month after treatment and reached a maximum around 4 months after treatment. The median time to progression among the 17 responding patients was 10.2 months. Though this therapy does not appear to alter the natural history of low grade lymphoma, Rituximab does offer a minimally toxic and highly active treatment for patients with this disease.

The availability and activity of the anti-CD20 antibody has led to large number of prospective clinical studies that seek to define the optimum use of this novel therapy. Ongoing studies within ECOG include a randomised clinical trial comparing CHOP chemotherapy to CHOP plus Rituximab in elderly patients with diffuse aggressive lymphoma. A second study randomises to patients with low grade lymphoma to consolidation treatment with Rituximab versus observation after chemotherapy-based induction therapy.

Modulation of multidrug resistance

Non-Hodgkin’s lymphomas are among the most chemotherapy-responsive of human cancers. However, despite increases in dose intensity and optimisation of chemotherapy scheduling, substantial numbers of patients with advanced stage intermediate and high grade lymphoma still fail to attain a complete remission with initial therapy or relapse following treatment. One reason chemotherapy fails to cure a larger portion of patients is due to multidrug resistance (MDR). The MDR phenotype is due to the expression of P-glycoprotein (P-gp), an energy dependent efflux pump that actively transports a variety of drugs out of cells. Of clinical importance, P-gp transports several classes of important chemotherapy agents such as vinca alkaloids, epipodophyllotoxins, anthracyclines as well as paclitaxel, mitomycin-C, and mitoxantrone [10].

The gene MDR1 codes for P-gp and the expression of the MDR phenotype [11]. The importance of MDR1 in lymphomas is suggested by several lines of evidence. First, an increased incidence of MDR1 expression is seen in patients with relapsed or treated lymphomas when compared to samples from untreated patients [12-14]. Second, MDR1 expression has been reported to be a significant prognostic variable in both untreated and relapsed non-Hodgkin’s lymphoma [15, 16].

Many non-cancer drugs and other compounds are transport substrates for P-gp, and can reverse MDR by competitive inhibition of P-gp. These drugs include calcium channel blockers, steroids, immunosuppressives, and cyclosporines. The effectiveness of modulating MDR in humans with lymphomas has been limited thus far. Miller reported a complete response rate of 25% using combination chemotherapy, CVAD, with verapamil in patients with relapsed NHL [14]. However, cardiac side effects limited the escalation of verapamil. Wilson reported a response rate of 20% (1 of 35 CR) to EPOCH (infusional combination chemotherapy) with R-verapamil in NHL patients who were stable or refractory to EPOCH alone. Responses correlated with an intermediate level of MDR1 expression. Cardiac toxicities again were dose limiting [17]. These studies suggest potential efficacy in MDR modulation, although the effectiveness to date in human studies has been limited by side effects of the modulating agent and only partial inhibition of P-gp.

PSC 833 (Valspodar) is a new, non-immunosuppressive, cyclosporine analog. Its in vitro activity is 5-10 times greater than cyclosporine A. It has shown considerable activity in reversing drug resistance in mouse models [18]. A phase I study conducted at Stanford University of etoposide and oral PSC 833 found that PSC 833 at a dose of 5 mg/kg every 6 hours for 15 doses is well tolerated. Pharmacodynamic effects are consistent with a doubling of the area under the curve with an increase in hematologic toxicity requiring a 50% dose reduction of etoposide when used in combination with PSC 833. Nadirs were equivalent to those seen with etoposide given as a single agent at full dose. The dose limiting toxicity of PSC 833 was cerebellar ataxia, which occurred at a dose of 6 mg/kg every 6 hours but was completely reversible within 12 to 24 hours after the last dose.

ONCEP is a combination chemotherapy regimen derived from CEPP, which has a complete response rate of 34% in relapsed non-Hodgkin’s lymphoma [19]. A phase II trial at Stanford University of ONCEP found a response rate of about
are necessary to account for the pharmacokinetic effects of acceptable toxicities. Dose modifications of about three-fold ple MDR-related agents can be combined with PSC 833 with tinues to accrue patients. Thus far, we have shown that multi-
response of any duration (0% vs 73%). The study con-
sceeded to autologous bone marrow transplantation. None of
tients having grade 4 neutropenia and 5 with fever also. Ataxia
phosphamide 650 mg/m$^2$ on day 2, etoposide 30 mg/m$^2$ on
administration. Overall, 7 patients achieved a complete re-
with an inability to walk without assistance during PSC 833
was mild with 15 experiencing transient unsteady gate and 1
ontrolled between tumour cell MDR1 expression and tumour remission with ONCEP-PSC. Because of the expected pharmacokinetic interactions, the doses of MDR-
related agents were reduced to approximately one-third of
the standard doses without PSC 833.

Patients were required to have non-Hodgkin’s lymphoma
that was refractory to or relapsed after chemotherapy. No more than three prior courses of chemotherapy were allowed for intermediate or high grade lymphomas or four prior courses for low grade lymphomas. Informed consent and adequate performance status as well as hepatic, cardiac, renal, and marrow function was required.

Treatment consisted of PSC 833 at 5 mg/kg orally every 6 hours for 15 doses. Patients started chemotherapy after the 5th dose of PSC on day 2. Treatment consisted of vincristine 0.75 mg on day 2, mitoxantrone 3.0 mg/m$^2$ on day 2, cyclophosphamide 650 mg/m$^2$ on day 2, etoposide 30 mg/m$^2$ on days 2, 3, and 4, and prednisone 40 mg/m$^2$/d for 10 days orally, days 2–11. Cycles were repeated every three weeks and con-
tinued until two cycles beyond best response. Patients eligi-
bile for bone marrow transplantation proceeded to transplan-
tation if adequate cytoreduction was obtained.

Twenty three patients have been enrolled thus far. Histologies have included mantle cell (3), small non-cleaved (1), follicular small cleaved (2), and diffuse mixed or diffuse large cell (12). Twelve patients had two to three prior chemo-
therapy regimens, and 16 patients had progressive disease or a remission lasting less than 12 months before study entry. Hematologic toxicity was expectedly prominent with 16 pa-
tients having grade 4 neutropenia and 5 with fever also. Ataxia
was mild with 15 experiencing transient unsteady gate and 1
with an inability to walk without assistance during PSC 833 adminstration. Overall, 7 patients achieved a complete re-
response or minimal amount of disease while 4 more had a
partial response (overall response rate 48%). Six patients pro-
ceded to autologous bone marrow transplantation. None of the 7 patients who had progressive disease entering the study responded compared to 11 of 15 patients who had achieved a prior response of any duration (0% vs 73%). The study con-
tinues to accrue patients. Thus far, we have shown that multi-
ple MDR-related agents can be combined with PSC 833 with acceptable toxicities. Dose modifications of about three-fold are necessary to account for the pharmacokinetic effects of PSC 833. ONCEP-PSC is an active regimen in relapsed lymphoma. However, definitive proof that the modulation of multidrug resistance can improve survival will require a randomised clinical study comparing treatment with and without a MDR modulator.

References


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