REVIEW ARTICLE

LARGE B CELL LYMPHOMA—YEAR BY YEAR

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Non Hodgkin's Lymphoma (NHL) comprises a group of lymphoproliferative disorders the frequency of which continues to rise. Although many classification systems exist for identifying specific histological subtypes, NHL is generally divided into indolent (low-grade) and aggressive (intermediate- and high-grade) forms. Large B Cell Lymphoma (LBCL) is one of the commonest aggressive NHLs. The aim of this review is to provide a general overview of NHL, its clinically practicable cellular classification, epidemiology and in depth overview of the evolution of treatment of LBCL during the past 5 years. Current guidelines from National Cancer Institute (NCI), USA and National Institute on Clinical Excellence (NICE), UK are mentioned and recommendations according to our own set-up are suggested.

Keywords: Non-Hodgkin's Lymphoma, Large B Cell Lymphoma, Rituximab

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.[1] The frequency of NHL over the past 3 decades has doubled.[2] 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.[3,4] 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.[5] 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.[6] 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.[7-10] 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.[11-13]

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 leukaemias 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 leukaemia and B-cell small lymphocytic lymphoma are simply different manifestations of the same neoplasm, as are lymphoblastic lymphomas and acute lymphocytic leukaemias. 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.[11-13]

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 lympho-proliferative diseases

1. **Plasma cell disorders**
   1. Bone.
   2. Extramedullary.
      1. Monoclonal gammopathy of undetermined significance.
      2. Plasmacytoma.
      3. Multiple myeloma.
      4. Amyloidosis.
2. **Hodgkin's lymphoma**
   1. Nodular sclerosis Hodgkin's lymphoma.
   2. Lymphocyte-rich classical Hodgkin's lymphoma.
   3. Mixed-cellularity Hodgkin's lymphoma.
   4. Lymphocyte-depleted 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).
   4. Extranodal marginal zone B-cell lymphoma (MALT lymphoma).
   5. Nodal marginal zone B -cell lymphoma (monocytoid B-cell lymphoma).
   6. Splenic marginal zone lymphoma (splenic lymphoma with villous lymphocytes).
   7. Hairy cell leukaemia.
   8. Mycosis fungoides/Sézary syndrome
   9. T-cell granular lymphocytic leukaemia
   10. Primary cutaneous anaplastic large cell lymphoma/ lymphomatoid papulosis (CD30+).
   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). Distinguish:
      1. Mediastinal large B-cell lymphoma.
      2. Follicular large cell lymphoma (grade 3).
      3. Anaplastic large cell lymphoma (CD30+).
      4. Extranodal NK-/T-cell lymphoma, nasal type/aggressive NK-cell leukaemia/ blastic NK-cell lymphoma.
      5. Lymphomatoid granulomatosis (angiocentric pulmonary B-cell lymphoma).
      6. Angioimmunoblastic T-cell lymphoma.
      7. Peripheral T-cell lymphoma, unspecified.
      1. Subcutaneous panniculitis-like T-cell lymphoma.
      2. Hepatosplenic T-cell lymphoma.
      8. Enteropathy-type T-cell lymphoma.
      9. Intravascular large B-cell lymphoma.
   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+).
   6. Mantle cell lymphoma.
   7. Polymorphic posttransplantation lymphoproliferative disorder (PTLD).
   8. AIDS-related lymphoma
   9. True histiocytic 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.[14] 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.[15] The risk of NHL increases steadily from childhood through the eighth decade of life; on average, patients are in their early 40s at diagnosis.[15,16] 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, Ehrlich[22] 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 Milstein[23] 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 antimouse antibodies (HAMAs). Occurring in approximately 30% of patients treated with murine MAbs, HAMAs reduce the effectiveness of subsequent infusions by binding MAbs, thus allowing their rapid clearance from the systemic circulation.[24,25]

Production of human MAbs followed soon that have a longer half-life, and a greatly reduced potential for immunogenicity compared with murine MAbs.[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]

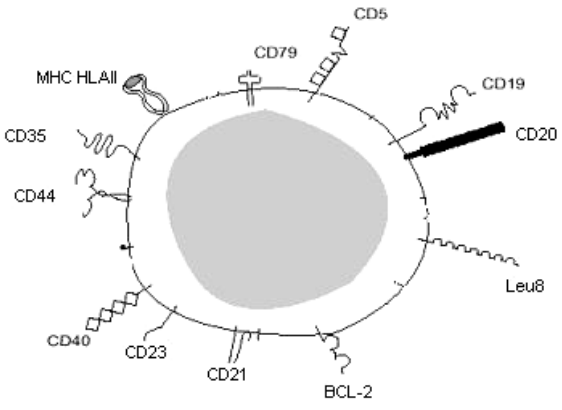

Figure-1: Surface-antigen targets for monoclonal antibody therapy in B cell lymphoma.

Table-1: Comparison of Different Treatments of Large B Cell Lymphoma

Author (Year)	Patient Characteristics	Treatments	Results	*p* value
Miller *et al*[35] 1998	Stage I/II NHL No, Age, PS & LDH matched	CHOP 8 Vs CHOP 3 + DXRT	CR 73% vs 75% FFS 64% vs 77% 5 Year Survival 72% vs 82%	*p*= 0.06
Coiffier *et al*[36] 1998	Patients 54 (30 LBCL) Relapsed, PD Post BMT	R – CHOP	ORR – 32% CRs – 10%	No. too small
Link *et al*[37]	Patients 31	R – CHOP	ORR – 96% CRs – 63% PRs – 33%	No. too small
Czuzcman *et al*[40] 1999	38 Patients Phase II Study	R-CHOP	CR 55% PR 40%	No. too small
Coiffier *et al*[41] 2002 (GELA)	Patients 399, LBCL Age > 60 years	R–CHOP Vs CHOP	CR = 76% vs 63% At 2 Years OS = 70% vs 57% EFS = 57% vs 38%,	*p*=0.005 *p*=0.007 *p*= 0.002
Sehn *et al*[42] 2003	Patients 152 vs 142	R-CHOP Vs CHOP	At 2-years PFS = 71% vs 52% OS = 77% vs 53%	*p*< 0.05 *p*< 0.05
Pfreundschuh *et al*[4] 2004	Phase 3 trial Patients 326, LBCL ≤ 60 years IPI 0 or 1	R-CHOP Vs CHOP/CHOP like	Stopped at 15 Months TTF = 81% vs 58%, PD = 5% vs 16% 2 Years Survival 95% vs 85%	*P*< 0.000005 *P* < 0.0005 *P* = 0.0026
Miller *et al*[43] 2004	Patients 62, LBCL IPI – 1	CHOP 3 + RT + 4 Rituximab Compared with historical CHOP3 + RT	At 2.4 years PFS = 94% OS = 95% Historical Response Rate 70%	No. too small

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.[32-38]

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).[26] The murine variable regions selectively bind to the CD20 antigen expressed on the surface of both normal B lymphocytes and most B-cell lymphomas. The presence of a human constant region allows rituximab to bind to Fc receptors on human effector cells (e.g., lymphoma cells, macrophages, and neutrophils) to mediate both complement- dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity and decreases its immunogenicity.[26] In vitro, rituximab has been shown to inhibit cell proliferation, induce apoptosis, and sensitise lymphoma cells to the effects of certain chemotherapy agents.[34,35] 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.[26]

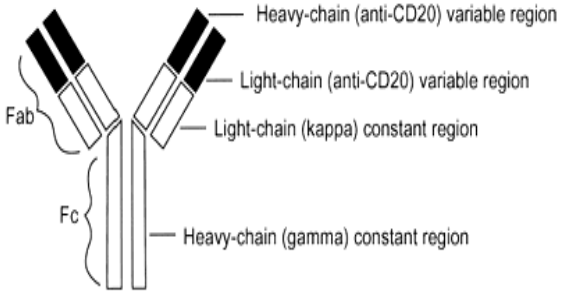

Figure-2: Diagram of structure of rituximab.
Rituximab is a chimeric antibody of the immunoglobulin G1 kappa type with murine anti-CD20 variable-sequence regions (filled areas) and human constant-sequence regions (open areas)

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.[44] The National Cancer Institute of America recommends Rituximab-CHOP for patients with non-contiguous CD20 positive stage II, III or IV LBCL.[45] We need to define our guidelines for optimum treatment of LBCL patients keeping in view our financial constraints.

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REFERENCES

1. Armitage JO: Treatment of non-Hodgkin's lymphoma. N Engl J Med 1993;328(14):1023-30.
2. American Cancer Society. Cancer Facts and Figures 2006. Atlanta: American Cancer Society;2006.
3. Coiffier B, Lepage E, Briere J , Herbrecht R, Tilly H, Bouabdallah R *et al*. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. New Engl J Med. 2002;346:235-242.
4. Pfreundschuh MG, Trümper L, Ma D, Sterborg A, Pettengell R, Trneny M *et al*. Randomized intergroup trial of first-line treatment for patients </=60 years with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL) with a CHOP-like regimen with or without the anti-CD20 antibody rituximab-early stopping after the first interim analysis. Proc Am Soc Clin Oncol. 2004;23:556.
5. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer 1982;49(10):2112-35.
6. Pugh WC. Is the working formulation adequate for the classification of the low grade lymphomas? Leuk Lymphoma 1993; 10(Suppl):1-8.
7. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML *et al*. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84(5):1361-92.
8. Pittaluga S, Bijnens L, Teodorovic I, Hagenbeek A, Meerwaldt JH, Somers R, *et al*. Clinical analysis of 670 cases in two trials of the European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group subtyped according to the Revised European-American Classification of Lymphoid Neoplasms: a comparison with the Working Formulation. Blood 1996;87(10):4358-67.
9. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998;16(8):2780-95.
10. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood 1997;89(11):3909-18.
11. Pileri SA, Milani M, Fraternali-Orcioni G, Sabattini E. From the R.E.A.L. Classification to the upcoming WHO scheme: a step toward universal categorization of lymphoma entities? Ann Oncol 1998;9(6):607-12.
12. Harris NL, Jaffe ES, Armitage JO. Lymphoma classification: from R.E.A.L. to W.H.O. and beyond. Cancer: Principles and Practice of Oncology Updates 1999;13(3):1-14.
13. Jaffe ES, Harris NL, Chan JKC. Proposed World Health Organization Classification of Neoplastic Disease of Hematopoietic and Lymphoid Tissue. Am J Surg Pathol 1997;21(1):114-21.
14. Seow A, Lee J, Sng I, Fong CM, Lee HP. Non-Hodgkin's lymphoma in an Asian population: 1968–1992 time trends and ethnic differences in Singapore. Cancer 1996;77(9):1899.
15. Ries LAG, Kosary CL, Hankey BF . eds. SEER cancer statistics review, 1973-1996. National Cancer Institute, 1999; NIH publication No. 99-2789.
16. American Cancer Society. Cancer resource centre, non-Hodgkin's lymphoma. www.cancer.org/cancerinfo (accessed 2006 March 11).
17. Shipp MA, Mauch PM, Harris NL. Non-Hodgkin's lymphomas. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology. 5th ed. Philadelphia: Lippincott-Raven 1997:2165-217.
18. Lin AY, Tucker MA. Epidemiology of Hodgkin's disease and non-Hodgkin's lymphoma. In: Canellos GP, Lister TA, Sklar JL, eds. The lymphomas. Philadelphia: Saunders; 1998:43-61.
19. Dinse GE, Umbach DM, Sasco AJ, Hoel DG, Davis DL. Unexplained increases in cancer incidence in the United States from 1975 to 1994: possible sentinel health indicators? Annu Rev Public Health 1999;20:173.
20. Delves PJ, Roitt IM. The immune system. First of two parts. N Engl J Med 2000;343(1):37.
21. Hockenbery DM, Zutter M, Hickey W, Nahm M, Korsmeyer SJ. BCL2 protein is topographically restricted in tissues characterized by apoptotic cell death. Proc Natl Acad Sci USA 1991;88(16):6961.
22. Ehrlich P. On immunity with specific reference to cell life. Proc R Soc Lond Ser B. 1900; 66:424-48.
23. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975;256:495-7.
24. Multani PS, Grossbard ML. Monoclonal antibody-based therapies for haematologic malignancies. J Clin Oncol. 1998;16:3691-710.
25. Leget GA, Czuczman MS. Use of rituximab, the new FDA-approved antibody. Curr Opin Oncol. 1998;10:548-51.
26. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, *et al*. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 1994;83:435-45.
27. Maloney DG, Press OW. Newer treatments for non-Hodgkin's lymphoma: monoclonal antibodies. Oncology. 1998 (suppl 8):63-76.
28. Maloney DG. Unconjugated monoclonal antibody therapy of lymphoma. In: Grossbard ML, ed. Monoclonal antibody-based therapy of cancer. New York: Dekker; 1998:53-79.
29. Glennie MJ. Overview of monoclonal antibody-based targets for antibody therapy of lymphoma. In: Biological therapy of lymphoma. Baylor-Simmons Cancer Centre. Data from: Barclay AN, Brown MH, Law SKA. The leukocyte antigen facts book. 2nd ed. London: Academic Press;1997:3.
30. Anderson KC, Bates MP, Slaughenhoupt BL, Pinkus GS, Schlossman SF, Nadler LM. Expression of human B cell-associated antigens on leukaemias and lymphomas: a model of human B cell differentiation. Blood. 1984;63:1424-33.
31. Longo DL, DeVita VT Jr, Jaffe ES. Lymphocytic lymphomas. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology. 4th ed. Philadelphia: Lippincott; 1993:1859-927.
32. Maloney DG, Grillo-López AJ, Bodkin DJ, White CA, Liles TM, Royston I *et al*. IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood. 1997;90:2188-95.
33. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME *et al*. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma:

half of patients respond to a four-dose treatment program. J Clin Oncol. 1998; 16:2825-33.
34. Davis TA, White CA, Grillo-López AJ, Velásquez WS, Link B, Maloney DG *et al*. Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: results of a Phase II trial of rituximab. J Clin Oncol. 1999;17:1851-7.
35. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM *et al*. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J M ed 1998;339:21.
36. Coiffier B, Haioun C, Ketterer N, Engert A, Tilly H, Ma D, *et al*. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multi-centre Phase II study. Blood. 1998;92:1927-32.
37. Vose JM, Link BK, Grossbard ML , Czuczman M, Grillo-Lopez A, Fisher RI. Long-term update of a phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. Leuk Lymphoma. 2005 Nov;46(11):1569-73.
38. Maloney DG, Smith B, Appelbaum FR. The antitumor effect of monoclonal anti-CD20 antibody therapy includes direct anti-proliferative activity and induction of apoptosis in CD20 positive non-Hodgkin's lymphoma cell lines. B lood. 1996;88:637. Abstract.
39. Demidem A, Lam T, Alas S, Hariharan K, Hanna N, Bonavida B.. Chimeric anti-CD20 (IDEC-C2B8) monoclonal anti-body sensitizes a B cell lymphoma cell line to cell killing by cytotoxic drugs. Cancer Biother. 1997;12:177-86.
40. Czuczman M, Grillo-Lopez AJ, White CA. Rituximab/CHOP chemoimmunotherapy in patients with low grade lymphoma (LG/F NHL): progression free s urvivals (PFS) after three years (median) follow-up. Blood. 1999:94.Abstract 432.
41. Coiffier B, Lepage E, Briere J , Herbrecht R, Tilly H, Bouabdallah R *et al*. CHOP chemotherapy plus ritux imab compared with CHOP alone in el derly patients with diffuse large B-cell lymphoma. New Engl J Med. 2002;346:235-42.
42. Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, *et al*. Introduction of combined CHO P-rituximab therapy dramatically improved outcome of diffuse large-B-cell lymphoma (DLBC) in British Col umbia (BC). Blood 2003;102:29a Abstract 88.
43. Miller TP, Unger JM, Spier C, Stea B, Cantu E, LeBlanc M *et al*. Effect of adding rituximab t o three cycles o f CHOP plus involved-field radiotherapy for limited-stage aggressive diffuse B-cell lymphoma (SWOG-0014). Blood. 2004;104:49a.
44. National Institute of Clinical Excellence. Technology Appraisal 65, Rituximab for ag gressive non-Hodgkin's lymphoma. www.nice.org.uk. (Accessed 21 March 2006)
45. National Cancer Institute. Tre atment of Common Cancers. Non-Hodgkin's Lymphoma. http://nci.nih.gov/cancertopics/pdq/treatment/adult-non-hodgkins/healthprofessional. (Accessed 21 March 2006)

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