INTRODUCTION
Non-Hodgkin’s lymphoma (NHL) encompasses a heterogeneous group of lymphoproliferative disorders that vary in clinical course, prognosis, and management depending on histological subtype, tumour bulk, and other patient-specific factors. The frequency of NHL over the past 3 decades has doubled. It has been known for more than 30 years that some patients with NHL can be cured using chemotherapy. In the past decade, advances in molecular medicine have provided exciting insights into the biology of NHL. The viral and bacterial aetiology of certain lymphomas has now been well established. Cell surface antigens have been defined that provide targets for therapy with monoclonal antibodies and radioimmunotherapy. Moreover, knowledge of critical cell signalling pathways and the results of gene expression analyses have provided opportunities for targeted therapy with novel small molecules. Treatment outcomes have improved, mostly related to the introduction of rituximab. Several trials have shown the usefulness of this monoclonal antibody, both in indolent and aggressive histologic subtypes. This has proven to be an effective and tumour-selective treatment for prolonging survival in patients with NHL, especially LBCL. In addition to rituximab, the optimal role of radioimmunoconjugates is continuing to evolve. A number of novel targeted agents are also being evaluated, and preliminary data are now available.

With these advances, improved survival has been observed in patients with aggressive NHL, and there is great optimism for patients with indolent histology as well.

CELLULAR CLASSIFICATION
Historically, uniform treatment of patients with NHL has been hampered by the lack of a uniform classification system. In 1982, results of a consensus study were published as the Working Formulation. The Working Formulation combined results from 6 major classification systems into 1 classification. This allowed comparison of studies from different institutions and countries.

As the understanding of NHL has improved and as the histopathologic diagnosis of NHL has become more sophisticated, with the use of immunologic and genetic techniques, a number of new pathologic entities have been described. In addition, the understanding and treatment of many of the previously described pathologic subtypes have changed. As a result, the Working Formulation has become outdated and less useful to clinicians and pathologists. Thus, European and American pathologists have proposed a new classification, the Revised European American Lymphoma (REAL) Classification. Since 1995, members of the European and American Hematopathology societies have been collaborating on a new World Health Organization (WHO) classification, which represents an updated version of the REAL system.

The WHO modification of the REAL classification recognizes 3 major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer (NK)-cell neoplasms, and Hodgkin’s lymphoma. Both lymphomas and lymphoid leukemias are included in this classification because both solid and circulating phases are present in many lymphoid neoplasms and distinction between them is artificial. For example, B-cell chronic lymphocytic leukemia and B-cell small lymphocytic lymphoma are simply different manifestations of the same neoplasm, as are lymphoblastic lymphomas and acute lymphocytic leukemias. Within the B-cell and T-cell categories, 2 subdivisions are recognized: precursor neoplasms, which correspond to the earliest stages of differentiation, and more mature differentiated neoplasms.
The more than 20 clinicopathologic entities mentioned in the REAL classification can be divided into the more clinically useful indolent or aggressive lymphomas as follows:

Modified REAL Classification of lymphoproliferative diseases

1. **Plasma cell disorders**
   1. Bone.
   2. Extramedullary.
      1. Monoclonal gammopathy of undetermined significance.
      2. Plasma cell myeloma.
      3. Multiple myeloma.
      4. Amyloidosis.

2. **Hodgkin’s lymphoma**
   2. Lymphocyte-rich classical Hodgkin’s lymphoma.

3. **Indolent lymphoma/leukaemia.**
   1. Follicular lymphoma (follicular small-cleaved cell [grade 1], follicular mixed small-cleaved and large cell [grade 2], diffuse small-cleaved cell).
   2. Chronic lymphocytic leukaemia/small lymphocytic lymphoma.
   3. Lymphoplasmacytic lymphoma (Waldenström’s macroglobulinemia).
   7. Hairy cell leukaemia.
   8. Mycosis fungoides/Sézary syndrome
   9. T-cell granular lymphocytic leukaemia
   11. Nodular lymphocyte predominant Hodgkin’s lymphoma

4. **Aggressive lymphoma/leukaemia.**
   1. Diffuse large cell lymphoma (includes diffuse mixed-cell, diffuse large cell, immunoblastic, T-cell rich large B-cell lymphoma).
   Distinguishing:
   1. Mediastinal large B-cell lymphoma.
   2. Follicular large cell lymphoma (grade 3).
   3. Anaplastic large cell lymphoma (CD30+).
   5. Lymphomatoid granulomatosis (angiocentric pulmonary B-cell lymphoma).

7. **Peripheral T-cell lymphoma, unspecified.**
   2. Burkitt’s lymphoma/Burkitt’s cell leukaemia/Burkitt’s-like lymphoma.
   3. Precursor B-cell or T-cell lymphoblastic lymphoma/leukaemia.
   4. Primary CNS lymphoma
   5. Adult T-cell leukaemia/lymphoma (HTLV 1+).
   7. Polymorphic posttransplantation lymphoproliferative disorder (PTLD).
   8. AIDS-related lymphoma
   10. Primary effusion lymphoma.
   11. B-cell or T-cell prolymphocytic leukaemia

**EPIDEMIOLOGY**

The NHLs and Hodgkin’s lymphoma are the most commonly occurring haematologic malignancies in the United States. They now represent 4% to 5% of all new cancer cases and NHL ranks at 6th and 5th commonest malignancies among males and females respectively in the year 2006.² NHL is second fastest growing cancer in terms of mortality. International NHL incidence rates vary as much as fivefold. The highest reported incidence rates are in the United States, and also Europe and Australia; the lowest rates have generally been reported in Asia.⁴ Among children, lymphomas are the third most frequent malignancy, representing 15% of paediatric malignancies with 1700 new cases each year. The estimated one year survival rate is 70%, while the 5- and 15-year rates approximate 50% and 35%, respectively.⁵ The risk of NHL increases steadily from childhood through the eighth decade of life; on average, patients are in their early 40s at diagnosis.¹³,¹⁶ Owing to the substantial number of productive years lost, NHL ranks fourth among all cancers in the United States in terms of societal economic impact.¹⁷

In the USA, since the early 1970s, incidence rates for NHL have nearly doubled and more recently, increasing incidence is confined to women.² This striking rise in NHL incidence rates has been referred to as an epidemic of NHL. The reasons for this are not entirely clear though some attribute it to the AIDS epidemic, an aging population, and the widespread practice of organ transplantation.¹⁵,¹⁷,¹⁸ Many investigators have postulated that a ubiquitous environmental or toxic exposure may be responsible.¹⁹ Although there have
been increases in most histologies, the largest increases have occurred in patients with aggressive lymphomas attracting more clinical trials.

MOLECULAR BIOLOGY OF LBCL

T cells and B cells undergo two major phases of differentiation: antigen independent and antigen dependent. Antigen-independent differentiation occurs in the primary lymphoid organs without exposure to antigen and produces a pool of lymphocytes that are capable of responding to antigen (naive or virgin T and B cells). On exposure to antigen, the naive lymphocyte undergoes “blast transformation” and becomes a large, proliferating cell, which gives rise to progeny that are capable of direct activity against the inciting antigen: antigen-specific effector cells. The early stages of antigen-dependent differentiation are proliferating cells, whereas the fully differentiated effector cells are less mitotically active. Thus, neoplasms that correspond to proliferating stages of either antigen-independent or antigen-dependent differentiation are likely to be aggressive, whereas those that correspond to naive or mature effector stages are likely to be indolent.

Cell Surface Antigens

B cells express pan-B-cell antigens (CD19, CD20, CD22, CD40, and CD79a), HLA class II molecules, complement receptors (CD21 and CD35), CD44, Leu-8 (L-selectin), and CD23; some express the pan-T-cell antigen, CD5, whereas others do not.20 Resting B cells also express Bcl-2, which promotes survival in the resting state.21 CD5-positive naive B cells have sIg that often has broad specificity [cross-reactive idiotypes (Ids)] and reactivity with self-antigens (autoantibodies). Targeted therapies have been developed against some of these antigens and a few have been extremely successful.

Evolution of MAb Therapy

Nearly 100 years ago, Ehrlich22 proposed his “magic bullet” theory for targeting cancer cells with antibodies. His approach involved the production of immunoglobulin proteins (antibodies) in response to repeated immunizations of animals with foreign cells, with resultant binding of these antibodies to cell-surface antigens and induction of cell lysis and death. Antibody technology did not advance significantly until 75 years later, when Köhler and Milstein23 described their hybridoma methodology for producing antibodies from a single clone of cells, for which they were awarded the Nobel Prize in 1984. Their technology facilitated unlimited production of murine-derived antibodies with improved affinity and specificity for targeted antigens. Drawbacks included poor host effector-cell responses and immune system stimulation that resulted in the development of human antimmune antibodies (HAMAs). Occurring in approximately 30% of patients treated with murine MAb, HAMAs reduce the effectiveness of subsequent infusions by binding MAb, thus allowing their rapid clearance from the systemic circulation.24,25

Production of human MAb followed soon that have a longer half-life, and a greatly reduced potential for immunogenicity compared with murine MAb.26,27 Antigens found solely on the cancer cell surface are termed tumour-specific antigens and are desirable targets for MAb therapy. A number of criteria need to be met for an antigen to be an ideal target for unconjugated monoclonal antibody therapy:28

- The target antigen is expressed ONLY on all tumour cells, not on critical host cells.
- No significant toxicity would ensue if all antigenically positive tumour cells are eliminated.
- The target antigen is expressed in high numbers and does not mutate.
- There are no variant antigen types to form complexes with the antibody.
- The antigen is not shed or secreted and does not undergo modulation during or after treatment.
- Additionally, the antigen is integral to cell survival.

B-cell lymphomas are considered ideal models for intervention with MAb therapy owing to the expression of several well-defined surface antigens, including the CD20 antigen (Figure-1).29 The CD20 antigen is a membrane-embedded protein expressed on the cell surface in more than 90% of B-cell lymphomas and some chronic lymphocytic leukemias.30 This antigen fulfils most of the required criteria.31

Figure-1: Surface-antigen targets for monoclonal antibody therapy in B cell lymphoma.
Table 1: Comparison of Different Treatments of Large B Cell Lymphoma

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Patient Characteristics</th>
<th>Treatments</th>
<th>Results</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller et al 1998</td>
<td>Stage II/II NHL, No. Age, PS &amp; LDH matched</td>
<td>CHOP 8 Vs CHOP 3 + DXRT</td>
<td>CR 73% vs 75%</td>
<td>5 Year Survival 72% vs 82%</td>
</tr>
<tr>
<td>Coiffier et al 1998</td>
<td>Patients 54 (30 LBCL) Relapsed, PD Post BMT</td>
<td>R – CHOP</td>
<td>ORR – 32%</td>
<td>CRs – 10%</td>
</tr>
<tr>
<td>Link et al 1999</td>
<td>Patients 31</td>
<td>R – CHOP</td>
<td>ORR – 96%</td>
<td>CRs – 63%</td>
</tr>
<tr>
<td>Czuzcman et al 1999</td>
<td>Phase II Study</td>
<td>R-CHOP</td>
<td>CR 55%</td>
<td>PR 40%</td>
</tr>
<tr>
<td>Coiffier et al 2002 (GELA)</td>
<td>Patients 399, LBCL Age &gt; 60 years</td>
<td>R-CHOP Vs CHOP</td>
<td>CR = 76% vs 63%</td>
<td>At 2 Years</td>
</tr>
<tr>
<td>Sehn et al 2003</td>
<td>Patients 152 vs 142</td>
<td>R-CHOP Vs CHOP</td>
<td>At 2-years</td>
<td>PFS = 71% vs 52%</td>
</tr>
<tr>
<td>Pfreundschuh et al 2004</td>
<td>Phase 3 trial Patients 326, LBCL ≤ 60 years IPI 0 or 1</td>
<td>R-CHOP Vs CHOP/CHOP like</td>
<td>Stopped at 15 Months</td>
<td>TTF = 81% vs 58%,</td>
</tr>
<tr>
<td>Miller et al 2004</td>
<td>Patients 62, LBCL, IPI – 1</td>
<td>CHOP 3 + RT + 4 Rituximab Compared with historical CHOP 3 + RT</td>
<td>At 2.4 years</td>
<td>PFS = 94%</td>
</tr>
</tbody>
</table>

MAbs for the Treatment of Malignancies

MAbs directed against tumour antigens may be administered either in an unconjugated form or conjugated to a toxin or a radioactive isotope. Compared with traditional chemotherapy regimens, MAbs may provide greater selectivity for tumours and thus a reduced potential for bone marrow suppression and other potentially life-threatening systemic toxicities. Given their different mechanisms of action and nonoverlapping toxicity profiles, the response to MAb therapy should theoretically be unaffected by the development of resistance to prior chemotherapy regimens. In addition, the combination of MAbs and chemotherapy may be safe and effective for treating patients with B-cell lymphomas. Several MAb preparations currently available or under study for use in the treatment of various haematologic malignancies have been described.

The chimeric structure of rituximab comprises human IgG 1 and kappa-chain constant regions and heavy- and light-chain variable regions from a murine antibody to CD20 (Figure 2). In vitro, rituximab has been shown to inhibit cell proliferation, induce apoptosis, and sensitise lymphoma cells to the effects of certain chemotherapy agents. This synergistic interaction suggests the potential for enhanced treatment efficacy when rituximab and chemotherapy are combined. After rituximab administration, antibody-coated B cells are rapidly depleted from peripheral blood, lymph nodes, and bone marrow.

CONCLUSION

Treatment of Large B Cell Lymphoma has leaped in the last 5 years. Rituximab has played a pivotal role in this scenario. This can be safely regarded as the
largest change in survival brought in the history of Oncology. In UK patients with CD20 positive stage II, III or IV LBCL are offered Rituximab-CHOP combination. The National Cancer Institute of America recommends Rituximab-CHOP for patients with non-contiguous CD20 positive stage II, III or IV LBCL. We need to define our guidelines for optimum treatment of LBCL patients keeping in view our financial constraints.

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REFERENCES

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