Non Hodgkin lymphoma in adolescents and young adults

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Introduction

Non-Hodgkin lymphomas (NHL) represent a rather heterogeneous group of malignacies that affect any age group, but which show some peculiarities in terms of prevalence of histological subtypes in specific age sub-groups. Adolescence, considered as the age between 15 and 20 years and young adulthood, from 20 to 30 years, are characterised by a gradual decrease of NHL typical of childhood, mainly Burkitt and lymphoblastic lymphoma, and the progressive appearance of NHL that are more frequent in adults, such as the large B-cell lymphomas.

In the young age population, the incidence of NHL progressively increases with age reaching, in the most recent updates, 14 and 21 cases per million in the age categories 15–19 and 20–24 years, respectively [1] (Fig. 1). NHL is the second most frequent cancer in individuals aged 15–29 years (after malignancies of the genital tract) [2].

In most countries, adolescents with malignant disease may be referred to either paediatric or adult departments and, accordingly, they are registered more or less frequently in clinical trials. At present, little information is available on adolescents and young adults with NHL and many questions are still open.

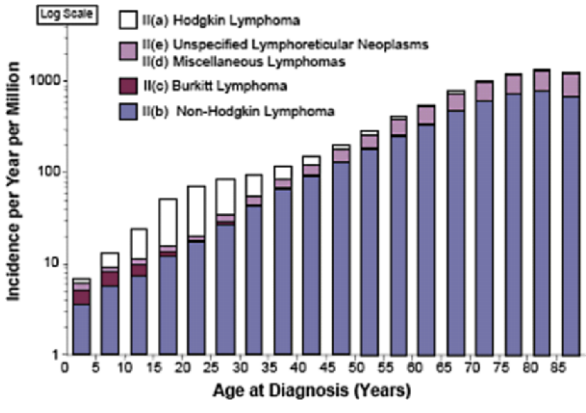

Fig. 1. Incidence of malignant lymphoma in the USA subdivided by age categories in individuals younger that 45, SEER, 1975–2000.

We do not know in most instances whether age has a prognostic impact on NHL; whether results are different when patients are treated according to paediatric or adult protocols and if there is any difference in NHL biology in adolescents and young adults compared to other age groups.

Etiology

Similar to adults, the causes of NHL in adolescents and young adults are mostly unknown. Several risk factors have been suggested to play a role in NHL, including immunodeficiency syndromes, HIV infection, immunosuppressive therapies, Epstein–Barr virus (EBV) or helicobacter pylori infection and environmental factors, such as tobacco or chemical exposure. EBV has been linked to Burkitt lymphoma in countries with limited resources, but it has a causative role also in lymphomas originating in patients undergoing immunosuppressive therapy after organ transplantation.

Histology

Based on the most widely used WHO NHL classification [3], the most frequent NHL subtypes found in adolescents and young adults are: Burkitt, lymphoblastic, diffuse large B cell lymphoma (DLBCL) and anaplastic large cell lymphoma (ALCL). As pointed out above, the prevalence of different histological types varies with age within the same geographical area (Fig. 2) and the most frequent histological types characteristic of childhood are gradually substituted with more typical adult types, including large B cell NHL and follicular NHL. Histology is at present the basis for the diagnosis of NHL, although other most recent technical approaches have shown to be of value in the definition of the tumour subtypes, including the gene expression profile in selected subgroups of NHL [4].

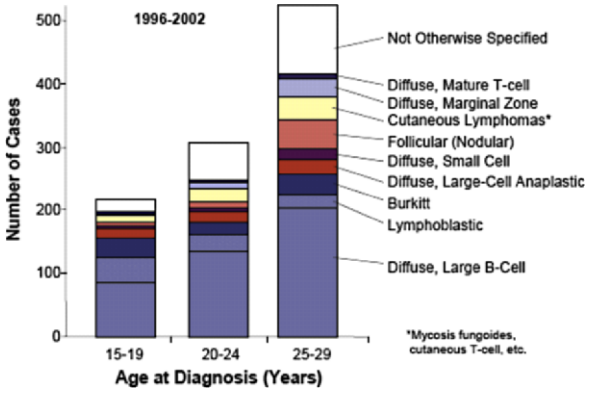

Fig. 2. Histological subtypes of non-Hodgkin lymphoma, SEER, 1996–2002.

Clinical presentation

Clinical presentation of NHL in adolescents and young adults greatly depends on the site of the disease, histological subtype and extent of the disease.

Burkitt lymphoma and DLBCL arise generally in the abdomen or Waldeyer's ring. Peripheral lymph nodes are less commonly involved, more likely in DLBCL than in Burkitt lymphoma. Abdominal masses may present with symptoms caused by compression of adjacent structures, including gastrointestinal tract, ureters and the biliary tract. Ascites is often observed and in this case paracentesis will reveal tumour cells with a typical L3 morphology. Ovarian involvement is common in girls. Burkitt's lymphoma has peculiar features in equatorial Africa, where jaw localisation is frequent in young age and facial region may be involved by the tumour in adolescents with masses that may cause compression of cranial nerves, including III, IV, VI. Jaw involvement is rare in sporadic Burkitt but when present, is often associated with bone marrow infiltration, in contrast to African Burkitt's.

Lymphoblastic lymphoma most often originates in the thymus, although other sites including peripheral lymph-nodes may be involved. The more frequent T-cell precursor lymphoblastic lymphoma often presents with a mediastinal mass which may be life threatening and is often associated with pleural effusion. In this case cytological examination of effusion together with flow-cytometry analysis may allow diagnosis, thus avoiding general anaesthesia that would be required for tumour biopsy. A lymphoma that arises in the thymus and is characteristic of adolescence and young adults is the primary mediastinal B-cell lymphoma (PMBCL), more frequent in females than males.

ALCL has a more variable presentation with frequent nodal involvement, sometimes painful and extranodal sites, including skin, may be involved at diagnosis. Peripheral nodes are most frequently involved, followed by retroperitoneal nodes and mediastinal mass [5,6].

Diagnosis and staging

Diagnosis mostly rests on histological evaluation, but cytological examination of intracavitary effusions or bone marrow (BM) smears may be a valuable alternative for diagnosis when anaesthesia and surgical procedures may put the patient at anaesthetic risk, due to a large mediastinal mass. In addition to standard morphological and immunohistochemical evaluation, flow cytometric analysis, cytogenetic and molecular characterisation of the tumour cells are recommended.

A rapid diagnosis is essential for very aggressive NHL, such as Burkitt and lymphoblastic lymphoma, given that complications arising from the presence of the tumour, such as tracheal compression or renal failure caused by the mass effect or by the metabolic consequences of a large and rapidly growing tumour, can be of serious impact on the patients. Standard imaging studies, including ultrasound, CT and MR scan are widely used to determine disease extent, whereas more recent technologies, such as PET scan, are only at the early stages of application in the routine management of NHL in adolescence. Accurate assessment of response requires that sites of disease at diagnosis be precisely documented as their re-evaluation during treatment may give relevant information that may lead to changes in therapy. In general it is advisable to calculate the volume of significant tumour masses as their modification may have an impact on the overall treatment strategy and ultimately on outcome.

With regard to the imaging studies to be considered at diagnosis, CT scan is probably the most widely used and recommended approach for abdominal lymphoma, but in this case ultrasound may also be of great value. Ultrasound is readily accessible and usually inexpensive and can be repeated frequently. In our experience it can sometimes complement CT scan in the definition of disease extent. The imaging study of choice depends not only on the localisation of the disease, but also on the health care settings: in countries with limited resources for example, ultrasound may be most frequently used, as CT may not be widely available or be too costly.

MRI is generally the most useful procedure when lymphoma is localised to the head and neck or

Table 1
Staging systems in use for non-Hodgkin lymphoma

St. Jude's (Murphy's) Staging System for Paediatric NHL	
Stage I	A single tumour (extranodal) or single anatomical area (nodal) with the exclusion of the mediastinum or abdomen.
Stage II	A single tumour (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm. A primary gastrointestinal tract tumour, usually in the ileocoecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected.
Stage III	Two single tumours (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All the primary intrathoracic tumours (mediastinal, pleural, thymic). All extensive primary intra-abdominal disease, unresectable. All paraspinal or epidural tumours, regardless of other tumour site(s).
Stage IV	Any of the above with initial CNS and/or bone marrow involvement.
Ann Arbor Classification Used in Adult NHL	
Stage I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) which may be accompanied by a contiguous involvement of an extralymphatic organ or site (II_E)
Stage III	Involvement of lymph node regions on opposite sides of the diaphragm, which may be accompanied by involvement of the spleen (III_S) or by a localised involvement of an extralymphatic organ or site (III_E) or both (III_{SE})
Stage IV	Disseminated involvement of one or more extralymphatic organ or tissues, with or without associated lymph node involvement.

when central nervous system involvement needs to be assessed. Fluorodeoxyglucose (FDG) PET imaging has a well defined role for Hodgkin's disease (HD) in adults. In NHL, where radiation therapy is not routinely used for treatment, a PET scan at diagnosis that may define all the active sites of disease does not appear as relevant as in HD. In T-cell NHL and PMLBCL that arise in the mediastinum, PET may have a role similar to that observed in HD in that residual CT or MRI lesions after chemotherapy may indicate the need for radiation therapy. In this case, PET may be used to distinguish inactive disease from viable tumour residue that may represent an indication for radiation therapy [7]. As more experience is accumulating in children and adolescents it has become apparent that false positives may occur [8].

Staging is usually based on the St. Jude's classification for children, where extranodal sites are frequently involved whereas adults mostly use the Ann Arbor classification (Table 1). Although St. Jude's classification has been of great help to clinicians for many years in the stratification of patients, with the advent of more intensive therapies that are now in use for children and young adults this staging system has become less effective in the decision process on treatment [9] and some modification may be warranted.

In adults the International Prognosic Index (IPI) is also used to classify patients for therapeutic purposes [10]. These differences, and the limited applicability of the IPI to rapidly growing tumours encountered in younger ages, makes it difficult to compare childhood and adult studies. For a complete staging, BM aspirate and central nervous system (CNS) fluid examinations are also routinely performed, whereas bone marrow biopsy is not always required. In addition to morphological examination of BM smear and microscopic analysis of cerebrospinal fluid (CSF), recent reports on childhood NHL suggest the need for prospective studies to evaluate minimal disseminated disease as BM infiltration by lymphoma cells at diagnosis may have prognostic implications [11,12].

Burkitt's lymphomas and DLBCL

Burkitt's lymphoma and DLBCL are treated with the same chemotherapy approach or with similar regimens based on the concept of high dose-intensity chemotherapy. High dose methotrexate (MTX), high dose cytarabine (ARA-C) and cyclophosphamide (CPM), in conjunction with vincristine, anthracyclines, VP16 and corticosteroids, are the most active drugs in this disease. A stepwise increase in the overall dose-intensity in most chemotherapy regimens has resulted in significantly improved outcomes in these NHLs. Results from the LMB protocols of the French Society of Paediatric Oncology [13], more recently

extended and conducted in collaboration with the COG and UKCCSG groups, and from the German BFM group [14], have demonstrated that an overall survival in the range of 90% is achievable in B-cell NHL of childhood. Other national groups have obtained comparable results using similar strategies [15,16] that have a total duration of treatment, even in high stage disease, usually less than 5 months.

Few data are available on Burkitt's lymphoma in young adults and adolescents, but it would seem that when treated with the same protocol, their outcome is similar independently of the age category [17]. From the recent trials conducted in Europe and in the USA on childhood and adolescent B-cell NHL it became clear that high dose Ara-C is important for the improved outcome of CNS positive patients and patients with advanced stage disease. High-dose MTX is also critical and its relevance is highest in advanced stage disease. As recently reported, not only the dosage of MTX, but also the infusion time has an impact on outcome [18]. CNS positive patients may be those who benefit most from the use of high-dose MTX, as suggested recently by a randomised international study on high-risk CNS positive B-cell NHL [19]. Intrathecal therapy is also important for CNS prophylaxis.

Another aspect of relevance for the successful treatment of B-cell NHL of childhood is the time interval between subsequent chemotherapy cycles. The FAB LMB96 study demonstrated an inferior outcome when patients were administered the second cycle of chemotherapy after more that 21 days from the first cycle compared with a shorter time interval [20]. This aspect may be of special consideration for adolescents and young adults who seem to have a lower compliance to treatment than children and it should be kept in mind by physicians in charge of such patients [21]. Although some studies have suggested that patients older than 15 years may have a worse outcome, EFS of young adults treated with paediatric protocols in the same department may reach similar results. The question of whether this is the case remains to be demonstrated because the information available is still very limited.

DLBCL is treated according to the therapeutic protocols used for Burkitt disease. EFS of DLBCL is comparable to Burkitt lymphoma in children, whereas it is less satisfactory in adults, thus raising the question of whether DLBCL may differ biologically in different age groups and whether adolescent DLBCL may be an intermediate biological entity. Because it has been demonstrated that adding rituximab to CHOP is of benefit in adult B-cell NHL, the combination of CHOP and monoclonal antibody is the current approach in adult DLBCL, whereas paediatric oncologists rely on a more aggressive chemotherapy.

A peculiar type of DLBCL is the primary mediastinal large B-cell lymphoma (PMLBCL). This disease affects young individuals with a female prevalence. Similarly to other B-cell NHL of childhood and adolescence, it is a rapidly growing tumour that localises to the mediastinum and is characterised by a varying degree of sclerosis that in part can justify the slow tumour reduction during treatment and the frequent residual mass at the end of chemotherapy. Because patients affected by PMLBCL are treated either in adult or paediatric haemato-oncology units, this disease represents a real challenge and a possible ground for collaboration between paediatric and adult haemato-oncologists. In fact, although the disease may be biologically identical in adolescents, young adults and older individuals, approaches vary depending on the settings where patients are taken care of. In general, a more aggressive chemotherapy, similar to that in use for Burkitt lymhoma, is applied in children [22] whereas a more generous use of radiation therapy is used in adults [23]. Thus, the optimal treatment of this disease, aimed to achieve the highest probability of cure with the lowest burden of long term side- effects, is yet to be determined.

Lymphoblastic lymphoma

Lymphoblastic lymphomas are of T-cell lineage in the great majority (more than 75%) and localise to the mediastinum in more that 80% of the cases, whereas the less frequent B-cell lineage lymphomas have various primary sites, including peripheral lymph-nodes, skin, and bone. The peak incidence is in adolescence and young adult populations.

In childhood, lymphoblastic lymphoma is treated with chemotherapy regimens used for acute lymphoblastic leukaemia, thus reaching a long term OS in the range of 80–90% without the use of radiation therapy [24–26]. In the adolescent and young adult group, OS varies from 40 to 60%. Improvements in the adult population of lymphoblastic lymphoma patients have been achieved using leukaemia-like protocol, but results are generally lower compared to paediatric series [27]. Impressive results have been obtained recently also in advanced stage disease with the BFM90 protocol that achieved an EFS of 90% in a series of T-cell lymphoblastic lymphoma, without the need for radiotherapy [26]. Small series of adolescents and young adults were treated with regimens that included

autologous or allogeneic HSCT, thus suggesting a role for high-intensive chemotherapy and possibly for an allogeneic graft versus lymphoma effect. This was also suggested by a retrospective analysis of autologous versus allogeneic stem cell transplantation, where a higher relapse rate was observed in the autologous subgroup [28].

From the biological point of view, only 10–20% of lymphoblastic lymphomas are of B-cell lineage. In this case, mediastinal localisation is less frequent whereas more common primary sites are peripheral lymph-nodes, tonsils, skin, bone and soft tissues.

Cancer cells appear morphologically identical to those of acute lymphoblastic leukaemia and are characterised by a very immature appearance with finely dispersed chromatin, small or absent nucleoli and a scant cytoplasm. T- or B-lymphoblasts express terminal deoxynucleotidyl transferase (TdT) and respectively express on the cell surface a number of T-cell specific antigens, including CD2, CD5, CD7 together with the CD4 or CD8, or early B-cell markers, including CD10, CD19, HLA-Dr, CD20, and CD22. Several genetic alterations have been reported in lymphoblastic lymphoma, but they have been mostly described in cohorts of patients where acute lymphoblastic leukaemia and lymphomas were included. Indeed, little information is available on cytogenetics and molecular genetics of lymphoblastic lymphoma and this is possibly due to the difficulty of obtaining representative tumour tissue in most cases. Furthermore, no clinical characteristic has been described so far that impact prognosis, making it impossible to identify subgroups of patients who may benefit from different treatments. In general, the treatment of adolescents and young adults affected by lymphoblastic lymphoma by using paediatric leukaemia-type chemotherapy of 12–24 months duration, has improved the OS of these patients and a progressive increase in survival rates has been observed in this as other NHL during the last 25 years (Fig. 3). More effort should be undertaken in order to increase our knowledge on the biology of lymphoblastic lymphoma and on the differences that may exist in this disease in children versus adolescents and young adults. Additionally, it may be of relevance for the optimal management of patients affected by lymphoblastic lymphoma to clarify other questions, such as whether the cellular events that regulate this disease are the same as in T-cell lymphoblastic leukaemia. Because few targets have been identified in T-cell lymphoblastic lymphoma compared to B-cell NHL and ALCL, any therapeutic improvement will be possible only if we can gain a better definition of prognostic factors and a better knowledge of the biology of the disease.

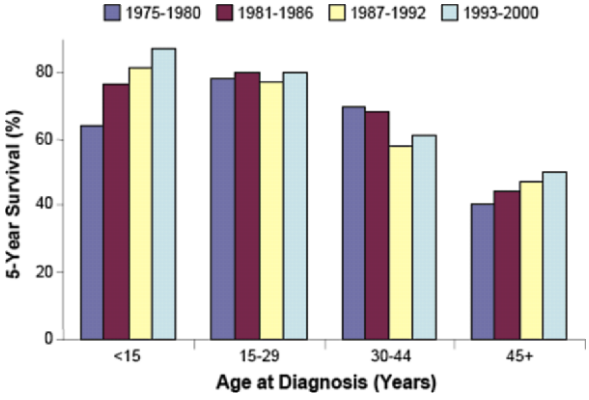

Fig. 3. Five-year survival for all lymphoma by era from 1975–2000, SEER.

Anaplastic large cell lymphoma

ALCL is a more recent entity compared to the other NHL reported above. It was first described in 1985 and has very distinct clinical and biological features. There is a bimodal age distribution in the incidence of ALCL being the first peak in the third decade and a second peak in the sixth and seventh decades of life. It is the least frequent form of NHL in adolescents, accounting for less than 10% of all NHL. Although it has been suggested that incidence of ALCL may be higher in East and South-East Asia, uncertainty remains over the real incidence of the disease in the different areas of the world.

Biologically, ALCL is characterised by the chromosomal translocation involving the *alk* kinase and a partner gene (most often *npm*) thus giving rise to a chimeric protein that can be detected by the anti-ALK monoclonal antibody. The chimeric proteins usually possess oligomerisation domains that allow to form dimers active in several biological pathways and that can ultimately influence cell growth and differentiation. The most frequent NPM-ALK can form heterodimers with wild type NPM that contains a nuclear localisation signal, thus causing the chimeric protein to localise both in the cytoplasm and in the nucleus, as demonstrated by standard cytochemical assessment using an anti-ALK antibody. Although the majority of ALCL are positive for *alk* rearrangements, the prevalence varies with age being 90–95% in children, 50–60% in adults and in the range of 90% in adolescents [29].

Several histological variants of ALCL have been described, including the classic form (70% of all cases), the lymphohistiocytic variant that contains a

large number of histiocytes admixed with tumour cells, and the small cell variant with a prevalence of small cells and few hallmark cells (pleomorphic, large tumour cells with abundant cytoplasm and horseshoe or kidney-shaped nuclei). Cancer cells tend to infiltrate the lymph-node following a sinusoidal pattern, but diffuse effacement of nodes may also be observed. ALCL cells have a high propensity to spread to extra-nodal tissues and sometimes this is the sole localisation of the disease. Often, and this is more frequent in older patients, skin can be the only site of disease and this may represent a different clinical entity as it may show a wax and waning behaviour and usually does not require treatment until other sites are involved. In this case almost invariably the disease comprises CD30 positive, but ALK negative cancer cells. The great majority of ALCL are of T- or, less frequently, of null phenotype and it is now believed that ALCL of B-cell phenotype is exceptional, if existing. In addition to T-cell specific markers (CD2, CD3, CD5, CD7, CD45RO, CD43) granzyme, epithelial membrane antigen and clusterin are frequently expressed in ALCL and represents useful markers in the differential diagnosis with Hodgkin's disease.

ALK expression represents the most characteristic feature of ALCL and has a biological as well as a clinical relevance: it is an important marker for the histological diagnosis, but it has also a prognostic value. In fact its expression has been associated with a better prognosis in adults [30] and it may in part explain the generally better outcome in childhood, where it has a high prevalence, compared to adults: adolescents seem to have an expression similar to children but a definitive demonstration of this feature is still lacking.

Certainly, based on ALK expression, we can identify two major subgroups of ALCL based on the presence or absence of the ALK-fusion protein. As a consequence some authors subdivide ALCL into ALK-negative ALCL and ALK-positive ALCL, also called ALKoma, suggesting that the expression of ALK may be the most relevant feature of the disease with an impact on prognosis. In addition to ALK expression, it has been reported that CD56 expression may influence outcome in the adult population, being the CD56-positive ALCL more aggressive than the negative counterpart [31].

Considering the largest series of ALCL published so far, particularly those including children, multivariate analysis pointed out several negative prognostic factors, including mediastinal involvement, visceral involvement and high LDH serum level, all of which had a negative prognostic impact [6]. A first report from the German BFM Group demonstrated a significant impact on prognosis only for skin involvement [32] by Cox analysis, although univariate analysis identified also splenomegaly as a risk factor. A subsequent series of 89 children from the same group revealed lung involvement, splenomegaly and B-symptoms as risk factors in univariate analysis, but only B-symptoms maintained a significant negative prognostic impact when analysed by Cox regression model [5]. The UK experience confirmed, by multivariate analysis, the increased risk of failure in case of visceral or mediastinal involvement [33]. Similar observations have been published from single institution series [34].

A retrospective analysis of prognostic factors conducted by the European Intergroup for Childhood non-Hodgkin's Lymphomas [35] on 235 children with ALCL treated with similar short pulse chemotherapy protocols in Germany, France and UK national paediatric oncology groups (BFM, SFCE and UKCCSG, respectively) has identified three poor prognostic factors by multivariate analysis: mediastinal involvement (relative risk of failure 2.1; $P = 0.004$); visceral involvement defined as lung, liver or spleen involvement (relative risk of failure 2.1; $P = 0.006$) and skin lesions in the presence of other disease localisations (relative risk of failure 1.9; $P = 0.02$). Based on these findings two major prognostic groups of ALCL could be identified: a good prognostic group without skin, mediastinal or visceral involvement and a 3-year event free survival of 87% and overall survival of 92%, and a poor prognostic group characterised by skin and/or mediastinal and/or visceral involvement that showed a 3-year event free survival of 61% and overall survival of 76%.

Stage according to St. Jude or Ann Arbor classifications does not have a significant prognostic impact in paediatric ALCL thus suggesting that those staging systems may indeed be not useful for ALCL in children. Differently, we and others have recently reported that minimal disseminated disease represent a negative prognostic feature [11,12].

Treatment of ALCL has shown significant variations during the years and different approaches in children compared to adults. In North America, children with ALCL have for a long time been treated in the trials for large cell lymphomas, regardless of the immunological subtype. Reports published so far include patient series treated either based on stage of disease according to the St. Jude staging system, as in the BFM protocols, or treated independently of stage as in the French group. In most European collaborative groups ALCL was treated following a strategy in use for B-cell NHL,

based on four to six 5-day chemotherapy cycles. The Kaplan–Meier estimated 5-year event-free survival was 76% overall in the BFM experience [6], and 66 to 83% in the French protocols at 3 years for the two different risk-groups [5]. Another recent report is the UKCCSG study, based on chemotherapy cycles similar to the French protocol, achieved an OS and EFS at 5 years of 65% and 59% respectively [33]. These differences may reflect different characteristics of patients enrolled with regard to risk factors.

The experience of US paediatric oncology groups is based on the use of chemotherapy regimens containing in general more anthracyclines, as in the CHOP schema used at St. Jude Children's Hospital [36] or in the APO regimens used by the POG Group [37].

An exception to this chemotherapy strategy based on short chemotherapy pulses is the Italian experience based on the modified leukaemia-like treatment LSA2-L2 protocol. Despite the longer duration of treatment the results achieved were not superior to the outcome observed with shorter treatment strategies [38,39]. Table 2 reports a summary and features of the most significant paediatric ALCL trials. Interestingly, CNS involvement at diagnosis was rare in all of the series, suggesting that CNS prophylaxis may be less intense than in other NHL. The features and outcome for adolescents do not appear to differ significantly from children, but this aspect deserves further consideration in the future clinical trials on ALCL. It should be noted that, differently from other types of NHL, ALCL patients may recur frequently, but can also more frequently be rescued by second line therapies. Among second line treatment, a variety of approaches have been attempted, ranging from rather non intensive chemotherapy such as weekly vinblastine to more aggressive therapies including high-dose intensive chemotherapy followed by autologous or allogeneic BMT. The role of the different strategies remain to be clarified, both in the paediatric and adult settings. By comparison, there is less information on the optimal treatment to be adopted in ALCL of adulthood. A number of studies were based on the CHOP regimen, but MACOP-B or similar regimens were also used. On a series of 90 patients treated with F-MA-CHOP or MACOP-B, a 5-year OS of 60% and 63% for classic type ALCL and Hodgkin-like ALCL, respectively, were obtained [40]. ALCL represent a very intriguing subtype of NHL that offer several possibilities of research to determine the optimal treatment strategy and a field where collaboration between adult and paediatric haematologist may address joint efforts.

Table 2
Characteristics and treatment results of paediatric ALCL patient series reported

Author	Number of patients	Treatment regimen	Radiotherapy on primary site[a]	CNS prophylaxis	CR rate (%)	Overall survival (%)	Event free survival (%)	Treatment duration (months)
Vecchi *et al.*, 1993 [39]	13	modified LSA2-L2	Yes	Yes	100	100 (4-yrs)	62.9 (4-yrs)	24
Sandlund *et al.*, 1994 [36]	18	CHOP or MACOP-B ± maintenance	Yes	na	na	84 (5-yrs)	57 (5-yrs)	
Reiter *et al.*, 1994 [32]	62	BFM83, 86, 90	No	Yes	93	83 (9-yrs)	81 (9-yrs)	2–5
Brugieres *et al.*, 1998 [6]	82	COP-COPADM	No	No	95	83 (3-yrs)	66 (3-yrs)	7–8
Massimino *et al.*, 1995 [34]	27	institutional protocol for lymphoblastic NHL	Yes	No	100	84 (8-yrs)	72 (8-yrs)	8–24
Seidemann *et al.*, 2001 [5]	89	BFM90	No	Yes	na	na	76 (5-yrs)	2–5
Williams *et al.*, 2002 [33]	72	COP-COPADM	No	Yes	82	65 (5-yrs)	59 (5-yrs)	5
Mora *et al.*, 2003 [25]	19	LSA2-L2	Yes	Yes	na	84 (5-yrs)	56 (5-yrs)	24
Laver *et al.*, 2005 [37]	86	APO+ maintenance	Yes	Yes	na	88 (4-yrs)	72 (4-yrs)	12
Rosolen *et al.*, 2005 [38]	34	modified LSA2-L2	Yes	Yes	88	85 (10-yrs)	65 (10-yrs)	24

[a] Criteria for administration of RT varied for some series based on the enrolment period, on disease extension or on response to induction therapy. na = not available.

Conclusions

NHL has increased in incidence during the last 25–30 years and this is particularly evident in the adolescent/young adult age groups. Differently from adults though, the histological subtype distribution is significantly different, representing the age group between 15 and 30 years, the category of patients where NHL typical of children become less frequent and where the follicular and mantle cell lymphoma manifest as well defined entities.

Outcome of patients with NHL has improved during the last two decades. The most significant improvement was achieved in children and young adolescents with an OS augmented from 50% to over 85%. Progress was also observed in the age category 15–30 years, but less strikingly than in younger patients who fare better (Fig. 4). Few comparative studies have analysed biology and genetic characteristics of adolescent and young adult NHL relative to other age groups, thus making it difficult to draw conclusions on whether results that still differ for this age category may depend on disease characteristics, on therapy or other features. Other 'environmental' issues are yet unclear as to whether they may play a role in the overall outcome of this NHL patient population: among them, it may be of interest to consider the role that the paediatric unit may have versus an adult haematology department or whether compliance to treatment by patient may be influenced by the physician and nurses in charge of adult versus paediatric patients and how the health-care personnel comply with the indication of the therapeutic protocol.

As this is a rather peculiar category of patients, if we aim to improve our knowledge and the outcome of NHL in adolescents and young adults, a close collaboration between paediatric and adult oncology groups is warranted.

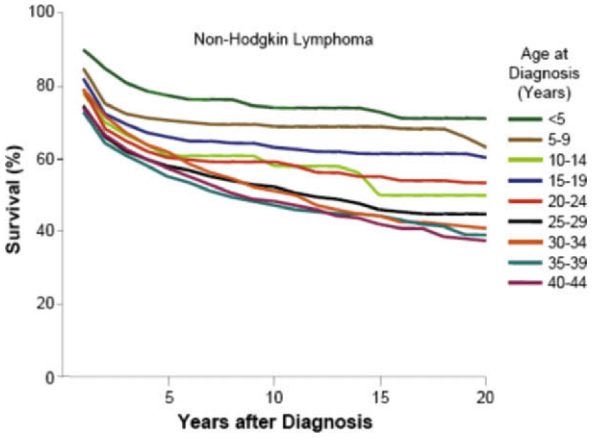

Fig. 4. Survival rates for non-Hodgkin lymphoma, SEER 1975–1998.

Conflict of interest statement

None declared.

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