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Clinical Characteristics and Treatment Outcome of 218 Patients with Non-Hodgkin's Lymphoma in a Singaporean Institution

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ABSTRACT

A retrospective analysis of 218 patients with non-Hodgkin's lymphoma (NHL) seen at a single institution in Singapore over a ten-year period was conducted. Twenty percent, 56% and 24% of patients had low-, intermediate- and high-grade disease respectively using the Working Formulation, and 25% of patients immunophenotyped had T-cell NHL. Forty-nine percent had primary extranodal disease, with the commonest sites of involvement being the gastrointestinal tract, nasal cavity, and tonsils. 86% and 73% respectively of patients with intermediate and high grade disease received combination chemotherapy as first line treatment, with CHOP being the most commonly used regime. Seventy-four percent of patients with low grade lymphoma received first line chemotherapy, 5% each was treated with radiotherapy or surgery alone, and 21% was treated symptomatically. Patients with low grade B-cell lymphoma had a 5-year survival of 80% and 10-year survival of 42%. One-year survival for intermediate and high grade B-cell lymphoma was 76% and 42%, while 2-year survival was 67% and 42% respectively. 1-, 2-, and 3-year survival for patients with T-cell lymphoma was 67%, 46% and 37% respectively. The difference in survival between low-, intermediate- and high-grade B-cell lymphoma was statistically significant ($p = 0.0018$ using the log rank test), but that between B- and T-cell lymphoma was not. Using the Cox regression model, International prognostic index, grade and extranodal disease were found to be statistically significant predictors of survival ($p = 0.0001$, $p = 0.0157$, $p = 0.0343$) respectively.

Keywords: Singaporean Asians, non-Hodgkin's lymphoma

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INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is currently the 8th commonest cancer among Singaporean males[1]. Asian lymphomas are distinct from Western lymphomas in having a high incidence of T- and primary extranodal disease and low incidence of follicular disease[2]. Singapore is a unique multi-racial Asian country with Chinese, Malays and Indians forming the major ethnic groups. Thus, disease patterns here may deviate from that of other Asian communities. A retrospective analysis of all non Hodgkin's lymphoma cases seen in a single Singaporean institution over a ten-year period is conducted to evaluate clinical patterns, treatment and outcome and to compare these features with other Asian and Western series.

PATIENTS AND METHODS

A retrospective analysis of all patients with lymphoma seen at our institution from 1987 to 1996 was conducted. To be eligible for the study, each patient was required to have biopsy-proven lymphoma. Patient information and tumor characteristics, treatment and outcome were retrieved from the hospital clinical records. All patients had a complete history and physical examination on initial presentation. Tissue for histology was obtained from surgical biopsy of tumor. Further work-up included chest radiograph, full blood counts, blood biochemistry, CT scan of the abdomen, marrow aspirate, and trephine biopsy. No patient underwent staging laparotomy. Patients were staged according to the Ann Arbor system[3], and those with intermediate or high-grade non-Hodgkin's lymphoma were categorized according to the International Prognostic Index[4], which takes into account the age and the performance status of the patient, the LDH level, extranodal involvement and stage of disease.

Tumor was graded using the Working Formulation[5]. Immunophenotyping was performed using reactivity against CD3, CD45, CD20, and CD79. Additional immunohistochemistry tests such as reactivity against CD30 are performed in selected cases when necessary.

Tumor response was assessed using standard criteria. Complete response was defined as the total disappearance of all symptoms and clinically detectable disease lasting for a minimum of 4 weeks. Partial response was defined as a 50% or greater reduction of all measurable tumor, without the appearance of new lesions for at least 4 weeks.

Progressive disease was defined as an increase in size of any pre-existing measurable or evaluable lesions by more than 25%, or the appearance of any new lesion[6].

The overall survival time was measured from the date of diagnosis to the date of death or last follow-up visit using the Kaplan Meier product limit method[7]. Time to treatment failure was calculated from the start of therapy to disease progression or death, whichever occurred first.

RESULTS

From 1987 to 1996, 241 case records were reviewed, of which 23 were Hodgkin's lymphoma, and 218 were Non-Hodgkin's lymphoma. Accordingly, NHL constituted 91% of all lymphoma cases seen in our institution over the ten-year period.

The patient and tumor characteristics are detailed in Table I. The male to female ratio was 1.18 and the median age was 56 (range 12 to 92). Seventy-six percent was Chinese, 10% Malay, and 5% Indian. Forty-seven percent reported B-symptoms. Forty-nine percent of patients had primary extranodal disease, with the commonest sites being the gastrointestinal tract, nasal cavity, and tonsils (Table II). The stomach is the commonest gastrointestinal site, comprising 50% of all gastrointestinal NHL.

One hundred and eighty eight patients were immunophenotyped, of which 48 and 140 patients had T- and B-cell lymphoma respectively. Two hundred and thirteen patients had their tumor graded according to the Working Formulation, and 20%, 56% and 24% had low-, intermediate- and high-grade disease respectively.

Table I – Patient and tumor characteristics in non-Hodgkin's lymphoma, n = 218

Sex	
Male	118
Female	100
Age	12 – 92, median 56
Duration of symptoms	< 1 week to 4 years Median 4.5 weeks
Race	
Chinese	165
Malay	22
Indian	11
Others	20
Stage	
I	49
II	53
III	36
IV	78
B symptoms	
Present	101
Absent	121
Not specified	6
Primary Extranodal	106
1 site	95
2 sites	10
3 sites	1
Immunophenotype	
B cell	140
T cell	48
Unknown	30

An attempt was made to categorize the patients in this study using the REAL classification[8] based on the reported histology. Two hundred patients could be categorized (Table III), of which 52% and 11.5% had diffuse large and follicular B-cell lymphoma respectively, and 10% had an unspecified type of peripheral T-cell lymphoma. Six percent of patients presented with nasal type T/NK cell lymphoma, and 6.5% had MALT lymphoma.

Table II – Extranodal sites of involvement in NHL
Patient number = 106
No. of extradodal sites = 118

Gastrointestinal	49	
Stomach	24	(MALT in 6)
Small intestine	12	(MALT in 2)
Large intestine	13	
Head & Neck	36	
Nasal/nasoppharynx	14	
Tonsil	13	
Maxillary sinus	3	
Tongue	2	
Lacrimal	2	
Salivary glands	2	
Others	33	
Female reproductive organs*	6	
Central nervous system	5	
Skin	5	
Testis	5	
Bone	5	
Lung	3	
Thyroid	3	
Pancreas	1	

* breast 3, uterus 1, vulva 1, parametrium 1

Table III – REAL classification, n = 200

B-cell neoplasms		
Precursor B-lumphoblastic leukemia/lymphoma	2	
Peripheral B-cell neoplasms		
B-CLL/PLL/SLL	5	
Lymphoplasmacytic lymphoma	5	
Mantle cell lymphoma	0	
Follicular lymphoma	23	
Marginal zone lymphoma		
MALT	9	(+4)**
Splenic marginal zone lymphoma with or without villous lymphocytes	1	
Hairy cell leukemia	0	
Plasmacytoma/plasma cell myeloma	0	
Diffuse large cell	104	
Burkitt's	4	
Precursor T-lymphoblastic lymphoma/leukemia	4	
Peripheral T-cell/NK cell neoplasms		
T-CLL/PLL	0	
LGL	0	
Mycosis fungoides/Sezary syndrome	1	
Peripheral T-cell		
Unspecified	20	
Specific		
AILD	3	
Nasal T	12	
Intestinal T	0	
Hepatosplenic	0	
Subcutaneous panniculitic	0	
Adult T-cell lymphoma/leukemia	0	
ALCL	4	

** 9 patients with MALT, 4 patients with MALT + transformed high grade to diffuse large. 10 GI sites (6 stomach, 3 small bowel, 1 large bowel), 2 breast, 1 lacrimal gland.

Eighty-six percent and seventy-three percent respectively of patients with intermediate and high grade disease received combination chemotherapy as first line treatment. The majority (88%) of chemotherapy patients received anthracycline-based combinations, with CHOP[9] being the most commonly used regime (65%). 21/37 patients with gastrointestinal lymphoma underwent surgical resection in addition to definitive chemotherapy. 118/140 patients with intermediate or high grade lymphoma who received first line chemotherapy were evaluable for response, of which 54% and 48% achieved complete response, 14% and 7% achieved partial response, and 32% and 45% failed primary treatment respectively. Forty-five patients were given second-line treatment, 37/45 (82%) with chemotherapy, and 18% with radiotherapy. 35/45 patients were evaluable for response to second line therapy, of which 20% and 34% achieved complete response and partial response respectively. All complete responders to second-line therapy received chemotherapy.

Of the 42 patients with low grade lymphoma, 74% received first line chemotherapy, 5% each were treated with radiotherapy or surgery alone, and 21% were treated symptomatically. Of the 31 patients who received first line chemotherapy, 52% received COP[10], 13% received chlorambucil with or without prednisolone, and 32% received anthracycline-containing combinations (6 CHOP, 3 CEOP[11], 1 m-BACOD[12]). 29/31 patients were evaluable for response, of which 34%, 52% and 14% achieved complete response, partial response and progressive disease respectively. Eighteen patients received second line treatment and beyond.

Five patients underwent autologous bone marrow transplant (ABMT) as part of salvage treatment; 4 for relapsed disease, and 1 for primary treatment failure. Two patients died within 60 days of ABMT. The remaining three patients achieved complete remission, two of whom relapsed 7 and 11 months later and subsequently died of disease despite third line treatment. The last patient is alive and disease-free 5 months from ABMT and 25 months from diagnosis.

Patients with low grade B-cell lymphoma had a 5-year survival of 80% and 10-year survival of 42%. One-year survival for intermediate grade and high grade B-cell lymphoma was 76% and 42%, while 2-year survival was 67% and 42% respectively. 1-, 2- and 3-year survival for patients with T-cell lymphoma was 67%, 46% and 37% respectively. The difference in survival between low-, intermediate- and high-grade B-cell lymphoma was statistically significant ($p = 0.0018$ using the log rank test[13]), while the difference in survival between B- and T-cell lymphoma was not. Using the Cox regression model[14], International prognostic index, grade and extranodal disease were found to be statistically significant predictors of survival ($p = 0.0001$, $p = 0.0157$, $p = 0.0343$), while race and sex were not.

The nasal T/NK cell NHL comprises 5.5% of the population. The majority of patients presented with stage I or II disease and were low risk when categorized with the International Prognostic Index (Table IV). The median failure-free survival was 4.8 months despite conventional first-line treatment with CHOP ± radiotherapy. Seven patients required second-line chemotherapy for relapsed disease, two of whom had high dose chemotherapy with autologous bone marrow transplant. Only 2/7 patients achieved complete remission but which was not durable. The median overall survival of the group was 8.0 months. Using the log-rank test, the difference in survival between this subset and that of diffuse large B-cell lymphoma and the unspecified form of peripheral T-cell lymphoma was statistically significant ($p = 0.049$).

DISCUSSION

The age-standardized incidence of non-Hodgkin's lymphoma in Singapore is 4.5 – 6 per 100,000 per year. It is the third commonest cancer for both males and females in the paediatric age group, and ranks third and eighth respectively among young male and female adults in the 15 – 34 year age group[1]. The incidence of NHL in Singapore, particularly in females has been increasing over the past 25 years, the cause of which is yet to be elucidated[15].

As in many other Asian series[2,16-18], our NHL population showed a high incidence of primary extranodal involvement. Extranodal lymphoma is distinct from nodal NHL in many ways ranging from treatment strategies to prognosis. The commonest extranodal site of involvement in our series is the gastrointestinal tract, with the stomach being the predominant organ involved. One quarter of our gastric NHL were mucosa-associated lymphoid tumors (MALT), for which eradication of Helicobacter pylori has been shown recently to have curative potential[19]. The risk of gut perforation and bleeding secondary to chemotherapy-induced tumor necrosis in primary gastrointestinal lymphoma has been well described[20]. The role of surgery in the treatment logarithm of primary gastrointestinal lymphoma is however still poorly defined. In our series, more than half the patients underwent surgical resection prior to definitive chemotherapy, the majority of whom had unsuspected pre-operative diagnosis of lymphoma. Nevertheless, there remains

Table IV – Nasal T/NK cell lymphoma, n = 12

Stage I	7
Stage II	5
IPI low risk	10
IPI low intermediate risk	2
Firstline treatment	
Chemotherapy alone	6
Chemotherapy + radiotherapy	4
Radiotherapy	2
Response to firstline treatment	
CR	5
PR	1
PD	5
NE	1
Median survival	8.0 months

a role for planned first line surgery particularly in lymphomas with greater depth of invasion to prevent gut perforation[21].

Nasal T/NK cell NHL is now recognized to be a distinct entity in the REAL classification. It is more commonly found in the East[22], and interestingly our observations suggest this entity to have a much poorer prognosis than the common high grade lymphomas such as diffuse large B-cell NHL, independent of the International Prognostic Index. This is in contrast with what has been reported by Liang et al[23], where limited stage disease is associated with favorable survival. Our observations suggest that conventional treatment may be inadequate for this entity with poor prognosis. Studies are needed to elucidate the molecular mechanisms underlying the poor treatment outcome and to provide a sound basis for prospective trials of new therapeutic strategies.

The treatment strategies observed in this series had largely conformed to standard therapy, with the majority of patients with intermediate or high grade disease receiving combination chemotherapy with CHOP being the dominant regime, and those with low grade lymphoma receiving either COP, chlorambucil ± prednisolone or symptomatic care. The treatment response and survival is comparable to that observed in other Western and Asian series.

A high-dose chemotherapy with autologous bone marrow transplant program was initiated in our institution since 1994. The outcome of the first 5 patients as reported in this series is not impressive partly attributed to the poor prognostic features of the patients. The role and timing of high dose chemotherapy in non-Hodgkin's lymphoma is yet to be defined. The use of this treatment strategy as part of first line treatment in poor prognostic groups may be associated with better outcome.

We report a retrospective analysis of over 200 patients seen over the last ten years with non-Hodgkin's lymphoma in a single institution. The tumor characteristics, treatment, prognosis and outcome are comparable to other Asian series. We see distinct subsets not commonly observed in the Western population such as the nasal T/NK cell NHL and extranodal lymphomas. Prospective studies to evaluate the pathogenesis, prognostic factors, treatment and outcome of these entities will be of interest.

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