VALIDATION OF INTERNATIONAL PROGNOSTIC INDEX FOR NON-HODGKIN'S LYMPHOMA IN NORTHEAST PENINSULAR MALAYSIAN MALAYS

By

DR ABU DZARR GANESH BIN ABDULLAH

Dissertation Submitted in Partial Fulfillment

Of The Requirements For

THE DEGREE OF MASTER OF MEDICINE
(INTERNAL MEDICINE)

UNIVERSITY SAINS MALAYSIA
2002

ACKNOWLEDGEMENTS

All praise due to Allah, the Sustainer of the Universe, the Most Merciful, the Bestower of Mercy, for allowing me to proceed and complete this study.

I would like to thank my supervisors, Professor Dr Aziz b Baba for his valuable advice in the preparation of this dissertation; Dr Than Winn from the Department of Community Medicine and Miss Asha for their statistical assistance; my colleagues for their unparallel support and not least my wife, Nafizah for her understanding, and the rest of my family for their patients and endurance.

ABSTRAK

Indeks Prognosis Antarabangsa (IPI) telah diketengahkan untuk menstratumkan risiko pesakit limfoma bukan Hodgkin (NHL) dan mengenalpasti subset pesakit berisiko tinggi yang mungkin tidak dapat bertindakbalas terhadap kemoterapi dengan memuaskan. IPI telah dibentuk berlandaskan model populasi pesakit berbangsa barat. Kami telah menlaksanakan suatu kajian longitudinal melibatkan pesakit NHL aggresif yang menerima rawatan di Hospital USM dari 1 haribulan Januari 1990 ke 31 haribulan Disember 2000. Kajian ini hanya melibatkan pesakit berbangsa Melayu. Ini bertujuan untuk menguji kesesuaian penggunaan IPI ke atas etnik tersebut. Ciri-ciri klinikal sepertimana yang telah diuji dalam model IPI yang asal, telah diuji ke atas kohort kami. Pencapaian pesakit dari segi kadar respons sempurna (complete response rate : CR), kadar kemandirian keseluruhan (overall survival rate: OS) dan kadar kemandirian bebas penyakit (disease free survival rate: DFS) bagi setiap faktor di atas telah di olah. Pada masa yang sama data-data yang diperolehi telah digunakan untuk membentuk profil penyakit NHL dalam populasi kami.

Daripada sejumlah 102 pesakit NHL, hanya 88 pesakit mempunyai keputusan histopatologi yang boleh dibaca untuk analisis pengkelasan. 75 (85%) adalah NHL aggresif jenis tersebar. 29% dari semua limfoma yang menjalani ujian imunofenotip terdiri dari limfoma sel-T.

Kohort seramai 45 pesakit limfoma Melayu telah dikenalpasti untuk analisis. 51% mengalami limfoma ekstranodal primer. Rangkaian Waldeyer's merupakan tapak ekstranodal yang paling kerap dicerobohi iaitu 18% dari semua pencerobohan, diikuti

oleh saluran pemakanan, tulang dan sum sum tulang setiap satu 11%. Selepas tamat rawatan kemoterapi CHOP, 51% dari pesakit mencapai respons sempurna (CR) dan 33% mencapai respons separa (PR). Respons keseluruhan ialah 84%. Kadar kemandirian 3-tahun ialah 45% manakala 5-tahun pula ialah 24%.

Setiap faktor klinikal telah di kaji dari segi hubungkaitnya dengan CR, OS dan DFS. Hanya status keupayaan cergas (ECOG 0 & 1) di dapati mempunyai hubungan bersignifikan dengan kadar CR yang lebih baik berbanding degan status keupayaan lemah (ECOG 2 – 4) p = 0.007. RR = 3.0 (95% CI 1.27 – 7.14). Jantina lelaki, umur pesakit di bawah 60, tahap perebakan terhad, saiz tumor yang tidak boyot, status keupayaan cergas, paras hemoglobin darah yang rendah, dan paras laktat dehydrodegenase (LDH) dan albumin dalam darah yang normal di dapati berhubungkait dengan kadar CR yang lebih baik tetapi hubungan ini kesemuanya tidak bersignifikan.

Status keupayaan cergas, kehadiran gejala B dan paras LDH dalam darah yang tinggi (>500iu/L) di dapati berhubungkait secara signifikan dengan kadar kemandirian keseluruhan (OS) yang lebih lama (P=0.0001, 0.02, 0.037) berbanding dengan pengenapnya iaitu status keupayaan lemah, ketiadaan gejala B dan paras LDH darah yang normal. Pencapaian lebih awal respons sempurna klinikal iaitu berikutan pusingan ketiga kemoterapi juga di dapati berhubungkait dengan kadar kemandirian keseluruhan yang lebih lama (P=0.017). Melalui analisis multivariate regresi Cox, hanya status keupayaan cergas berhubungkait secara bersignifikan dengan kadar kemandirian keseluruhan. (P=0.01). Nisbah hazad bagi status keupayaan cergas ialah 0.242 (95% CI: 0.083 – 0.71).

Kami tidak berjaya menunjukkan hubungkait yang bersignifikan secara statistik di antara anemia dengan kadar CR, OS dan DFS disebabkan kekurangan kuasa statistik di dalam kajian.

Hanya jantina perempuan di dapati mempunyai hubungkait yang signifikan secara statistik dengan kadar kemandirian bebas penyakit (DFS) (P=0.034). Walau bagaimanapun kenyataan ini adalah tidak sah disebabkan oleh jumlah pesakit yang kecil di mana maklumat jangka kemandirian bagi semua pesakit perempuan terdiri dari data tapis (censured data).

Secara ringkasnya, jumlah pesakit untuk kajian yang kecil telah mengakibatkan kajian ini mempunyai kuasa statistik yang lemah untuk menguji kenyataan-kenyataan hipotesis yang diajukan. Hanya status keupayaan sahaja di buktikan dapat meramal risiko kemandirian. Kajian ini menunjukkan faktor-faktor lain yang di ketengahkan oleh IPI, juga mempunyai corak hubungan dengan kadar kemandirian sepertimana yang diperhatikan pada model asal IPI. Walau bagaimanapun, hubungan ini tidak berupaya menunjukkan perbezaan yang signifikan desebabkan oleh kajian yang kurang kuasa statistik. Justeru itu, kami perkesimpulan bahawa kajian ini tidak dapat menunjukkan sebarang tanda yang boleh merencatkan penggunaan IPI dalam populasi kami. Sungguhpun demikian, memandangkan kadar kehadiran limfoma ekstra-nodal primer yang tinggi, model IPI tiga tahap yang telah di cadangkan untuk populasi pesakit Cina mungkin lebih wajar digunakan berbanding dengan model IPI empat tahap yang asal.

ABSTRACT

International prognostic index (IPI) was introduced to risk stratify non-Hodgkin lymphoma (NHL) patients and to identify high-risk patient who might not respond favorably to standard chemotherapy. IPI was modeled from a Caucasian based patient population. We undertook a single center, observational longitudinal study involving all available patients with aggressive NHL who had received treatment from Hospital USM between 1st Jan 1990 and 31st Dec 2000. We confined our study to adult Malay patients to test the applicability of IPI in this racial group. Individual presenting clinical features was categorized as in the IPI study, and the patients' outcome in terms of complete response (CR), overall survival (OS) and disease free survival (DFS) rates for each of the above features were determined. At the same time the available data was used to characterize NHL disease profile in our patient population.

From a total of 102 patients with NHL, only 88 patients had readable histopathology, in which 75 (85%) was diffuse aggressive NHL. T-cell lymphomas constitute 29% of all NHL with immunophenotype studies.

A final cohort of 45 Malay patients with aggressive NHL was established, 51% were of primary extra-nodal lymphoma. Waldeyer's ring was the commonest extra-nodal site involved (18%) followed by gastrointestinal tract, bone and marrow 11% each. 51% and 33% achieved complete clinical response (CR) and partial response (PR) correspondingly following CHOP chemotherapy. Overall response rate was 84%. 3-years survival rate was 45% and 5-years survival rate was 24%.

Individual clinical characteristics were studied in terms of its association with complete response rate (CR), overall survival rates (OS) and disease free survival rates (DFS).

Only good performance status (ECOG 0 &1) were found to be significantly associated with better CR rates compared to poor performance status (ECOG 2 to 4) p=0.007. RR=3.0 (95%CI 1.27 – 7.14). Male sex, age less than 60, limited disease, non bulky disease, good performance status, low hemoglobin, normal serum lactate dehydrogenase (LDH) and albumin were associated with higher CR rates but statistically not significant.

Good performance status, presence of B symptoms and elevated serum LDH (>500iu/L) were shown to be significantly associated with longer OS (P= 0.0001, 0.02, 0.037) compared to poor performance status, absence of B symptoms and normal serum LDH. Early achievement of clinical complete response following 3rd cycle of chemotherapy was also associated with longer overall survival (P=0.017). With Cox regression analysis, only good performance status was significantly associated with overall survival. (P=0.01). The hazard ratio for good performance status was 0.242 (95%CI: 0.083 – 0.71).

We were not able to show statistically significant association between anemia with CR, OS and DFS rates due to poor statistical power.

Only female gender was shown to have a significant association with better DFS rates (P=0.034) but this outcome was erroneous due to small patient numbers, in which survival data from the female gender group only consisted of censured data.

In summary, due to limited number of available patient for this study, we lacked statistical power to test our hypothesis. Only performance status was proven to prognosticate survival risk. Our study showed similar trends in survival outcome for other factors proposed in IPI, mimicking the trends seen in the IPI model. However these trends were not marked enough to become statistically significant in a poorly powered study. At this juncture, we conclude that there is no evidence to show that IPI is not applicable in our patient population. However, in the presence of high proportion of primary extra-nodal lymphoma the modified three tiers IPI suggested for Chinese population may be a more appropriate option compared to the four tiers IPI.

List of Figures

List of Tables

ABBREVIATION

NHL	=	**Non Hodgkin's Lymphoma**
WF	=	**Working Formulation**
CSF	=	**Colony Stimulating Factor**
IPI	=	**International Prognostic Index**
ECOG	=	**Eastern Cooperative Oncology Group**
DFS	=	**Disease Free Survival**
OS	=	**Overall Survival**
CR	=	**Complete Response**
PR	=	**Partial Response**
PENL	=	**Primary extra-nodal lymphoma**
LDH	=	**Lactate dehydrogenase**
ECWMM	=	**East Coast of West Malaysia Malay**

CONTENT

Page

INTRODUCTION

Non-Hodgkin lymphoma (NHL) consists of a family of heterogenous tumors with variable clinical course, shared by a common pathogenesis resulting from malignant clonal proliferation of cells in the lymphoid series. The fourth quarter of the twentieth century saw considerable evolution in the classification of NHL. The Working Formulation (Rosenberg SA et al, 1982) was preferred in the United States whereas Kiel's classification (Gerard-Marchant R et al, 1974) was more popular in Europe.

Working Formulation utilizes morphological features alone and was found to have predictive value for survival. The clinical outcomes of different categories vary considerably and are collectively graded into three groups; low grade, intermediate grade and high grade. For an overview see Table 1.1.

1.1 Aggressive NHL

In general, the high-grade subtypes have destructive growth pattern with frequent involvement of privileged sites (i.e. central nervous system, testes, etc). The lymphoma cell's cytology is atypical and anaplastic. From the clinical point of view, they are aggressive with shorter survival if without therapy and B symptoms are more common. Fortunately, they are more responsive to combination chemotherapy with better long-term remission and probable cures.

Table 1.1. Table showing Working Formulation for NHL. Adapted from (Rosenberg, SA. *et al.* (1982))

Low grade

A. Malignant lymphoma, small lymphocytic
   a. Consistent with CLL
   b. Plasmacytoid
B. Malignant lymphoma, follicular, predominantly small cleaved cell
   a. Diffuse areas
   b. Sclerosis
C. Malignant lymphoma, follicular, mixed, small cleaved and large cell
   a. Diffuse areas
   b. Sclerosis

Intermediate group

D. Malignant lymphoma, follicular predominantly large cell
   a. Diffuse areas
   b. Sclerosis
E. Malignant lymphoma, diffuse small cleaved cell
   a. Sclerosis
F. Malignant lymphoma, diffuse mixed, small and large cell
   a. Sclerosis
   b. Epitheloid cell component
G. Malignant lymphoma, diffuse large cell
   a. Cleaved cell
   b. Noncleaved cell
   c. Sclerosis

High grade

H. Malignant lymphoma, large cell, immunoblastic
   a. Plasmacytoid
   b. Clear cell
   c. Polymorphous
   d. Epitheloid cell component
I. Malignant lymphoma, lymphoblastic
   a. Convoluted cell
   b. Nonconvoluted cell
J. Malignant lymphoma, small noncleaved cell
   a. Burkitt's
   b. Follicular areas

Miscellanous

Composite
Mycosis fungoides
Histiocytic
Extramedullar plasmacytoma
Unclassifiable
Other

Distinctly, the low-grade subtypes are non destructive with an indolent clinical course, at times with spontaneous remission. The malignant cells cytology appears to resemble normal lymphoid population.

From the clinical perspective, cases are viewed either as indolent or aggressive lymphoma. The former include working formulation categories A, B, C, D and E and the later includes the remaining categories. Categories J and I are at times described as highly aggressive lymphoma. Aggressive lymphoma in spite of its terrifying expression can achieve cure with combination chemotherapy. However the responses are variable and have to be individualized, taking into account of numerous prognostic factors besides morphology. On the other hand, cure is a concept still foreign in indolent lymphoma.

One of the main drawbacks in Working Formulation was that different clinical entities of NHL are morphologically grouped together, into its respective working formulation categories. Their clinical behavior and response to treatment varies. Therefore the accumulated information over the years led to redefinition of disease entities reflecting both its clinical and pathological characteristics. Hence Working Formulation had been superseded by REAL and later WHO classification of NHL.

Kiel's classification (Table 1.2) was a separate system with emphasis on exact histogenesis, especially in its utilization of immunophenotyping in differentiating B from T cell lymphomas. Unfortunately it was not very useful in predicting clinical outcome. (Richards & Stansfeld, 1988)

Table 1.2. Classification of NHL under Kiel's classification and its equivalent counterpart under the Working Formulation.

Low grade neoplasia			High grade neoplasia		
	Lymphocytic, chronic lymphocytid/leukemia	A		Centroblastic	G
	Lymphocytic, other	A		Lymphoblastic, Burkitt's type	J
	Lymphaplasmacytoid	A		Lymphoblastic, convoluted cell type	I
	Centrocytic	E		Lymphoblastic, other (unclassified)	
	Centroblastic-centrocytic, follicular without sclerosis	B C D		Immunoblastic	H
	Centroblastic-centrocytic, follicular with sclerosis			High grade malignant lymphoma, unclassified	
	Centroblastic-centrocytic, follicular and diffuse, without sclerosis				
	Centroblastic-centrocytic, follicular and diffuse, with sclerosis				
	Centroblastic-centrocytic, diffuse	F			
Low grade malignant lymphoma, unclassified					
Malignant lymphoma, unclassified (unable to specify high grade to low grade)					
Composite lymphoma					

1.2 NHL in Asia

Among malignant lymphomas, Hodgkin's lymphomas were reported to be relatively common in western population with prevalence between 40.9% (Lee and Spratt, 1974) and 43.6% (Lennert, 1978). In Asian series however, Hodgkin's lymphomas only constituted 6%, 8.5% and 9.2% of the Japanese (Kadin et al, 1983), Thailand (Sukpanichnant S et al, 1998) and Hong Kong (Ho et al, 1984) studies respectively. Therefore NHLs forms the bulk of malignant lymphomas seen in Asian populations.

Geographically related variation in clinical and histopathological presentation in NHL is a recognized phenomenon. Burkitt's lymphomas, small intestinal lymphomas, and T-cell lymphomas are recognized entities which predominate in tropical Africa, the Middle East and Japan respectively (Shih and Liang, 1991).

1.2.1 Follicular NHL

Among NHLs, the incidence of follicular lymphomas is lower in Asian populations. Follicular lymphomas consist of 8.8%, 10% and 17.1% of all NHL in Chinese (Dong et al, 1980), Japanese (Kadin et al, 1983) and Hong Kong (Ho et al, 1984) series. On the contrary, it accounted for 44% in a US series (Jones et al, 1973) and 21.9% in a European series (Lennert, 1978). A recent Malaysian pathological report from University Hospital consisting of heterogenous East Malaysian ethnic background showed that

follicular lymphoma consisted only 5.8% of all NHL (Chai, 1999). The rest were of aggressive and highly aggressive variety.

1.2.2 Immunophenotype characteristics

Immunophenotype studies revealed contradicting observation in Japan compared to Western countries. B-cell lymphomas predominate in Western countries where only 10 to 20% of NHLs are of T-cell type. In contrast the proportion of T-cell lymphomas ranges from more than 70% of all NHLs in Kyusu and Southwest Japan to 40% in Nagoya (Kadin et al, 1983). The larger proportion of T-cell lymphomas/leukemias in Japan has been shown to correlate with the higher seroconversion to HTLV-1 retroviral infection in their population. Kyusu and Southwest Japan are known to be endemic for HTLV-1 infection.

Studies on immunophenotype characterization in other parts of Asia showed prevalence of T-cell lymphomas comparable to figures derived from areas in Japan non-endemic to HTLV-1 infection. The proportion of T-cell lymphoma was shown to be 39.4 (Shih et al, 1991) to 50% (Su et al, 1988) in Taiwan, 25% (Ho et al, 1984) to 34% (Ng et al, 1988) in Hong Kong and 28% (Xu et al, 1984) in China.

Chai (1999) presented a local distribution consisting of 84% B cell and the remaining 16% T cell NHL. His studied population consisted of 15.8% Malay, 12.1% Chinese, 1% Indian and 71% indigenous groups of Sabah

and Sarawak. The immunophenotype distribution mimics the pattern seen in Western NHL populations.

1.2.3 Primary extra-nodal NHL (PENL)

The frequency of primary extra-nodal NHLs in Asia varied from 28.5 to 45%. (Shih et al, 1991). In a Hong Kong Chinese series, it went as high as 60.6% more common than lymph node lymphomas. (Mok et al, 1997) the commonest site of involvement was the gastrointestinal tract accounting for 63% of all extra-nodal NHL (Ho et al, 1984) whereas in Japan it was the Waldeyer's ring. (Kadin et al, 1983). In the whole both the gastrointestinal tract and Waldeyer's ring were the commonest sites and are in keeping to features seen in Western studies. There has not been any clinical data publication on adult lymphoma characterization for the Malaysian population.

1.3 Treatment for Aggressive NHL

The introduction of the first multi-agent chemotherapy referred as C-MOPP or COPP (cyclophosphamide, adriamycin, prednisolone and procarbazine) was a major step in the management of patient with aggressive non-Hodgkin lymphoma. (De Vita et al, 1975) Its variant which became a widely used regimen, CHOP (cyclophosphamide, adriamycin, vincristine and prednisolone) with or without radiotherapy showed complete remission (CR) rate of 98% and disease free

survival (DFS) rate of 84% in patient with clinical stage I and II disease. (Miller and Jones, 1983)

In advanced stage (clinical staging III and IV) disease however, treatment outcome was not promising. Treatment with CHOP led to overall CR rate of 51% and DFS rate of only 31% (Armitage et al, 1984). Attempts were then made to formulate newer multi-agent chemotherapy, hence the birth of second and third generation regimens. Independently, MACOP-B, a second-generation regime was shown to improve CR rate in aggressive NHL to 84% and DFS rate to 75% but with increased toxicity. When these regimes were compared head to head with CHOP, they did not show significant improvement in either CR or DFS rates. A direct comparative study evaluating the outcome of CHOP against newer second generation regimes including m-BACOD (low dose methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone), ProMACE-CytaBOM (prendisolone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue), and MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophophomide, vincristine, prednisolone and bleomycin) showed no significant difference in DFS at three years between each group; CHOP and MACOP-B 41%, ProMACE-CytaBOM and m-BACOD 46%. Instead, fatal toxic reactions occurred less in CHOP (1%) compared to other regimes ProMACE-CytaBOM (3%), m-BACOB (5%) and MACOP-B (6%) (Fischer,1993). With regards to this, CHOP remained the mainstay chemo regime despite of its not so favourable outcome.

In the above study the CR rate, partial response rates and overall survival rates at 3 years for the CHOP arm were 44%, 36%, and 41% respectively (Fischer, 1993). At an average, CHOP regime led to cure in advanced stage aggressive non-Hodgkin's lymphoma in less than 40%.

1.4 Prognosticating NHL

There will certainly be a group of patient with cure rates even less than those presented above. Several methods have been devised to prognosticate and pick these unfortunate patients out. The presence or absence of a multitude of features has been shown to influence outcome. In fact in Table 1.1, we have seen that morphology alone plays a vital role. Several small studies had been carried out looking at individual factors and its influence on disease and treatment outcome.

Among the identified poor prognostic factors included:

Tumor bulk (Cabanillas et al, 1978);

Elevated Lactate Dehydrogenase (>500iu/l) (Ferraris et al, 1979);

Large tumor mass more than 10cm (Fisher et al, 1981);

B symptoms (Fisher et al, 1981);

Bone marrow involvement (Fisher et al, 1981);

Age > 45 years old (Koziner et al, 1982);

Central nervous system involvement (Littman & Wang, 1975);

Performance status (Fisher et al, 1981);

Mediastinal disease (De Vita et al, 1975)

And prior chemotherapy (Fisher et al, 1981);

1.4.1 Anemia

Anemia had been studied and was shown in univariate studies to be an independent adverse prognostic factor for overall survival and progression free survival regardless of bone marrow involvement or otherwise. However in multivariate analyses anemia was a significant prognostic factor in overall survival and progression free survival for the whole study population and those with bone marrow involvement but not for those without bone marrow involvement. (Moullet, 1998)

1.4.2 Biological markers

Over the last decade other factors have also been looked into for their prognostic value. Among them include various molecular biomarkers such as

- The over-expression of BCL-2 protein and BCL-2 gene rearrangement were shown to reduce overall disease survival in patients with diffuse large cell NHL (Gascoyne, 1997b).
- The simultaneous expression of Bax protein (a proapoptotic member of BCL-2 protein family) and BCL-2 heterodimer was

shown to be poor prognostic indicator in diffuse large NHL (Gascoyne, 1997a).

- The presence of high BCL-6 mRNA in tumors with diffuse large cell NHL predicts favourable prognosis. Those with high level BCL-6 had median overall survival of 171 months compared to 24 months in those with low level (Lossos, 2001).
- The presence of high serum concentrations of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were associated with unfavourable outcome with lower 5-years survival rate in different grades of lymphoma (Salven, 2000).

Today biomarker arrays are being used to predict prognosis in NHL patient. In centers where facilities are available it has superseded IPI as the main prognostic tool.

1.5 International prognostic index (IPI)

1.5.1 Prior to IPI

Prior to the introduction of IPI, therapies for aggressive lymphoma in adult were guided by the borrowed Ann Arbor classification (Table 1.3), which was originally developed for Hodgkin's lymphoma (Carbone et al, 1971). Management strategies for localized stage 1 and II disease differed from advanced stage III or IV disease.

The drawback to Ann Arbor classification was based on the fundamentals that patterns of disease spread in Hodgkin's differ from NHL. Hodgkin's lymphomas are nodal disease and commonly spread through contiguous groups of lymph nodes. A significant number of NHL are extra-nodal especially in Eastern populations, hence utilization of the above classification tends to lead to erroneous conclusions. These shortcomings led to the creation and verification of the International Prognostic index as described further below.

1.5.2 The development of IPI

The international prognostic index is a model in predicting outcome on patients with aggressive NHL on the basis of the patient's pretreatment

Table 1.3. Hodgkin's Disease: Ann Arbor Staging Classification
(Carbone et al, 1971)

Stage I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE). An optional recommendation is that the number of nodal regions involved be indicated by a subscript (e.g., II_3)
Stage III	Involvement of lymph node regions on both sides of diaphragm (III), which may also be accompanied by involvement of the spleen (IIIS), localized involvement of an extralymphatic organ or site (IIIe), or both (IIISE). Involvement confined to the spleen or lymph nodes above the celiac axis is designated III_1, while lymph node involvement below the celiac axis with or without splenic or lymph node involvement above the celiac axis is designated III_2.
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissue with or without associated lymph node enlargement.

A or B subclassification

The absence or presence of unexplained weight loss of more than 10% of body weight in the 6 months prior to diagnosis, unexplained fever with temperature above 38C, or night sweats is denoted by the suffix letter A (absence) and B (presence), respectively.

E subclassification

Designates localized involvement of a single extralymphatic organ or site. Liver and bone marrow involvement is always designated as PS IV disease

clinical characteristics. It is a composite model taking into account the various prognostic factors that were known to date to influence outcome. Each individual factor was initially studied on 1385 patients from centers in United States, Europe and Canada. It was carried out between 1982 to1987. Among the factors that were studied included sex, age, Ann Arbor staging, site of lymphomatous involvement, extranodal involvement, dimension of largest tumor, performance status, B symptoms, serum LDH, serum albumin and serum β2 microglobulin level. The above factors were evaluated by its influence on response rate, 5 years relapse-free survival rate and 5 years overall survival rate with CHOP as the standard chemotherapy.

The five pretreatment characteristics that remained independently significant in influencing overall survival were identified;

Age <= 60 years versus > 60 years

Localized disease (stage I and II) versus advanced disease (stage III or IV)

The number of extranodal sites of disease (<= 1 versus > 1)

Performance status (0 or 1 versus >=2)

Serum LDH level (<= 1 times normal versus >1 times normal)

See Table 1.4 for details

Table 1.4. Factors independently Prognostic of Overall Survival in the Training Sample of IPI model. (Adapted from Shipp et al, 1993)

Factors	Relative Risk	P value
No of patients (n = 1385)		
Age (<=60 vs >60)	1.96	<0.001
Serum LDH (<=1 x normal vs >1 x normal)	1.85	<0.001
Performance status (0 or 1 vs. 2 – 4)	1.80	<0.001
Stage (I or II vs III or IV)	1.47	<0.001
Extranodal involvement (<=1 site vs. >1 site)	1.48	<0.001

Hence the resulting model incorporate the following features

i. reflects the growth and invasive potential of the tumor (tumor stage, serum LDH level and number of extra-nodal disease sites)
ii. the patients response to the tumor (performance status)
iii. and the patients ability to tolerate intensive therapy (age and performance status)

For each of the above-mentioned factors, a score of 1 point is given for the presence of each poor risk feature. A cumulative score following the consideration of all the above 5 factors will decide the patients into four risk groups. (0-1: Low; 2: Low intermediate risk; 3: High intermediate; 4 or 5: High risk) The stratification into either one of these four groups was shown to directly correlate with complete response rate, relapse-free survival and complete survival rates. (See Table 1.5) The lower the risk, the higher the complete response, the relapse-free survival and the overall survival rate (Shipp, 1993).

A simplified version of age-adjusted IPI was derived from the study applicable for those below 60 years old but it will not be dealt with here (Shipp, 1993).

IPI was intially based on aggressive NHL (intermediate and part of high grade morphology categories based on working formulation) and on western populations. Since its introduction, it has been shown to be also

Table 1.5 Outcome According to Risk Group Defined by the International Index (Adapted from Shipp et al, 1993)

International index, n=2031	No of Risk Factors	Distribution of Patiens %	COMPLETE RESPONSE			SURVIVAL	
			RATE (%)	RELAPSE-FREE SURVIVAL		2-YR RATE (%)	5-YR RATE (%)
				2-yr rate (%)	5-yr rate (%)		
Low	0 or 1	35	87	79	70	84	73
Low Intermediate	2	27	67	66	50	66	51
High Intermediate	3	22	55	59	49	54	43
High	4 or 5	16	44	58	40	34	26

applicable in indolent low-grade lymphoma (Hermans, 1995) as well as lymphoma complicating AIDS. (Rossi, 1999)

1.5.3 IPI in Chinese

Further study was also carried out to validate IPI in Chinese populations. It was shown in a study that in the whole, IPI was applicable except for extra-nodular involvement, which was found to be non-significant. (Mok et al, 1998) This should not come as a surprise as the prevalence of extra-nodul NHL is higher in eastern populations. Table 1.6 describes further their findings.

Because of the non-significance of the degree of extra-nodal involvement in predicting prognosis in this study, a modified version of IPI was suggested. Instead of including all five characteristics, overall survival curves for three risk groups were constructed using only the first significant four. In this model the presence of one or no risk factors are classified as low risk, two risk factors as intermediate risk and three or four risk factors as high risk. The five years overall survival rates for the low, intermediate and high risk groups were 65.5%, 45.0% and 16.5% respectively ($P<0.001$). (Mok et al, 1998).

Table 1.6. Table showing 5-years survival rate of different prognostic factors in a study on Chinese subjects. (Mok, 1993)

Studied factors	Overall 5 years survival rates		Significance, P
Lactate Dehydrogenase	Normal	Abnormal	
	71.9%	42.8%	<0.001
Age	<=60	>60	
	62.5%	41.5%	0.004
Ann Arbor Staging	Stg I & II	Stg III & IV	
	64.1%	41.8%	<0.001
Performance Status	>=80	<=70	
	60.4%	33.2%	0.006
Extranodal involvement	0 & 1 sites	> 1 sites	
	56.3%	41.9%	0.382

1.6 What if someone has poor IPI indices

Several areas are being diligently studied to produce viable therapeutic options for those expected to respond poorly to standard CHOP chemotherapy. Studies to identify new chemo agents, the prevention of drug resistance, the introduction of colony stimulating factors and monoclonal antibodies into chemotherapy regimes were some of the measures undertook to address this issue (Fisher, 2000). The most promising advance was however the introduction of ablative chemotherapy with stem cells support into the armamentarium

1.6.1 Ablative chemotherapy with autologous stem-cell support

1.6.1.1 In Aggressive NHL

In principle autologous stem-cell transplant functions as a rescue mechanism, incorporated into a regime to allow a higher dose of intense chemotherapy that leads to myeloablation.

The preface to the incorporation of marrow stem cell transplant was the result of the Parma trial. Although the study was conducted on patients with relapse non-Hodgkin lymphoma, it paved the way for further studies on untreated lymphomas.

98 patients with high-risk, diffuse B-cell lymphomas were included in a study comparing high-dose sequential chemotherapy followed by myeloablative therapy and hematopoietic stem-cell support versus standard MACOP-B protocol. The results were promising. Following a median of 55 months, the former study group had significantly better complete response (96% versus 70%) and freedom from disease progression (84% versus 49%) and event-free survival (76% versus 49%).

However, overall survival after 7 years of follow up was not statistically improved (73% versus 62%). In terms of fatal toxic reactions both groups had similar outcome, 8% in the former and 6% in the later.(Gianni, 1997) Nevertheless, its toxicity is certainly higher when compared to standard CHOP regime.

Between 1991 to1995, 124 patients with aggressive NHL were randomized into either one of the following groups. First was the conventional chemotherapy group using VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisolone, and bleomycin) followed by DHAP (cisplatin, cytarabine and dexamethasone), if relapsed or failed to achieve remission. Secondly was VACOP-B followed by high dose myeloablation therapy and autologous bone marrow transplant. In this study there was no significant difference in terms of CR rates (75% versus

73%); in overall DFS rates (60% versus 80%) or progression-free survival rates (48% versus 60%). The 6-years survival probability was 65% in both arms. (Santini, 1998).

Both the above-randomized studies echoed a disappointing outcome following an initial excitement from results of nonrandomized trials that showed superiority of high-dose chemotherapy plus autologous bone marrow transplant over conventional therapy. However when these study samples were reanalyzed to include only subjects with high-intermediate and high risk international prognostic index groups there was a statistically significant improvement in disease-free survival and progression free survival (Fisher, 2000).

1.6.1.2 In High Risk IPI Aggressive NHL

One study although not randomized worked specifically on the high risk international prognostic index patients. In this study carried out by the Italian Multiregional non-Hodgkin's Lymphoma Study Group (IMRNHLSG), 50 patients with diffuse large-cell non-Hodgkin Lymphoma classified as high-risk under the international prognostic index underwent sequential high-dose chemotherapy with autologous bone marrow transplant. 72% achieved complete response and at a median of 32 months follow up, disease free survival rate was 69% and overall survival was

56%. (Vitolo, 1997) Prior to the above study, before1992 IMRNHLSG treated patients with advanced diffuse large cell lymphoma with similar risk profiles with MACOP-B protocol. As a historical control, 42% of these patients achieved complete remission and the 3-years survival rate was only 29%. (Vitolo, 1992)

The above data appear to suggest that, selectively patients with non-Hodgkin lymphoma with high risk profile benefit the most from upfront high-dose chemotherapy and autologous bone marrow transplant

2.0 OBJECTIVE OF STUDY

By the 1990's, haemopoietic stem cell transplant was made available at limited centers in Malaysia. Currently, it has already been applied as a treatment option for selected patients with acute leukemia and lymphoma. Following the establishment of our hematology unit in Hospital USM in Kelantan in 1983, we are now in the process of upgrading our services to include haemopoetic stem cell transplant services. We cater our services mainly for populations in the east coast of Malaysia, the state of Kelantan and Terengganu in particular, who are predominantly Malay.

As we have described above, only selected patients with non- Hodgkin's lymphoma (NHL) will benefit from high dose chemotherapy and autologous marrow transplant. Those with high-risk IPI scores are the ones who will benefit the most. However the IPI index was derived from studies on Caucasian populations. When the IPI index was validated in a study on Chinese populations, extra-nodal involvement was found to be not a significant prognostic factor. We are unsure of the utility of IPI in our patient population who are predominantly Malay. From our clinical experience we tend to see much more extra-nodal NHL, similar to the Chinese study, but this statement will need validation and we intend to study this issue in this exercise.

We included patients from our center with aggressive NHL with similar characteristics as to those described in the IPI project into this study. They included those treated with either chemotherapy alone or chemotherapy and