



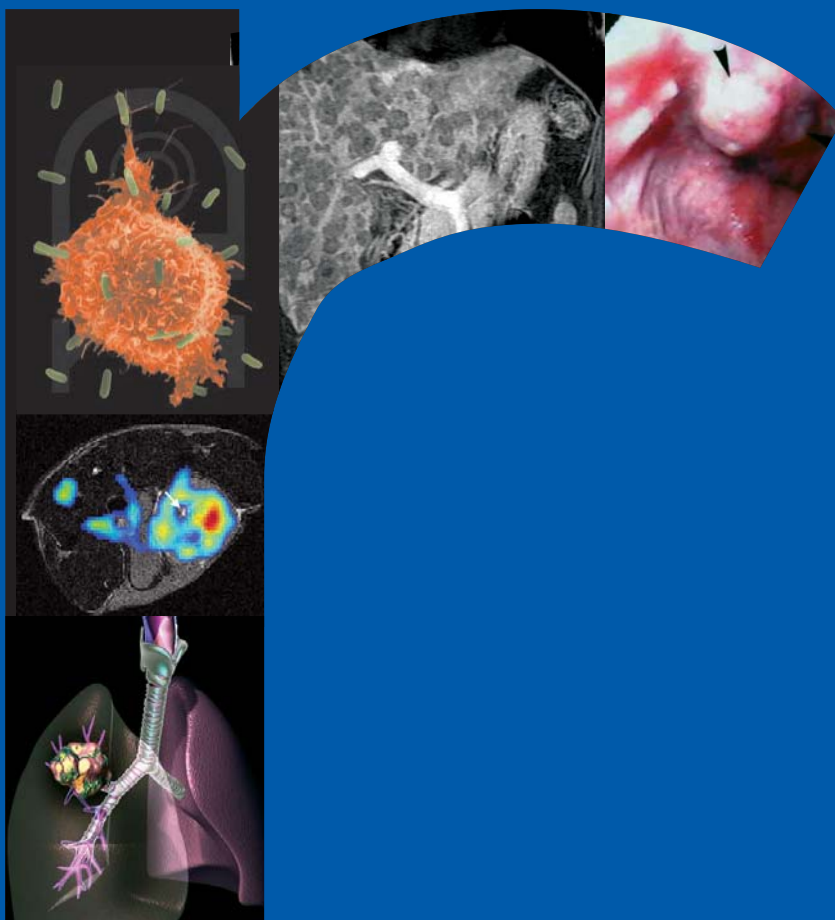
ISSN 0973-9653

CANCER NEWS

VOL 5

NO 5

DECEMBER 2011



**RAJIV GANDHI CANCER INSTITUTE AND
RESEARCH CENTRE**

Website: www.rgci.org

PATRON

Shri B L Joshi

GOVERNING COUNCIL

Chairman: Shri Rakesh Chopra
Vice Chairman: Smt Jyotsna Govil
Hony Secretary: Shri Pramod Maheshwari
Hony Treasurer: Shri O P Nayar
Principal Advisor: Shri K K Mehta

Members

Shri Madan Agarwal
 Shri R K Ahooja
 Shri R N Bansal
 Shri Lalit Bhasin
 Smt Harmala Gupta
 AVM H L Kapur (Retd)
 Dr Sunil Khetrapal
 ACM O P Mehra (Retd)
 Dr K V Swaminathan
 Shri B Swarup
 Representative of LG of Delhi

RESEARCH ADVISORY COMMITTEE

Dr K V Swaminathan
Chairman, RAC
 Prof A B Dey
Prof of Medicine & Research, AIIMS
 Dr K Satyanarayana
Sr DDG Publication & Information, ICMR
 Dr N K Grover
Medical Director, Vinayak Hospital
 Dr A Nandkumar
Sr DDG & Officer-in-Charge, NCRP, ICMR
 Dr Anurag Mehta
Director Laboratory Services, RGCI&RC
 Dr Rama Mukherjee
Managing Director, ARAHC Pvt Ltd
 Director Research RGCI&RC
 Member Secretary, RAC

RESEARCH & ANALYSIS TEAM

Editor: Dr D C Doval
Director Research

Ms Rupal Sinha *Research Officer*
 Mr Saud Azam *Research Officer*
 Ms Atika Dogra *Research Officer*
 Dr Urmi Sarkar *Research Officer*
 Ms Anamika Mishra *Research Officer*
 Ms Swarnima Jaitley *Prin. Research Officer*

Typing AssistanceMr Alok Kumar *Junior Executive***From the Desk of Director Research**

The past decade has witnessed a number of developments in the field of lymphoma. Despite remarkable advances in diagnosis and treatment, the disease continues to rank as a leading cause of cancer-related mortality. The "Special Feature" covers 'Novel Target Agents in Lymphoma'. Molecular and genetic features have already been integrated into diagnostic and therapeutic schemes of various lymphomas. A special gratitude to Dr Shripad Banavali, Head, Dept of Medical Oncology, Tata Memorial Center, Mumbai, for providing a "Guest Article" on 'Molecular Biology and Genetics of Lymphomas'.

"Perspective" gives an overview of 'PET-CT in Lymphoma'. Stem cell transplantation is viable alternative treatment in lymphomas. "In Focus" highlights an evidence based review on 'Hematopoietic Cell Transplantation'. 'Evolving Strategies in Management of Pediatric Non-Hodgkin Lymphoma' is being covered under "Recent Advances".

The Institute is thankful to Dr Reddy's Laboratories Ltd. for supporting this issue of Cancer News. We acknowledge the contributions made by clinicians of the Institute. View and suggestions from readers on Cancer News are welcome.

Wishing our readers a Happy, Prosperous and Healthy New Year 2012!

Dr D C Doval

CONTENTS

- **Special Feature:** Novel Target Agents in Lymphoma [3-5]
- **Guest Article:** Molecular Biology and Genetics of Lymphomas [6-7]
- **Perspective:** PET-CT in Lymphoma [8-9]
- **In Focus:** Hematopoietic Cell Transplantation in Lymphoma: Why & When; Evidence Based Review [10-12]
- **GYNAECON-2011** [12]
- **Research & Development:** HCV Infection & Liver Dysfunction in B-Cell NHL; Key Lymphoma Research Findings; Possible New Drug Targets for DLBCL; Tumor Suppressor Gene Silencing and Lymphoma [13]
- **New Technology:** Adcetris to Treat Two Types of Lymphoma; Breakthrough in Diagnosis of Lymphoma of Skin; Resminostat for Hodgkin's Lymphoma; Second Cancer Risk after Chemotherapy for HL [14]
- **Clinical Trials:** ABVD versus BEACOPP for Hodgkin's Lymphoma; Bortezomib Added to R-CVP for FL; Treatment for Primary Testicular DLBCL; Vaccine for Follicular Lymphoma [15]
- **Watch-Out:** Biomarker Panel for Lymphoma Diagnosis; Expansion of NK Cells and Therapeutic Uses; Method of Treating Mantle Cell Lymphoma; Methods of Use for Cyclophosphamide Analogs [16]
- **Globe Scan:** Soy Intake and Non-Hodgkin Lymphoma (Japan); Farmlife and Lymphoma (New Zealand); Treatment Option for NHL (UK); IMRT for Lymphoma (USA) [17]
- **Recent Advances:** Evolving Strategies in Management of Pediatric Non-Hodgkin Lymphoma [18-19]

This publication aims at disseminating information on pertinent developments in its specific field of coverage. The information published does not, therefore, imply endorsement of any product/process/producer or technology by RGCI&RC.

Printed and Published by: Rajiv Gandhi Cancer Institute & Research Centre, Sector - 5, Rohini, Delhi - 110 085

Printed at: Sagar Printers & Publishers, 1880 Udaichand Marg, Kotla Mubarakpur, New Delhi - 110 003

SPECIAL FEATURE**NOVEL TARGET AGENTS IN LYMPHOMA****Introduction**

Despite remarkable advances in diagnosis and treatment, lymphoma continues to rank as a leading cause of cancer-related mortality. Current treatments for non hodgkin's lymphoma (NHL) are not optimally effective, with relapse and resistance to chemotherapy being common and the risk of secondary malignancies an ongoing concern. Long-term prognosis in patients who relapse with aggressive NHL, such as diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) after induction therapy typically, is dismal. Discovery of new treatments that prolong survival and are less toxic represents an urgent unmet medical need.

In recent years, advances in NHL have produced information critical to our understanding of cell growth, proliferation, and cell death in malignant cells. The intracellular machinery and signaling cascades that are active in lymphomas have been dissected and reveal multiple potential targets for new agents. These advances in our understanding have spawned several clinical investigations of novel agents, several of which now appear to have clinically relevant single-agent activity in malignant lymphoma. This review will focus on some of these exciting novel therapeutic agents.

Immunomodulating Agents

Immunomodulating agents (IMiDs) have both immunomodulatory and anti-angiogenic properties. Lenalidomide and pomalidomide have been shown to decrease cell proliferation. Lenalidomide increases the recruitment of natural killer (NK) cells by stimulating dendritic cells and modifying the cytokine microenvironment. By modulating the immune system through dendritic cells and NK cells, by changing the cytokine milieu, and by their anti-angiogenic effects, IMiDs in combination with rituximab resulted in augmented in vivo anti-tumor effects against B-cell lymphoma.

Several phase 2 trials have been conducted to treat aggressive lymphoma. In the first study which was performed on 49 patients with the most common DLBCL histology (53%), the overall response rate (ORR) was 35% for all patients and 19% for DLBCL.

An interesting finding was observed in the retrospective analysis of the clinical outcomes of 18 patients with DLBCL treated with lenalidomide, germinal center B-cell (9 patients) compared with non-germinal center B-cell (9 patients) phenotype. There was a significant difference in clinical ORR to lenalidomide between patients with non-germinal center B-cell and germinal center B-cell disease (77% vs. 11%). It was associated with an increase in median PFS, 336 days compared with 72 days for patients who were non-germinal center B-cell and germinal center B-cell phenotype, respectively.

Proteasome Inhibitors

The proteasome has been identified as a novel target in cancer cells, given the role it plays in cell cycling, growth, and survival. The proteasome is responsible for the degradation of ubiquitinated proteins, and there are more proteasomes in malignant compared with normal cells. The first proteasome inhibitor, bortezomib (Btz), has become an important treatment in the management of multiple myeloma and has more recently been shown to have activity in lymphoma. A second proteasome inhibitor, carfilzomib, is now being studied in phase 1 and 2 trials.

In a study, Btz as a single agent produced responses in a group of relapsed NHL patients. Of 29 evaluable patients with MCL, the ORR was 41% with 20.5% complete response (CR) and 20.5% partial response (PR). In the other B-cell NHL patient group, 4 of 21 patients responded (19%). In a second trial, of 24 NHL patients who had relapsed after a median of 3 previous therapies, the ORR was 58% with a 50% response in MCL and 77% response in follicular NHL. In a larger study ("Pinnacle") overall responses were seen in 45 of 141 (32%) relapsed MCL patients, with 8% CR/CR unconfirmed and 24% PR. The median time to progression (TTP) was 6.7 months and for responding patients 12.4 months. The results of this trial led to the Food and Drug Administration approval of Btz for treatment of relapsed MCL.

Enzastaurin

The protein kinase C (PKC) and phosphoinositide 3-kinase (PI3K)/protein kinase 3 (AKT) pathways are known to promote tumor-induced angiogenesis and tumor-cell survival and proliferation. It has been reported that PKC-beta expression increases in patients with refractory DLBCL, linking increased PKC-beta expression to decreased patient survival.

In the first trial evaluating the efficacy of a PKC- β inhibitor, enzastaurin, the drug was orally administered as a single agent to 55 patients with refractory DLBCL until disease progression. The treatment was well-tolerated. The overall response rate was reported at 7% (4 of 55 patients), including three complete remissions and one stable disease. Four patients remained free of disease progression for more than 20 months.

Spleen Tyrosine Kinase Inhibitors

Most B-cell malignancies express the B-cell receptor (BCR), which is critical for the survival and proliferation of both murine and human B-cell lymphomas. The primary outcome of BCR signaling activation is spleen tyrosine kinase (Syk) activation. A subset of ABC subtype DLBCL cell lines exhibit coordinate overexpression of the BCR signaling cascade. In such cell lines, targeted inhibition of Syk abrogates BCR signaling and induces apoptosis.

R406 is a potent and selective inhibitor of Syk, and fostamatinib is a prodrug available in oral formulation. A phase 1/2 trial was conducted to evaluate the efficacy of Syk inhibitors as a single agent in patients with refractory B-cell NHL. Dose-limiting toxicity included neutropenia, diarrhea, and thrombocytopenia. In total, 68 patients were enrolled. The overall response rate was evaluated at 23% (one complete and four partial responses in 23 patients).

mTOR Inhibitors

The mammalian target of rapamycin (mTOR) kinase is an essential mediator of growth signaling that originates from PI3K. The PI3K pathway is often deregulated as a result of the mutation or amplification of AKT. mTOR activation by AKT leads to cell proliferation and survival by modulating critical molecules, such as cyclin D1. Rapamycin and the rapalogs are specific inhibitors of mTOR and can induce cell death in vitro. There are four mTOR inhibitors being studied currently: rapamycin, temsirolimus, everolimus, and deforolimus.

Temsirolimus was mainly studied in MCL, but it also shows some activity in DLBCL with an ORR of 28%, a CR of 12%, and a median PFS of 2.6 months. Everolimus (RAD001) has shown activity in a variety of hematological neoplasms. This oral agent was tested in 37 very heavily pretreated aggressive

lymphoma cases. The ORR was 32% (7 of 20 DLBCL). The median duration of response was 5.5 months. These data confirmed that mTOR inhibitors have substantial activity in malignant lymphoma and warrant further studies.

Histone Deacetylase Inhibitors

Over expression of certain genes is often caused by gene deletion or duplication. Expression can be affected by epigenetic factors, such as histone proteins regulated by acetylation. Several groups of histone deacetylase inhibitors (HDACIs) have been developed, and they all show activity in lymphoma, mostly cutaneous. HDACIs have been shown to promote apoptosis and to inhibit angiogenesis.

Bcl-2 Inhibitors

The Bcl-2 family includes proapoptotic and antiapoptotic proteins, and the balance of these can control whether a cell lives or dies. Cancer cells are known to have altered expression of these proteins, and up-regulation of antiapoptotic Bcl-2 proteins is associated with tumorigenesis and resistance to chemotherapy. Inhibition of these antiapoptotic proteins can restore normal apoptosis mediated by caspase activation.

ABT-263 is an oral BH-3 mimetic that inhibits multiple Bcl-2 family proteins, including Bcl-2, Bcl-w, and Bcl-X, all of which are prosurvival molecules found in lymphoma. In a phase 1 study which used 2 dosing schedules, responses (3 PR, 7 major response) were seen in 42 patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), follicular lymphoma (follicular lymphoma), and natural killer (NK)/T-cell lymphoma.

New Agents Targeting DNA Synthesis

Bendamustine: The chemical structure of bendamustine suggests the possibility of both alkylator-like activity as well as that of purine nucleosides. Furthermore, in vitro and in vivo data show noncross resistance to commonly used alkylators, such as cyclophosphamide and chlorambucil. This agent activates p53 dependent stress pathways leading to apoptosis and inhibits mitotic checkpoints. DNA damage is more extensive and it occurs with slower and different DNA repair pathways than other alkylators.

A phase 2 trial of bendamustine in patients with rituximab-refractory or intolerant, indolent, or transformed

lymphoma showed an overall response of 77%. Responses were observed in alkylator-refractory (61%) and fludarabine refractory (62%) patients, confirming the in vitro data that suggested non-cross resistance. Of the 74 evaluable patients, there were 34% CR/CR unconfirmed and 43% PR, with a median response duration of 6.6 months. Bendamustine is now approved for treatment of CLL and more recently, relapsed indolent NHL not responding or progressing within 6 months after rituximab-based therapy.

Pralatrexate: Pralatrexate, like other antifolates, interferes with DNA synthesis and cell replication by reversibly inhibiting dihydrofolate reductase, which prevents formation of necessary purine nucleotides. It is cell cycle specific (S phase). An early study showed pralatrexate to be more effectively internalized in malignant cells than methotrexate as the result of the presence of the reduced folate carrier, which is expressed only in malignant and fetal tissue. Once internalized, it is polyglutamylated, resulting in intracellular accumulation. It is less effective as an inhibitor of dihydrofolate reductase than methotrexate, but because of its greater intracellular accumulation, it has more antitumor activity and theoretically, less toxicity in the normal tissue.

Pralatrexate was studied in a phase 1/2 trial where 20 patients with relapsed/ refractory non-hodgkin and hodgkin lymphoma were treated. The maximum tolerated dose (MTD) was determined to be 30 mg/m² every week for 6 of 7 weeks. Of 4 patients with T-cell disease, all achieved a CR. There was stable disease at best in patients with B-cell disease.

Targeting Regulatory T-Cells with Use of Denileukin Diftitox

Denileukin diftitox (Dd) is a fusion protein composed of IL-2 binding sequences and active fragments of diphtheria toxin. It was approved for treatment of CD 25 positive cutaneous T-cell lymphoma (CTCL) several years ago and is now being investigated in treatment of other lymphomas. Because CD25 positive naturally occurring regulatory T-cells (Treg cells) are highly expressed in B-cell lymphoma and suppress other intratumoral immune cells, the use of Dd to deplete Treg cells may be of clinical benefit.

Dd is approved for use in CD25 positive CTCL that is refractory or persistent after previous therapy. Interestingly, patients whose CTCL was CD25 negative

also had responses (31%), suggesting off-target effects. This agent was, therefore, also tested in B-cell lymphomas. A study showed good response rates (24.5%) in aggressive NHL subtypes, with responses seen in both CD25 negative and CD25 positive tumors.

Use of New Drugs in Rational Combination

As discussed earlier, multiple new agents targeting various pathways important for malignant cell growth have shown clinical activity in lymphoma as single agents. Unfortunately, in these studies a minority of patients responded, and the duration of benefit was short lived. Clearly, combining these agents with other effective therapy may enhance the combination resulting in greater benefit for lymphoma patients.

Combining New Agents with Rituximab: Bendamustine has been combined with rituximab for relapsed indolent lymphoma, and the authors of 2 published trials show high overall response rates of 90-92% with a high CR rate of 41-60%. Similarly, lenalidomide has been added to rituximab and in a study of 30 patients with low-burden indolent lymphoma, an ORR of 86% was seen with 79% CRs. This result supports the hypothesis that IMiDs enhance antibody-dependent cell-mediated cytotoxicity. Dd has been combined with rituximab in patients with relapsed B-cell NHL. Eighty percent of these 38 patients were refractory to rituximab, and still the OR was 32%.

Addition of Novel Agents to Existing Lymphoma Regimens: Proteasome inhibition can be safely added to alkylator-based therapies and several combinations have encouraging results. Combinations include Btz-R-CVP, Btz-R-CHOP, Btz-fludarabine and rituximab, Btz- cyclophosphamide, dexamethasone, rituximab (CyBorD-R), Btz-Hyper-CVAD etc.

Conclusion

It is postulated that many of these novel agents will play an important role in the management of NHL. It is also likely that modern paradigms will evolve in the management of lymphomas. However, we also need to be conscious of potential toxicities and be certain these combinations are safe. With the advent of these novel therapeutic agents, cure in majority of lymphoma patients may soon be a reality.

(Dr Ullas Batra, Consultant, Dept of Medical Oncology)

GUEST ARTICLE

MOLECULAR BIOLOGY AND GENETICS OF LYMPHOMAS

Significant advances have been made in the understanding of molecular biology and genetic diversity of lymphomas. Molecular and genetic features have already been integrated into diagnostic schema of various lymphomas and are being exploited as potential target for specific therapies in different molecular subtypes of lymphoma. Detailed cytogenetic analysis and, more recently, the application of high throughput technology, such as gene expression profiling (GEP), have deepened our understanding of molecular background of lymphoma genesis. We discuss important genetic features of Diffuse Large B cell Lymphoma (DLBCL), Burkitt's Lymphoma (BL), Follicular Lymphoma (FL) and Mantle Cell Lymphoma (MCL) in this review.

Diffuse Large B Cell Lymphoma

DLBCL is the most common lymphoma affecting adults and displays a striking heterogeneity at the clinical, genetic, and molecular level. Commonly observed genetic abnormalities that likely contribute to pathogenesis include translocation of BCL-6, BCL-2, cMYC and FAS (CD 95) mutation and aberrant somatic hypermutation (SHM) as summarized in table below.

Table: Major Recurring Genetic Events in DLBCL

Genetic defect	Frequency	Location	Mechanism of deregulation
BCL6	35%-40%	3q27	t(3; . . .) and SHM
BCL2	t(14; 18)-13% amplification 24%	18q21	t(14; 18) and gene amplification
cMYC	15%	8q24	t(8; . . .) and SHM
FAS(CD95)	20%	10q24	Death domain mutations, ?SHM
SHM	45%	Physiologic: Ig(v), FAS, BCL6 Aberrant: BCL6, PIM 1, cMYC, PAX5, RhoH/TTF, ?FAS	SHM
p53	16%	17p	Mutation, deletion

Besides the above, a few other important abnormalities are observed less frequently.

REL: REL encodes a component of nuclear factor kappa β (NFK β) heterodimer and amplification of chromosome 2 p 13 (seen in 14% of DLBCL patients) is associated with increased NFK β activity.

Certain chromosomal imbalances have been observed in DLBCL frequently and some of which may influence prognosis. Poor outcomes have been associated with abnormality of 1q, 5, 7q and 14 where gain of 3p has been associated with improved prognosis. Role of these abnormalities in pathogenesis of DLBCL is unclear.

Gene Expression Profiling in DLBCL: GEP had helped to highlight similarities between subset of tumors and normal B cells (cell of origin signatures), identifying features associated with unfavorable responses to empiric combination chemotherapy (eg. GC like versus activated B cell like etc) and define robust and highly reproducible DLBCL subtype with comprehensive transcriptional signatures. Examination of molecular signature of DLBCL subtype with adverse outcomes has revealed genes and pathways associated with poor response to treatment. Few of them (eg. protein kinases C β (PKC β), cAMP-specific phosphodiesterase PDE4B and NFK β) have been credentialed and targeted for possible therapeutic interventions.

Burkitt's Lymphoma

The cytogenetic hallmark of all variants of Burkitt's lymphoma is the translocation involving MYC gene. This leads to the deregulated expression of MYC which is transcription factor regulating different genes involved in proliferation, differentiation and apoptosis. MYC mutations are also frequently detected in BL and some of these have been shown to have increased transforming activity. Diversity of breakpoint localization in different subtypes of Burkitt's lymphoma suggests that formation of the translocation takes place at different stages of B-cell development. Secondary genetic alterations are relatively less common in BL.

Gene expression profiling studies further characterized sporadic BL on the molecular level. GEP have identified a subset of cases diagnosed as DLBCL according to current WHO criteria, but with a typical gene expression profile of BL. Role of intensified BL, like chemotherapy, in this subtype needs to be examined in clinical trials. GEP studies have constructed molecular classification of BL based on the expression of certain prominent gene expression signatures. Besides MYC and its target genes, a distinct subset of genes expressed in normal germinal center of B cell was found to be expressed at higher levels in BL while expression of MHC class 1 genes and NFK β target genes was reported to be lower in BL compared to DLBCL.

Grey Zone Between Burkitt's Lymphoma and Diffuse Large B Cell Lymphoma

Not only the morphological and immunophenotypic, but cytogenetic features also overlap between DLBCL and BL. However, the precise discrimination between DLBCL and BL is of significant clinical importance. Although GEP delineates BL on the molecular level from DLBCL, at the same time it broadens this diagnostic category, because gene expression defined BL group also includes some cases with morphological features of DLBCL. Such grey zone lymphoma shows more frequent cMYC breakpoints when compared to DLBCL and occasionally involving non Ig partner in this translocation.

Follicular Lymphoma

Although classified as indolent, small subset of patient have a poor prognosis because of progressive disease or transformation to an aggressive lymphoma.

Hallmark cytogenetic alteration of FL, t(10;18) (seen in 85% cases) juxtaposes BCL-2 gene to IgH enhancer, leading to constitutive expression of BCL-2, leading to impaired apoptotic signaling. This alteration alone is not sufficient to produce a fully malignant phenotype and at least one secondary cytogenetic alteration is detected in majority of cases of FL.

Fifteen percent of cases of FL do not over express BCL-2 and pathogenetic mechanism is poorly understood. Similarly, recurrent cytogenetic abnormalities associated with transformation have been identified but pathogenesis needs to be elucidated.

Gene Expression Profiling in Follicular Lymphoma: GEP studies have suggested that besides intrinsic features of malignant cells, tumor infiltrating cells contribute to the outcome of FL patients. These different gene expression signatures (IR 1-gene coding T cell marker and IR 2-gene expressed by follicular and dendritic cells) were associated with good and poor prognosis respectively. These signatures have fueled the investigators to study the role of immunohistochemistry in predicting the prognosis of individual patient.

Mantle Cell Lymphoma

Mantle Cell Lymphoma (MCL) has recently become the target of much basic research because of its unique outcome with current therapeutic approach.

t(11;14) resulting in over expression of cyclin D1 alone is not sufficient for lymphomagenesis (summarized in figure). MCL carries a high number of secondary

molecular alterations. High degree of genetic instability that is characteristic of MCL, suggests alteration of DNA damage response pathway as another pathogenetic mechanism in this lymphoma. Studies have shown frequent inactivation of ATM gene (10-75% cases), (rarely down regulation of its downstream target CHK) as well as inactivation of TP 53 and overexpression of MDM2 (negative regulator of p53), later particularly in blastoid morphology.

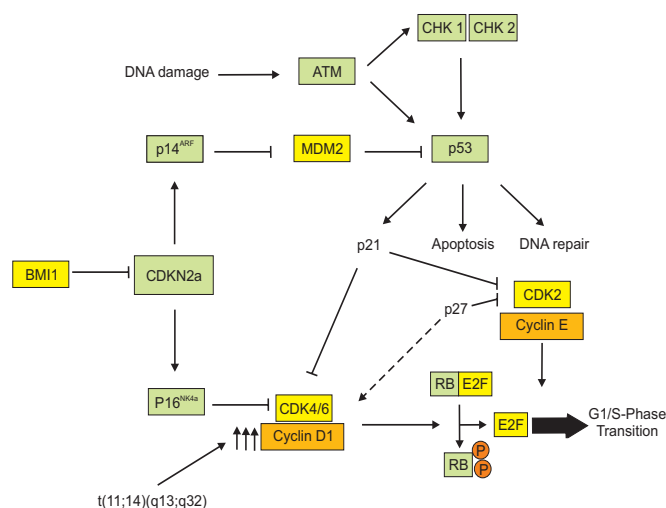


Figure: Overview of perturbed cell cycle regulation and DNA damage response in mantle cell lymphoma. Molecules with increased expression or function in MCL are colored in orange; molecules with decreased expression or function are colored in green. The characteristic translocation t(11;14)(q13;q32) leads to constitutive overexpression of cyclin D1 and, thus, to inappropriate cell cycle progression in the absence of mitogenic stimuli.

Gene Expression Profiling in MCL: GEP studies have revealed two important things in MCL. First is identification of overexpression of cyclin D2/ D3 in cyclin D1 negative MCL and second GEP defined signature predictive of outcome of MCL termed proliferative signature.

Summary

We have made a significant progression in our understanding of the molecular biology and the definition of underlying genetic alteration in lymphoma. Such understanding has revealed important targets for therapeutic intervention and is contributing in diagnosis and prognostication of different molecular subtypes of lymphomas.

(Dr Bahusaheb Bagal, Assistant Professor; Dr Shripad Banavali, Professor & Head; Dept of Medical Oncology, Tata Memorial Center, Mumbai)

PERSPECTIVE

PET-CT IN LYMPHOMA

Introduction

The lymphoproliferative disorders which are broadly divided into Hodgkin's & non-Hodgkin's lymphoma (NHL) as a group, account for one of the common malignant diseases of the general population. Although the annual incidence of NHL is increasing, the 5-year survival rate is improving in conjunction with constant refinements in clinical management aimed at achieving the highest remission rates with the lowest risk of treatment related complications. Integration of PET-CT into routine oncologic imaging has further improved baseline staging and facilitated functional evaluation of disease behavior, metabolic response to therapy and earlier detection of disease recurrence. Consensus guidelines have been published that set out updated response criteria for evaluation of response to therapy in tumors & PET-CT is assigned a central imaging role. Optimal management of lymphoma requires that the interpreting physician understands the natural history of lymphoma, pit falls of imaging and interpretation based on multiple factors. This includes the type of lymphoma, time of scan, coexisting other condition and disease pattern recognition. Thus the most effective use of PET-CT requires multi-disciplinary collaboration between different clinical modalities.

Detection

PET can be useful only in cases wherein the absence of any clinically palpable peripheral lymphadenopathy, suitable sites of biopsy can be localized with this modality. In comparison to CT, PET-CT has the advantage of depicting sites of lymphoma that are both accessible and metabolically active and therefore most likely to yield a true positive outcome.

Initial Staging

Interpretation of PET being independent of size criteria, has greater sensitivity and accuracy of delineating diseased lymphnodal sites accurately and also has greater sensitivity of detection of sites of extra nodal involvements. PET can indicate the overall disease burden by the level of metabolic activity of lymphomas which co-relates with aggressiveness of disease and LDH levels and is a prognostic predictor. In general, indolent follicular

lymphoma is associated with a low grade metabolic activity and a low LDH level whereas higher intensity of metabolic activity is seen in more aggressive lymphoma with higher LDH levels. Low grade lymphoproliferative disorders include both B-Cell and T-Cell disorders. These lesions typically have low grade or no abnormal metabolic activity.

Unexpected sites of nodal or extranodal involvement can thus be delineated based on the aggressiveness of disease. Certain lymphomas are generally difficult to detect with routine PET-CT protocols. These include primary CNS lymphoma, testicular or gastric lymphoma.

These might require modification of acquisition techniques. Definite bone marrow involvement can be detected with PET imaging during staging in a large number of cases away from the accessible biopsy site and can give clue to the appropriate site of biopsy.

Assessment of Response

Initially evaluation of response in lymphomas was limited to the size reduction seen in CT scans. Residual lymphnodal mass was common and it was difficult to differentiate post-treatment fibrosis from active disease. PET can differentiate between these two and helps in determining the extent of residual disease. Extent of metabolic response helps in prognosticating the disease and helps in separating responders from non-responders effectively. It is important to note that not only PET negativity of lesions is important but also how soon it becomes negative is more important in prognostication and risk stratification. Most frequent difficulties encountered in interpretation of post-treatment PET-CT scans include differentiating residual FDG uptake due to lymphoma from metabolic activity due to post-treatment inflammation, co-existing infective and normal physiologic metabolic activity. Therefore, timing of scan is important to differentiate these parameters. It is also important to know about the patients clinical condition, extent of neutropenia, other supportive treatments in interpreting these scans accurately.

Detection of Recurrence & Follow Up

Evidence suggests that metabolic imaging can help in detection of early recurrence. Comparison with serial studies are mandatory in increasing the specificity of detection. In situations a histological proof may be required in case the site of suspected recurrence is different from the original site of disease. PET is useful as a single modality in routine surveillance of these groups of patients.

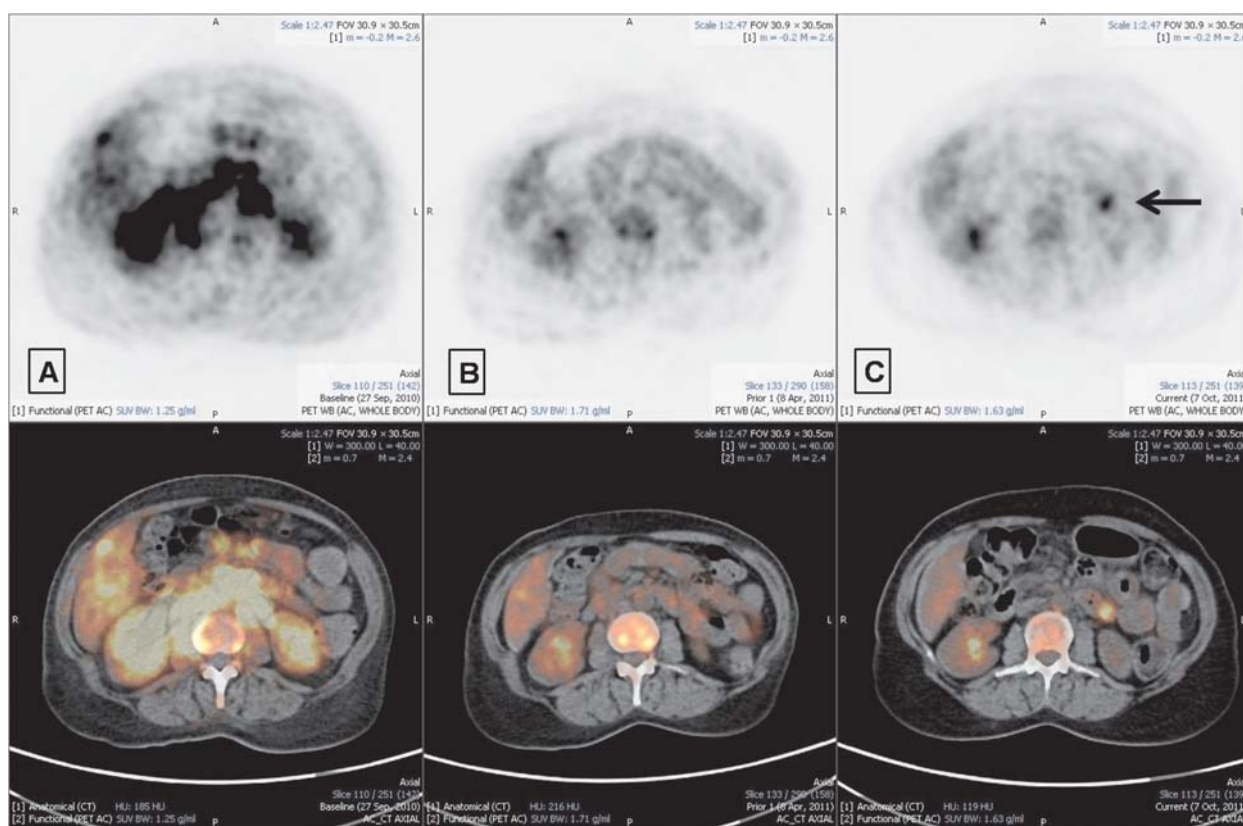


Fig: ^{18}F FDG PET-CT study showing extensive metabolically active lymphonodal disease during staging (A) and complete metabolic response at the end of treatment (B). Follow up study (C) shows evidence of early metabolic recurrence in one of the areas of initial disease.

Utility in Stem Cell Transplantation

There is evidence that PET-CT can be used for selection of patients for stem cell transplantation. Persistent metabolically active disease after salvage chemotherapy before stem cell transplantation is predictive of poor progression free survival.

Evidence Based Recommendation

Proper staging & specificity of the investigative modality is very important during staging for individualization of therapy and prevention of excessive unwarranted treatment which may lead to complications. There is moderate evidence the PET can alter management if used during staging and should be obtained routinely in addition to conventional workup. It is considered more valuable in Hodgkin's disease (HD) and early stage aggressive non Hodgkin's lymphoma (NHL). PET was considered less useful in indolent NHL. There is moderate evidence regarding the usefulness of role of PET in evaluating marrow infiltration and is recommended in staging and restaging as it can detect multifocal sites of bone marrow involvement. In restaging, suspected recurrence, assessing residual mass or assessing progression after completion of initial treatment,

there is moderate evidence to suggest that PET enables the administration of treatment appropriate to the level of disease, ultimately leading to improved patient outcomes and is thus recommended. Detection of early and even preclinical relapse is feasible with PET for administering appropriate salvage therapy at the appropriate time.

Conclusion

PET-CT is the best discriminator of disease load. It does away with the need for multiple, many time needless, investigations. It can reduce the number of futile unwarranted interventions, over and under treatment. It justifies the overall cost effectiveness by saving many man hours and money in certain situations.

PET-CT in lymphoma is of value in initial staging of high risk patients. It helps in predicting response, enabling the treating oncologist to switch early for non-responders. It leads to better stratification for optimal treatment, accurate identification of ineffective treatment, early recurrence evaluation & ongoing risk stratification and management. From the perspective of a practicing oncologist, it substantially improves the management of lymphomas.

(Dr PS Choudhury, Director, Dept of Nuclear Medicine)

IN FOCUS

HEMATOPOIETIC CELL TRANSPLANTATION IN LYMPHOMA: WHY & WHEN; EVIDENCE BASED REVIEW

Lymphoma is the fifth leading cancer in human beings and constitutes approximately 4% of all cancers. Annual incidence is estimated at 150-227 per million in various registries. Lymphoma is broadly classified into Hodgkin Lymphoma and Non Hodgkin lymphoma.

Non Hodgkin Lymphoma (NHL)

The classification of lymphoma continues to evolve, with more than 30 subtypes described in the new WHO Lymphoma Classification. The subtypes are categorized based on B-cell or T-cell and natural killer cell lineages, and are further characterized by their histologic, immunologic, genetic, and clinical features. The majority of lymphoid malignancies are of B-cell lineage with diffuse large B-cell lymphoma (DLCL) and follicular lymphoma (FL) comprising over half of all lymphomas.

Survival rates for NHL vary widely, depending on the lymphoma type, stage, age of the patient, and other variables. According to the American Cancer Society, the 5-year relative OS rate for patients with NHL is 63%. A significant proportion of patients still fail to attain a complete remission or relapse after attaining a remission. A variety of salvage regimens has been used for these patients, but results of treatment with these regimens are disappointing, and only a few patients achieve long-term disease-free survival (DFS).

Role of Hematopoietic Cell Transplantation

The landmark Parma trial proved the superiority of autologous hematopoietic cell transplantation (HCT) for patients with chemotherapy-sensitive, diffuse aggressive lymphoma compared with standard decadron, cytarabine, and cisplatin (DHAP) therapy. Relapse less than 12 months from diagnosis and elevated lactate dehydrogenase at relapse are predictors of poorer survival in patients in the trial. The International Prognostic Index (IPI) score at the time of relapse is predictive of outcome in patients receiving additional DHAP therapy, but not for patients receiving heterotopic liver transplantation (HLT) and autologous HCT.

As appreciated from the Parma trial, a significant proportion of patients with relapsed or refractory diffuse aggressive lymphoma will not proceed to autologous HCT, most often due to chemotherapy resistant disease,

but also due to intolerance of salvage therapy or ineligibility due to comorbidities, age, bone marrow or CNS involvement. An Italian Intergroup risk assessment for patients with first relapse of DLCL indicated that only 20% of relapsed patients received HLT and autologous HCT.

Efforts to improve the outcome of the relapsed, refractory diffuse aggressive lymphoma patients include the application of immunotherapy in the peritransplant period, such as radiolabelled antibodies, more effective salvage chemotherapy, mobilization of tumor-free grafts, more effective preparatory regimens, post-transplant immunotherapy, and allogeneic HCT.

The ideal approach to the use of rituximab or radiolabeled antibody therapy for the patients proceeding to HCT is yet to be determined, emphasizing the continued need for well-designed and appropriately conducted clinical trials. The CORAL study initially compared treatment with R-ICE (rituximab, ifosfamide, etoposide, carboplatin) vs R-DHAP (rituximab, dexamethasone, cytarabine and cisplatin) and showed the regimens to be comparable, although R-ICE had fewer serious adverse events. Next, patients were randomly assigned to maintenance rituximab or observation following autologous stem cell transplant (ASCT). No differences were observed between the arms in terms of event free survival (EFS), progression free survival (PFS), or overall survival (OS).

A meta-analysis of randomized trials evaluating the use of HLT and autologous HCT as first-line treatment for patients showed no conclusive benefit in EFS or OS for patients receiving HLT and autologous HCT. The benefit of consolidation with HLT and autologous HCT after R-CHOP chemotherapy is demonstrated in Southwest Oncology Group-led S9704 phase III trial for advanced stage H-Int and High IPI diffuse aggressive NHL. Early autotransplant improves PFS for responders, including those induced with R-CHOP, with a stronger outcome seen for those with High IPI grade.

In general, the role of allogeneic HCT for patients with DLCL has been limited. Comparisons of outcomes of myeloablative allogeneic HCT with those after autologous HCT found decreased relapse rates with allogeneic HCT but increased treatment-related fatalities. The use of reduced-intensity conditioning (RIC) has resulted in a substantial reduction of transplant-related fatalities. Baron et al recently published a report demonstrating 31% 3-year survival with allogeneic HCT using RIC in patients with aggressive lymphomas who had previously experienced treatment failure with autologous HCT. Given

the poor prognosis of such patients, this outcome raises the possibility of a broader role of RIC followed by allogeneic transplantation for aggressive lymphomas.

On the basis of retrospective studies and at least one prospective randomized trial, autologous transplantation for patients with relapsed FL seems to extend DFS and OS. Whether patients with recurrent FL can be cured using autologous HCT is unsettled, with at least one study showing a late plateau in the survival curve of patients undergoing transplantation for relapsed disease. The role of autologous HCT for FL in first remission has been the subject of at least 3 randomized trials. All three showed improved DFS with transplantation, but none showed improved OS at present. Results after further follow-up will be of great interest, but given the large number of emerging therapies for FL, including alternative antibodies, vaccines, and radio-immunoconjugates, it seems unlikely that autologous HCT will assume a large role in initial therapy.

Because of a high incidence of transplant-related toxicities, allogeneic transplantation using high-dose preparative regimens has generally been limited to patients with advanced disease. More recently, encouraging results have been reported with the use of RIC followed by allogeneic transplantation in patients with recurrent FL. The Seattle group presented data on 46 patients with FL, median age of 54 years, who had received an average of six prior regimens. The 3-year estimated OS and PFS rates were 52% and 43%, respectively. Khouiri et al reported even more impressive results, albeit in a group of patients treated earlier in their disease course, with an 85% 3-year DFS rate and an 88% OS rate among 47 patients.

The role of HCT in less common lymphomas, such as mantle-cell lymphoma (MCL) and T-cell lymphoma, is less clear, largely because of difficulties in performing broad phase II and randomized phase III studies on these rarer histologic subtypes. National Comprehensive Cancer Network (NCCN) recommends autologous HCT as consolidation for MCL and Alk negative T-cell lymphoma after initial therapy as these patients are improving with chemotherapy alone. Autologous HCT using a novel preparative regimen that includes high-dose I-131 tositumomab has shown promise in recurrent MCL. A single randomized trial of autologous HCT as part of initial therapy of MCL has been conducted. It showed that HCT significantly prolonged DFS, with a less apparent impact on OS, in part because autologous HCT was used as salvage therapy for some of the control group.

MCL seems to be quite sensitive to a graft-versus-tumor effect and early results of reduced-intensity transplants for recurrent disease show considerable promise. Although data are limited, encouraging results have also been reported with allogeneic HCT using RIC in peripheral T-cell lymphomas.

Hodgkin Lymphoma (HL)

More than 50% of HL patients, including those with advanced disease, can be cured with a wide variety of chemotherapy regimens. There has been a dramatic decline in HL mortality, and the 5-year survival rate is now approximately 85%. A major focus of new treatment regimens involves the reduction of late toxicities of HL treatment. Although most patients with HL are cured with initial therapy, a significant proportion of patients still fail to attain a complete remission or relapse after attaining a remission. A variety of conventional-dose second-line (salvage) regimens has been used for these patients, but results of treatment with these regimens are disappointing, and only few patients achieve long-term DFS.

Adverse prognostic factor—autologous hematopoietic cell transplantation for HL:

- Short initial remission (<12 months)
- Systemic symptoms at relapse
- Bulky or “nonminimal” disease at transplant
- Extranodal disease at relapse or at transplant
- Extensive therapy before transplant
- Poor performance status
- Chemotherapy resistance

Role of Hematopoietic Cell Transplantation

The poor results of conventional-dose salvage therapy for relapsed and refractory HL has led to the use of high-dose therapy followed by autologous bone marrow transplantation (BMT) and peripheral blood hematopoietic cell transplantation for these patients. This approach is based on the steep dose-response curves exhibited by several drugs, and radiation therapy, and the fact that dose-limiting toxicities are often related to myelosuppression.

HL is the third most common indication for autologous HCT after multiple myeloma and NHL. Two randomized trials—A British National Lymphoma Investigation trial and The German Hodgkin’s Lymphoma Study Group and the European Group for Blood and Marrow Transplantation—have compared the results of conventional-dose salvage chemotherapy with autologous HCT for relapsed and refractory HL. Both

trials closed early because of poor accrual as some participants preferred autologous BMT and refused randomization. The 3-year EFS was very significantly higher in transplanted patients, compared with salvage chemotherapy only. The risk of disease progression was also significantly lower in transplanted patients, although differences in OS were not statistically significant.

The role of allogeneic HCT for HL is controversial. Results of high dose allogeneic HCT are poor, although most of patients were extensively pretreated and with advanced chemoresistant disease. Several groups of investigators have explored the use of RIC allogeneic HCT for HL to exploit potential graft-versus-Hodgkin's effects and to reduce transplant-related mortality. These studies have shown the feasibility of this approach in patients who have relapsed after autologous HCT, and in patients who are not candidates for allogeneic HCT using conventional myeloablative regimens.

Potential timing of autologous hematopoietic cell transplantation for Lymphoma:

- Failure to attain initial complete remission
- Primary refractory disease
- First partial remission
- First relapse
- Second or subsequent relapse
- First remission (in highly selected poor prognostic patients & poor risk histological subtype)

(Dr Shishir Seth, Consultant, Hemato-Oncology & Bone Marrow Transplant)

GYNAECON-2011

GYNAECON-2011 organized by Rajiv Gandhi Cancer Institute & Research Center (RGCI&RC), Delhi on 1st & 2nd Oct 2011, focused on "Recent Advances & Controversies in Gynae Cancer". The CME and live surgical workshop was attended by 100 delegates from all over the country.

The live operative session was performed by Dr Kenneth D Hatch, Professor, Dept of Obstetrics/ Gynaecology, University of Arizona School of Medicine, USA and Dr Sudhir Rawal, Organizing Chairperson and Director, Surgical Oncology, RGCI&RC. The inaugural function was presided over by Mr RK Chopra, Chairman, Mr DS Negi, CEO, Dr Rawal and Dr AK Dewan, Medical Director, RGCI&RC.

The scientific session covered "Early Diagnosis of Ca Cervix and Role of HPV" by Dr N Bhatla, Professor, AIIMS; video presentation by Dr Hatch on "Role of Exenteration in Gynaecological Cancers"; debate on "NACT followed by Radical Hysterectomy as Treatment of Choice in Locally Advanced Ca Cervix" by Dr Hatch and Dr Sheh Rawat, Sr Consultant, Radiation Oncology, RGCI&RC; video presentation on "Retroperitoneal Lymphnode Dissection in Gynae Cancer" by Dr Rama Joshi, Sr Consultant, BLK Hospital, Delhi; and panel discussion on carcinoma endometrium moderated by Dr Uma Singh, Professor, CSMMU, Lucknow.

The second day included sessions on "Role of Intraperitoneal Chemotherapy in Ca Ovary" by Dr Hatch; "Role of Fertility Sparing Surgery in Ca Ovary" by Dr Neeta Singh, Professor, AIIMS, Delhi; and "Dissecting Ureter in Radical Hysterectomy" by Dr Hatch; panel discussion on Controversies in Ca Cervix (Surgery vs Radiation) coordinated by Dr Sanjiv Misra, Professor, CSMMU, Lucknow; debate by Dr Hemant Tangaonkar, Professor, TMH, Mumbai in favour of and by Dr Lalit Kumar, Professor, IRCH, Delhi against the concept of "NACT should be given to all Ca Ovary patients". "Role of Bowel Resection and Peritoneal Stripping in Ca Ovary" was discussed by Dr SP Jaiswar, Professor, CSM Medical University, Lucknow; and Dr Manoj Sharma, Professor, MAMC, Delhi, spoke on management of gynae oncology emergencies. "Impact of Obesity in Surgical Treatment of Gynecological Cancers" was also discussed. This CME apprised the participants with the recent trends in gynecological onco surgeries.

(Dr Shveta Giri, Consultant; Dr Rupinder Sekhon, Sr Consultant; Dr Sudhir Rawal, Director, Dept of Surgical Oncology)



MEDRECON 2012
12th Annual National Conference



**Modern Trends and Techniques in
Medical Records & Statistics**

3rd & 4th February 2012

Organized by:

Health Record Association of India

&

**Rajiv Gandhi Cancer Institute & Research Centre
Sector-5, Rohini, Delhi-110085**

Tel: 011-47022139, Fax: 011-27051037

Mob: 9899377540

Email: medrecon2012@rgci.org

Website: www.rgci.org

RESEARCH & DEVELOPMENT

HCV Infection & Liver Dysfunction in B-Cell NHL

Scientists from National Institute for Health, Migration and Poverty, Italy, have evaluated the hepatitis C virus (HCV) infection prevalence and liver dysfunction in a cohort of B-cell Non-Hodgkin's Lymphoma (NHL) patients treated with immunochemotherapy. The study spanning from January 2006 to December 2009, covered 207 consecutive NHL patients treated with chemotherapy without rituximab (CHOP) or with rituximab (R-CHOP). Screening for HCV infection and baseline liver function tests were performed in all patients. The prevalence of HCV infection was 9.2% and higher than that observed in the general population in Italy (3%). Among the HCV-infected subjects, the incidence of hepatitis flares was 26.3% vs 2.1% among the HCV-uninfected individuals. Liver dysfunction can also occur as a consequence of rituximab-containing regimens in HCV-infected patients with NHL. Amongst the cases, no patient treated with chemotherapy without rituximab developed hepatitis flares. Therefore, the assessment of liver function and the screening of all patients with NHL for HCV infection before starting chemotherapy and monitoring of liver function tests and HCV-RNA serum levels during treatment are recommended.

(Scand J Infect Dis, Sep 12, 2011)

Key Lymphoma Research Findings

According to a new study conducted at BC Cancer Agency (BCCA) and Simon Fraser University, two-thirds of newly identified mutated genes are in some way linked to lymphoma. The report indicates that two newly discovered lymphoma related genes enable cancer cells to grow rapidly despite the body's regulatory systems. Fifty BCCA scientists discovered 109 genes with recurring mutations while they were in the process of sequencing the whole genomes of over 100 diffuse large B-cell lymphoma tumors. They then identified 26 of the repeatedly mutated genes as contributors to the disease. The study notes that the mutations inactivate MLL2 which usually works as a tumor stopping gene and thereby allows for the cancer cells to develop more quickly. The findings may help predict how individual lymphoma tumors will react to different treatments.

(Nature, Aug 18, 2011)

Possible New Drug Targets for DLBCL

Researchers at the University of Maryland School of Medicine, USA, have discovered a novel interaction between two proteins involved in regulating cell growth that could provide possible new drug targets for treating diffuse large B-cell lymphoma (DLBCL), the most common type of non-Hodgkin's lymphoma (NHL). The scientists report to have found a complex molecular and functional relationship between ERK (extracellular signal-regulated kinase), a protein that helps to regulate cell proliferation and survival, and CHK2 (checkpoint kinase 2), a protein that is involved in the cellular DNA damage response. They also demonstrated, for the first time, elevated levels of both proteins in DLBCL cells, compared to non-cancerous cells. Based on the findings, a combination therapy targeting both ERK and CHK2 could offer a potential new approach to treating DLBCL. These findings provide valuable new insight into the molecular make-up of this cancer that may lead to new targeted drug therapies.

(Univ of Maryland School of Med, July 20, 2011)

Tumor Suppressor Gene Silencing and Lymphoma

A team of scientists at the University of Pennsylvania has found that a cancer-causing fusion protein works by silencing the tumor suppressor gene IL-2R common gamma-chain (IL-2R γ). The team looked at a fusion protein called NPM-ALK. Anaplastic lymphoma kinase (ALK), which physiologically is expressed only by neurons in fetal life, causes cancer when it is mistakenly expressed in non-neural tissues as a fusion protein with nucleophosmin (NPM) and other partners. NPM-ALK works by silencing the tumor suppressor gene IL-2R γ . The team found that IL-2R γ expression is inhibited in T-cell lymphoma cells expressing NPM-ALK as a result of epigenetic silencing. Silencing of the IL-2R γ promoter via methylation is induced in malignant T-cells by NPM-ALK by activating another protein called STAT3. When IL-2R γ is expressed, NPM-ALK disappears from the cancerous T-cells, and they eventually die. This approach could potentially complement inhibition of fusion protein activity as is routinely done for BCR-ABL in chronic myelogenous leukemia and experimentally for ALK in lung carcinoma, lymphoma and other malignancies expressing ALK. The results suggest new targets for lymphoma and other types of cancer.

(Medical News Today, Aug 11, 2011)

NEW TECHNOLOGY

Adcetris to Treat Two Types of Lymphoma

The US Food & Drug Administration (FDA) approved Adcetris (brentuximab vedotin) to treat Hodgkin Lymphoma (HL) and systemic Anaplastic Large Cell Lymphoma (ALCL) under its accelerated approval program. Adcetris is an antibody-drug conjugate, allowing the antibody to direct the drug to a target on CD30 cells. Adcetris is to be used in patients with HL whose disease has progressed after autologous stem cell transplant or after two prior chemotherapy treatments. It may also be used in patients with ALCL whose disease has progressed after one prior chemotherapy treatment. The effectiveness of Adcetris in patients with HL, and ALCL was evaluated in single-arm trials involving 102 and 58 patients respectively. Complete or partial response was achieved in 73% of patients receiving Adcetris for HL and on average, these patients responded to the therapy for 6.7 months. Of the patients receiving Adcetris for ALCL, 86% experienced either a complete or partial response and responded on average for 12.6 months. Adcetris is new FDA approved treatment for HL since 1977 and first specifically indicated to treat ALCL.

(US FDA, Aug 20, 2011)

Breakthrough in Diagnosis of Lymphoma of Skin

Scientists from LEO Pharma, Exiqon, the University of Copenhagen, Gentofte Hospital and Rigshospitalet (Copenhagen University Hospital) have identified diagnostic biomarkers in the skin which make it possible to distinguish between lymphoma of the skin and chronic skin diseases like psoriasis, eczema and atopic dermatitis. Lymphoma of skin is difficult to diagnose as it can easily be confused with eczema, psoriasis or a fungal infection. Today no tests are available that can distinguish between malignant lymphoma and chronic skin inflammation at an early stage. By examining 200 patients with different types of skin diseases, researchers have demonstrated that the level of three types of microRNA in the skin makes it possible to determine with 95% accuracy, whether a rash is due to lymphoma of skin or a chronic skin disease. This discovery is a major breakthrough that will make it possible to diagnose lymphoma of the skin much sooner and with greater accuracy to the benefit of patients worldwide.

(LEO Pharma, Sep 5, 2011)

Resminostat for Hodgkin's Lymphoma

US Food & Drug Administration (FDA) has granted orphan drug designation to the oncology compound resminostat of 4SC AG in Hodgkin's lymphoma (HL). Resminostat was recently granted orphan drug designation by the FDA in another oncology indication, hepatocellular carcinoma (HCC). The oral pan-histone-deacetylase (HDAC) inhibitor resminostat is currently being developed in three different oncology indications: HCC, colorectal cancer, and HL. HDAC inhibitors modify the DNA structure of tumor cells to cause their differentiation and programmed cell death (apoptosis) and are therefore considered to offer a mechanism of action that has the particular potential to halt tumor progression and induce tumor regression. In a Phase II SAPHIRE study evaluating resminostat as a third-line treatment in relapsed/refractory HL patients which met its primary endpoint, showed a 33.3% overall response rate and 54.5% of patients achieving a clinical benefit from the treatment with resminostat. Orphan drug designation is granted by the FDA to promote the development of products that may offer therapeutic benefits for diseases affecting less than 200,000 people in the USA.

(4SC AG, Sep 26, 2011)

Second Cancer Risk after Chemotherapy for HL

Researchers from the Institute of Cancer Research, UK, have analyzed the effects of chemotherapy and radiotherapy in patients with Hodgkin's lymphoma (HL) to determine the risk of developing a second cancer among these patients compared to the general population. They followed 5,798 British HL patients, treated with chemotherapy in Britain from 1963-2001. Among these, 3,432 patients had also received radiotherapy along with chemotherapy. It was found that of the entire cohort, 459 people were found to have developed a second cancer, like Lung cancer, Non-Hodgkin's lymphoma and Leukemia. Following chemotherapy alone, the risk of secondary cancer peaked between 5 and 9 years after treatment ended, but when a patient received chemotherapy and radiotherapy, the risk of secondary cancer remained high for at least 25 years or longer. It was concluded that chemotherapy alone presents a lower risk of developing a secondary cancer later in life than the combined modalities of chemotherapy and radiotherapy.

(J Clin Oncol, Oct 3, 2011)

CLINICAL TRIALS

ABVD Versus BEACOPP for Hodgkin's Lymphoma

Researchers from the German Hodgkin Lymphoma Study Group have developed a regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP). The standard of treatment for advanced Hodgkin's lymphoma is the regimen of doxorubicin, bleomycin, vinblastine and procarbazine (ABVD). A total of 331 patients were enrolled in the phase 3 trial. Patients were randomly assigned to receive 6 cycles of ABVD or 8 cycles of BEACOPP. After treatment, patients showing progressions, residual disease or relapse, were treated with salvage therapy. Results showed that 7-year rate of freedom from first progression was 85% in patients who had received initial treatment with BEACOPP and 73% among those who had received ABVD based chemotherapy ($p=0.004$) and the estimated 7-year rate of freedom from second progression was 88% in BEACOPP groups, as compared with 82% in the ABVD group ($p=0.12$). The rate of complete response at the end of salvage therapy was higher among patients who had initially received ABVD than among those who had initially received BEACOPP (51% vs 35%). The study showed that treatment with BEACOPP, as compared with ABVD, resulted in better initial tumor control but long term outcome did not differ significantly between the two regimens.

(N Engl J Med, July 21, 2011)

Bortezomib Added to R-CVP for FL

Results from a multicenter phase II clinical trial in newly diagnosed advanced stage follicular lymphoma (FL) showed that adding Bortezomib (1.3 mg/m² days 1 & 8) to standard dose of R-CVP (BR-CVP) (rituximab, cyclophosphamide, vincristine & prednisone) was well tolerated with minimal toxicity and also achieved significantly better response. Between December 2006 and March 2009, 94 patients were given BR-CVP, of which majority of patients had high (47%) or intermediate (43%) FL. Only 90% patients completed the proposed eight cycles, of which 46 achieved complete response and 32 attained partial response, the overall response rate being 83%. A phase 3 trial comparing BR-CVP with R-CVP is planned.

(J Clin Oncol, Aug 1, 2011)

Treatment for Primary Testicular DLBCL

An international phase 3 trial has been conducted by International Extranodal Lymphoma Study Group (IELSG) and the Italian Lymphoma Foundation in patients of primary testicular lymphoma (PTL) for its better prognosis, by preventing the failure in contralateral testis, CNS and extra nodal sites. In this study 53 patients of stage I and II were recruited and treated with six to eight courses of rituximab added to cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP) every 21 days, four doses of intrathecal methotrexate (IT-MX) and radiotherapy to contralateral testis (30 Gy) for all patients and radiation to regional lymph nodes for stage II patients. Results showed that with median follow up of 65 months, 5 years progression free survival and overall survival rates were 74% and 85% and cumulative incidence of CNS relapse was 6% with no relapse in contralateral testis. This trial shows that combined treatment with R-CHOP, IT-MTX and radiotherapy provide a good outcome in patients with PTL.

(Clinical Oncology News, Aug, 2011)

Vaccine for Follicular Lymphoma

Follicular lymphoma (FL) accounts for 22% of non-Hodgkin lymphomas worldwide. Survival of FL patients has improved with newer types of chemotherapy but advanced-stage disease is still incurable. A team led by scientists at the University of Texas MD Anderson Cancer Center has reported that a lymphoma vaccine extends disease free survival by 14 months. The multicenter phase 3 trial is being conducted. A total of 234 patients were recruited in the trial and were first treated with chemotherapy combination known as PACE (prednisone, doxorubicin, cyclophosphamide, and etoposide). Of these patients, 117 had complete response for at least 6 months, whether the patients were given either vaccine or a placebo. During a median follow up period of 55.6 months, median time to relapse was 44.2 months for 76 vaccinated patients, compared with 30.6 months for 41 patients who received placebo. To make the vaccine, unique proteins from each patient's tumor are isolated and combined with a delivery agent and a growth factor and this mixture is injected back into the patient. This method of introducing vaccine induces antitumor immune response with very few side effects. In future, this finding may be applied to broader range of lymphoma patients and other types of cancers also.

(Medical News Today, June 1, 2011)

WATCH-OUT

Biomarker Panel for Lymphoma Diagnosis

Chen Jake Yue and Fang Shiao-fen of University of Indiana Research and Technology Corp, USA, have filed an application No. WO2011097476, entitled “4-Protein Biomarker Panel for the Diagnosis of Lymphoma from Biospecimen” in European Patent Office on 11th August 2011. The patent filed will allow the identification of a subject at risk for lymphoma. Altered expression of the lymphoma related biomarker panel indicates lymphoma and allows distinction between a lymphoma and a leukemia. It has been discovered that evaluating expression of a lymphoma related biomarker panel comprising of four biomarkers, TNFRSF8, FSCN1, BCL6 and PIM1, is significantly more informative than evaluating the expression of the biomarkers individually. Accurate classification of a subject at risk of lymphoma related disorder as being at risk for a lymphoma or at risk of for a leukemia allows optimization of therapeutic regimens and reduces exposure of a subject to the side effects from administration of less effective treatment regimen.

(European Patent Office, Oct 3, 2011)

Expansion of NK Cells and Therapeutic Uses

St Jude Children’s Research Hospital, USA, has been assigned US patent No. 8,026,097 entitled “Expansion of NK cells and therapeutic uses thereof”, published on 27th September, 2011. The invention relates to novel methods for preferentially activating & expanding natural killer (NK) cells, utilizing the stimulatory effects of IL-15 and CD137 ligand. It is based on the concept that expression of chimeric receptors on NK cells could overcome human leukocyte antigen mediated inhibitory signals, thus endowing the cells with cytotoxicity against otherwise NK resistant cells. The invention also provides a method for obtaining an enriched NK cells population suitable for transduction with a chimeric receptor comprising of preferential expansion of NK cells within a mixed population of NK cells and T-cells by co-culturing the mixed population of cells with a cell line that activates NK cells and not T lymphocytes. This NK activating cell line is composed of cells that (a) lack or poorly express major histocompatibility complex molecules, (b) express membrane bound interleukin-15 and a co-

stimulatory factor ligand, (c) activate natural killer cells, and (d) fail to activate T lymphocytes.

(USPTO, Oct 8, 2011)

Method of Treating Mantle Cell Lymphoma

Witzig Thomas E et al have filed an application No. 20110184010, published on 28th July 2011, in the USPTO for the invention “Methods of treating mantle cell lymphoma”. This invention relates to the use of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) in the treatment or inhibition of mantle cell lymphoma (MCL). Rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) is an ester of rapamycin. CCI-779 has in vitro and in vivo activity against a number of tumor cell types. It is hypothesized that CCI-779 delays the time of progression of tumors or time to tumor recurrence. CCI-779 binds to and forms a complex with the cytoplasmic protein FKBP, which inhibits an enzyme, mTOR (mammalian target of rapamycin, also known as FKBP12-rapamycin associated protein [FRAP]). Inhibition of mTOR’s kinase activity inhibits a variety of signal transduction pathways, including cytokine-stimulated cell proliferation, translation of mRNAs for several key proteins that regulate the G1 phase of the cell cycle, and IL-2-induced transcription, leading to inhibition of progression of the cell cycle from G1 to S. Thus, the invention provides a method useful in the treatment or inhibition of MCL.

(Freepatetnsonline, Oct 11, 2011)

Methods of Use for Cycloamine Analogs

Alfredo C et al have filed an application No. 20110230509 A1 entitled “Methods of use for cycloamine analogs” on September 11, 2011 in the US Patent Office. The invention relates to a method of antagonizing the hedgehog pathway. The method includes administering the compound orally, intravenously, or topically. The condition can be selected from the group consisting of skin cancers, breast cancer, pancreatic cancer, multiple myeloma, leukemia, Hodgkin’s disease etc. Inhibition of hedgehog pathway in certain cancers has shown to result in inhibition of tumor growth. Small molecule inhibition of hedgehog pathway activity has also been shown to result in cell death in a number of cancer types. Research in this area has focused primarily on the elucidation of hedgehog pathway biology and the discovery of new hedgehog pathway inhibitors.

(USPTO, Oct 18, 2011)

GLOBE SCAN

Soy Intake and Non-Hodgkin Lymphoma

A hospital based case control study in Japan has evaluated the association between soy consumption and risk of Non-Hodgkin Lymphoma (NHL) in 302 patients of NHL and 1510 age- and sex-matched control subjects. NHL is one of the common malignant tumors worldwide. Environmental factors, such as diet, have important association with risk of cancer. Although soy intake has been associated with a reduced risk of several cancers, its association with NHL is not known. It was found that soy intake was significantly associated with a reduced risk of NHL in women but not in men. This finding appeared consistent across NHL subtypes. Further studies to evaluate the mechanism behind the association between soy intake and lymphoma genesis are required.

(Japan: Ann Oncol, July 15, 2011)

Farmlife and Lymphoma

Researchers in New Zealand have found that children who grow up around livestock are at elevated risk for hematologic cancer in later life. It is suggested that this may be through, for example, exposures to specific viruses or other biological exposures that indirectly increase hematologic cancer risk by modulating the immune system. To explore this, data from the New Zealand Births, Deaths and Marriages registry, which records all deaths of individuals in the country as well as sex, cause of death, occupation, and occupations of both parents of the deceased, was analysed. Between 1998 and 2003, there were 94,054 deaths among individuals aged 35 to 85. A total of 3,119 of these were from hematologic cancer and the remaining 90,935 deaths were considered control. The most common cancers were non-Hodgkin's lymphoma, multiple myeloma and myeloid leukemia. It is suggested that the risk involved in growing up on a farm that raises livestock could be due to specific animal-related exposures rather than the farming environment in general. A possible explanation for the risk for hematologic cancer was the antigenic stimulation hypothesis, which suggested that early exposure to organic dust particles that contains mitogens might cause chronic immune system stimulation. This in turn might result in an increase in random DNA mutations that, over the long term, could result in carcinogenesis.

(New Zealand: Occupat Environ Med, July 29, 2011)

Treatment Option for NHL

The National Institute of Health and Clinical Excellence (NICE) at UK has recommended a new maintenance treatment that can help delay the growth and spread of follicular non-Hodgkin's lymphoma. The final guidance states that rituximab (Mabthera, Roche Products) can be used as first line maintenance treatment in people with follicular non-Hodgkin's lymphoma that has responded to first line induction therapy with rituximab in combination with chemotherapy. Standard clinical practice for NHL patients is for doctors to wait for the cancer to grow again following successful induction therapy, before giving them further treatment. However, the evidence presented to NICE's independent committee by the manufacturers, and advice from clinical specialists suggest that treating patients with rituximab maintenance after induction therapy may prevent the spread and growth of this cancer for at least 3-4 years.

(UK: Medical News Today, Jun 22, 2011)

IMRT for Lymphoma

According to new research from Fox Chase Cancer Center in USA, Intensity Modulated Radiation Therapy (IMRT) produces no major side effects and a high response rate in patients with extranodal lymphoma of the head and neck. Whether IMRT is the best radiation therapy for patients with extranodal lymphoma of the head and neck has not been previously investigated. Patients with extranodal lymphoma of the head and neck often undergo radiation therapy, but this treatment frequently damages the salivary glands and causes dry mouth, which can lead to problems with eating, speaking and swallowing. In the new study, the oncologists identified five patients with extranodal lymphoma of the head and neck who were treated with IMRT between 2007 and 2010. Four of these individuals also received chemotherapy. After treatment, the majority of patients showed improved outcomes and only minor symptoms. There were no occurrences of severe dry mouth, no relapses in the head and neck, and no evidence of tissue abnormalities appearing on positron emission tomography (PET) of these regions. Only one individual experienced a systemic relapse, and four people survived during a follow-up period. The findings show that IMRT helps to control local tumors while keeping side effects at a minimum.

(USA: Science Daily, Aug 15, 2011)

RECENT ADVANCES

EVOLVING STRATEGIES IN MANAGEMENT OF PEDIATRIC NON-HODGKIN LYMPHOMA

Non-Hodgkin lymphomas (NHL) are a group of clonal disorders of the immune system caused by the malignant transformation of lymphoid progenitor cells at a particular stage of differentiation. NHL represents 7% of all cases of pediatric cancer. Childhood NHL is different from that of adults in terms of invasiveness, cell of origin, genetic abnormalities and responsiveness to treatments. More than 95% of childhood NHL are high grade. Virtually all childhood NHL can be classified into one of three types: Burkitt and Burkitt like lymphoma including diffuse large cell lymphoma (DLBCL), lymphoblastic, and anaplastic large-cell. Each type exhibits unique histologic and molecular characteristics. Novel imaging techniques such as positron emission tomography, and molecular techniques to detect low-level marrow involvement, have enabled accurate risk stratification and assignment of treatment strategy.

Progress in the treatment of children and adolescents with NHL parallels that of childhood acute lymphoblastic leukemia. Investigators of most contemporary clinical trials report survival estimates approaching 90%. The excellent overall outcome of the children with NHL has been as a result of improved supportive care, better management of tumor lysis syndrome and other complications, better understanding of biology of disease and accurate risk stratification based treatment. However, the prognosis of primary refractory and recurrent NHL continues to remain poor and new strategies need to be evolved for these subset of patients. In this article we focus our discussion on recent emerging strategies in the management of NHL. For the sake of simplicity, the article has been divided into three parts: improvement in supportive care, diagnostic and staging modalities, and treatment.

Diagnostic and Staging Modalities

PET Scan for Staging and Response Assessment: PET scan is being currently used quite often for staging paediatric NHL. PET scan will upstage a small percentage of patients compared with computerized tomography (CT) and/or magnetic resonance imaging (MRI). Although there are no prospective studies demonstrating that its use improves outcome. There are, however, other potential roles, such as assessing the speed of response and confirmation of post-

therapy remission. Most patients achieve CR after 3-4 months of treatment and residual CT lesions, more often than not, contain only necrotic material. In view of the very high cure rate achieved at present, it would be difficult to design studies to demonstrate that delay to achieve PETCR could define a poor prognostic group. Early achievement of PETCR could, however, define a good prognostic subgroup in which therapy could be minimized.

Gene Expression Profiling: Newer methodologies, such as identification of genetic changes in tumor cells and genome-wide gene expression profiling, will become increasingly important for identifying biologically distinct subtypes and therapy targets. Therefore, whenever possible, following proper diagnostic classification of an individual patient, appropriate material should be preserved for future research (e.g. purified tumor cells, shock-frozen tumor tissue).

Subgroup-Directed Treatment and Evolving Therapies

Lymphoblastic Lymphoma: Both B-precursor and T-cell LLs are most effectively treated using ALL-based therapies, which include multidrug systemic chemotherapy and CNS prophylaxis. Currently, the most frequently used treatment regimens are the LSA2-L2 protocol in numerous modified forms and the Berlin-Frankfurt-Münster (BFM) group strategy, which was originally designed to treat children with ALL. Both protocols are divided into phases of induction, consolidation, reintensification, and maintenance. This approach has improved the survival of lymphoblastic lymphoma to about 80%, though prognosis of recurrent lymphoma remains quite poor. In the BFM series, the only survivors of T-LBL relapse received allogeneic HSCT. Therefore, allogeneic HSCT, as part of front-line treatment, may be an option for improving outcomes for relapse T-LBL.

The integration of new agents into treatment approaches is needed to improve outcome for these patients. One example of an agent of promise for treatment of T-LL is compound 506U78. Compound 506U78 (2-amino-9-B-Darabinofuranosyl-6-methoxy-9H-purine) is a water-soluble prodrug of ara-G (9-B-arabinofuranosylguanine), which is selectively toxic to T-lymphoblasts and results in inhibition of DNA synthesis. This agent is currently being used in combination with chemotherapy for the treatment of T-ALL (COG study AALL00P2). Immunotherapeutic approaches also offer potential benefit for LL due to the specificity and favorable toxicity profiles of these agents. Alemtuzumab (Campath-1H1) is a humanized monoclonal

antibody that targets the CD52 molecule that is widely expressed on T-lineage lymphoid cells. Another agent of potential promise is denileukin diftitox (DAB389IL2), an interleukin-2 receptor (IL-2R)-targeted diphtheria toxin. This immunotoxin targets T-cells by binding to the IL-2 receptor. Favorable responses to this agent have been observed in cutaneous T-cell lymphoma and small numbers of patients with NHL expressing IL-2R, and suggest that future treatment initiatives in LL may be warranted. Finally, the frequency of NOTCH1 activating mutations in T-cell leukemia provides compelling rationale for the future use of NOTCH-pathway inhibitors, such as γ -secretase antagonists, in precursor T-cell malignancies.

Burkitt and Burkitt Like Lymphoma: Short course, multiagent non cross resistant combination chemotherapy with intrathecal prophylaxis remains the backbone of treatment. The consistent improvement in the prognosis of children with BNHL has been mainly due to the use of higher dose systemic chemotherapy and the reduction in early toxic death by aggressive treatment of biochemical and infectious complications soon after diagnosis or during induction. With various clinical trials we have learnt that (1) Local radiotherapy can be safely omitted; (2) Chemotherapy cycles of moderate intensity (four to six agents) are sufficient to eradicate NHL; (3) Chemotherapy should last no longer than 6 months; (4) CNS-directed therapy is indicated for all patients. Despite improvement in survival of advanced disease, primary refractory and recurrent lymphomas still pose a formidable challenge.

The addition of the monoclonal anti-CD20 antibody rituximab to standard chemotherapy improved outcome of adults with NHL significantly. In vitro studies have demonstrated that this additive effect may be due not only to immunological cell kill but also chemosensitization by rituximab. Combined with existing regimens, it could be beneficial in two ways. First, to improve efficacy and secondly, it could maintain a comparable effect but allow a reduction in the dose of some of the more toxic agents, such as cyclophosphamide and doxorubicin. It is likely that rituximab will enter randomized evaluation in one of the large national groups in the near future.

Another agent, epratuzumab, an IgG1 chimeric antibody targeted to CD22, has been demonstrated to induce durable responses in adult B-NHL. The Children's Oncology Group is currently testing the safety, pharmacokinetics and efficacy of epratuzumab in children and adolescents with recurrent precursor B-ALL (COG ADVL0402).

Anaplastic Large Cell Lymphoma: The clinical and biologic characterization of this NHL subtype is still evolving; and treatment programs for this disease have differed vastly. Some teams use short-pulse chemotherapy which is similar to the treatment used for B-cell lymphoma and others treat patients with more prolonged leukemia-type chemotherapy. The results of early stage patients are excellent with both the approaches. Standard treatment for advanced disease needs to be defined. The role of novel therapeutic strategies, e.g. high-dose therapy followed by stem cell transplantation and anti-CD30 monoclonal antibodies labelled to toxins or radionuclides in the treatment of the poor prognostic category of systemic ALK-negative ALCL and specific inhibitors of the PI3-kinase for the treatment of NPM±ALK-positive ALCL will have to be assessed in future clinical trials.

Supportive Care

Patients with NHL often present with respiratory, cardiovascular, neurologic, renal, hemorrhagic, infectious, and metabolic complications. The rate of mortality due to these complications has been reduced to less than 1% by prompt recognition of signs and symptoms, careful clinical and laboratory evaluation, and early intervention. The availability of recombinant urate oxidase (rasburicase) has greatly facilitated the prevention and management of hyperuricemia. Rasburicase has also reduced the need for dialysis due to nephropathy and helped the clinicians to institute definitive therapy in time. Severe oro-intestinal mucositis, caused primarily but not solely by HD MTX, and severe neutropenia, are the most important acute toxicities promoting serious infections. Uses of growth factors, availability of better antimicrobial and improvement of diagnostic modalities have reduced toxic deaths to the tune of 1-3%.

Key Messages

- 1) More than 95% pediatric NHL are high grade and often present with oncological emergencies.
- 2) Improved outcome has been as a result of reduction in early toxic deaths coupled with accurate risk stratification based treatment strategy.
- 3) Current focus of trials is to optimize therapy for advanced Burkitt lymphoma, primary refractory and recurrent NHL by introducing novel agents and reducing short and long term toxicity for early stage disease.

(Dr Sandeep Jain, Consultant; Dr Gauri Kapoor, Sr Consultant, Dept of Pediatric Hematology and Oncology)

For prevention of chemotherapy induced
febrile neutropenia

^{Rx} **peg-grafeel**TM
Pegfilgrastim injection 6mg

All is well that begins well...

- ✓ The only single source of **pegfilgrastim** in the world
- ✓ Affordable way of preventing CIFN*

Prescribing information

Composition:

Each pre-filled syringe contains 6 mg of pegfilgrastim* in 0.6 ml solution for injection.

Indications and usage:

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Posology & method of administration:

One 6 mg dose (a single pre-filled syringe) of pegfilgrastim is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use:

Pegfilgrastim should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens. The onset of pulmonary signs may be preliminary signs of Adult Respiratory Distress Syndrome (ARDS). In such circumstances Pegfilgrastim should be discontinued at the discretion of the physician and the

appropriate treatment given. Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease. The safety and efficacy of pegfilgrastim for the mobilisation of blood progenitor cells in patients or healthy donors has not been adequately evaluated.. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Pregnancy, lactation and Paediatric patients:

The experience in children is limited. Pegfilgrastim should not be used during pregnancy unless clearly necessary. It should not be administered to women who are breast-feeding.

Incompatibilities:

This medicinal product must not be mixed with other medicinal products, particularly with sodium chloride solutions.

Special precautions for disposal:

Before administration, pegfilgrastim solution should be inspected visually for particulate matter. Only a solution that is clear and colourless should be injected. Excessive shaking may aggregate pegfilgrastim, rendering it biologically inactive. Allow the pre-filled syringe to reach room temperature before injecting.

Any unused product or waste material should be disposed of in accordance with local requirements.



Dr. Reddy's Laboratories Ltd.,

Global Generics-India
7-1-27, Ameerpet,
Hyderabad 500 016,
Andhra Pradesh, India.
www.drreddys.com

* Chemotherapy induced febrile neutropenia