

Childhood, adolescent and young adult non-Hodgkin lymphoma: state of the science

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The Fifth International Symposium on Childhood, Adolescent and Young Adult Non-Hodgkin Lymphoma (NHL), held in Varese, Italy, 21–24 October 2015, brought together many of the world's leading clinical and laboratory researchers involved in the study of NHL in young people (Fig 1). These included pathologists, immunologists, basic scientists and clinician researchers. As with the previous meetings, the goal was to provide updates on the biology and management of these disorders and opportunities, through the single session format, for maximal interdisciplinary interaction.

In this special edition, contributors to the meeting from various specialty areas provide overviews of major themes that were covered at the symposium. These themes include therapeutic strategies for the most common subtypes; namely, mature B-cell, lymphoblastic T cell and anaplastic large cell, as well as some less common types, such as peripheral T/natural killer (NK) cell lymphoma. Special consideration is given for adolescent and young adult patients, and management in resource-poor countries. Molecular genetics and lymphoma immunology, which now lead increasingly to novel therapeutic approaches, and aspects of translational biology and new targets, are included.

The most remarkable increase in patient survival has occurred in Burkitt lymphoma, where the refinement of regimens based on relatively simple and inexpensive chemotherapy now cure over 90% of children. The role of anti-CD20 monoclonal antibody therapy is in focus following demonstration of its effectiveness when combined with less intensive chemotherapy in adult high- and low-grade NHL. The results of the Children's Oncology Group pilot study of the Lymphome Malins B regimen combined with rituximab have

recently been reproduced in a large international trial for higher risk patients, and rituximab has proven to be of benefit. The effectiveness of urate oxidase has also been demonstrated in reducing the dangers of tumour lysis in patients with bulk disease. Both of these therapies remain expensive but, with the probable reduction in cost and development of bioequivalent generic preparations, their utilization should become more widespread. In these highly curable tumours, studies will now concentrate on the reduction of early and late morbidity, a strategy where novel biological therapeutics are likely to have a significant role in replacing conventional chemotherapies.

T lymphoblastic lymphoma and T lymphoblastic leukaemia have, to date, been treated with almost identical regimens and the former has an excellent outcome. There is now increasing evidence that there are fundamental differences in their molecular pathology, behaviour and treatment requirements. The use of novel approaches to evaluate early response, such as minimal residual disease or fludeoxyglucose (¹⁸F) positron emission tomography imaging, may allow early risk group stratification. Central nervous system irradiation has now been removed from most protocols and it seems likely that very high dose methotrexate is also not required in many patients. Molecular phenotype may predict both favourable (NeuroFibromatosis mutations) or poor outcomes (*RAS*, *PTEN* mutations)

Anaplastic large cell lymphoma has emerged as a subtype attracting particular interest with regard to its pathogenesis and therapeutic intervention, especially in relation to immune modulation. New mechanisms for the effectiveness of vinblastine and the potential for immunization strategies have been highlighted.

The less common lymphoma subtypes that are occasionally seen in young persons provide a particular challenge both with regard to diagnosis and management. Experienced haematopathologists are essential for accurate diagnoses and, more recently, molecular analyses have led to better understanding of cellular origin and are leading to new classifications. In some subtypes the treatment used in adults provide guidance for younger patients. Treatment strategies in nasal NK cell lymphoma, for example, which have been

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Fig 1. Leading international physicians and researchers in childhood, adolescent and young adult non-Hodgkin lymphoma gathered at the Centro Congressi Ville Ponti, Varese, Italy for the Fifth International Symposium on Childhood, Adolescent and Young Adult Non-Hodgkin Lymphoma, 21–24 October 2015. Photo courtesy of Jeffery Dankberg, President Pediatric Cancer Research Foundation (PCRF).

well evaluated in adults, could be studied in younger patients through collaborative international studies.

With the dramatic improvements in outcome of childhood NHL in the resource-rich countries it is appropriate that such inherently curable diseases are a focus for improvement in low- and middle-income countries. A number of important international collaborations have developed that support such initiatives and have been shown to enable delivery of curative and affordable regimens which restore children to good quality and productive lives in these communities.

Cooperation between adult and paediatric oncologists has been the hallmark of success in the evolution of effective therapy and age-appropriate supportive care for adolescents and young adults. The causes of differences in outcome compared with children are becoming clearer and are more complex than site of care, including biological risk groups, compliance and tolerance of therapy. There is much to be learned from all parties and it is likely that regimens developed in adult practice may be adaptable for paediatric use as much as the reverse. Examples include diffuse large B-cell lymphoma and mediastinal B-cell lymphoma.

Immunophenotyping, cytogenetics, molecular pathology, and now whole genome sequencing, has been critical in tumour classification, risk stratification and understanding the pathogenesis and is now providing guidance to novel, more targeted therapy. A clearer understanding of immune mechanisms is leading to a plethora of potential therapies in lymphoid malignancies. Next generation anti-CD20 antibodies include the fully human antibody ofatumumab, and obinutuzumab with enhanced Fc receptor binding. Alternative

targets in B-cell receptor related signalling pathways include the Bruton tyrosine kinase (BTK) inhibitor, Ibrutinib. Upregulation of programmed death ligand PDL1 (also termed CD274) in a range of lymphoid malignancies including anaplastic large cell lymphoma, primary mediastinal B-cell lymphoma and Epstein–Barr virus-driven NHL provides an alternative target for agents such as pembrolizumab. The development strategies to enhance endogenous immune mechanisms in acute leukaemias, such as chimeric antigen receptor modified T cell therapy and bispecific T cell engaging antibodies, may also prove applicable in NHL. Targets and mechanisms that are shared between lymphoma and leukaemia and across age groups are of particular interest as the population that might benefit is thus greater and of more attraction for commercial exploitation. With targets that are exclusive to the most rare children's cancers, translation from pre-clinical evidence to practical application often proves difficult to achieve.

This edition provides an overview of key issues relating to current and future management of NHL in younger patients and should help identify areas of common interest between adult and paediatric haematologists and oncologists, thus encouraging collaboration in both basic science research and translation into practice through national and international clinical trials.

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