

## CHAPTER 15 CHILDHOOD LYMPHOMA

### 15.1 Introduction

The majority of children with lymphoma have high-grade disease. Most key management principles apply to both children and adults.

All patients should be treated at paediatric oncology centres and entered into clinical trials where possible. This is feasible as all centres in Australia are associated with the United States Children's Oncology Group (COG).

### 15.2 Epidemiology

Lymphoma makes up about 7–8% of childhood cancers. About 40–50 new cases are diagnosed in Australia each year.<sup>1</sup> There is a male predominance that is most marked in lymphoblastic lymphomas. Apart from the role of EBV in Burkitt's lymphoma, aetiology for the majority is unclear. Genetic DNA fragility disorders such as ataxia telangiectasia account for very few cases.

### 15.3 Diagnosis and staging

The recommendations from Chapter 13 regarding the management of highly aggressive lymphomas in adults are equally relevant to children.

The four major subtypes of childhood lymphoma are defined as:

- small non-cleaved cell (Burkitt and Burkitt-like) (40%)
- lymphoblastic (30%)
- B-cell large-cell lymphoma (30%)
- anaplastic large-cell lymphoma (10%)

Childhood lymphoma is usually extranodal at presentation. A majority (75%) present with advanced disease. The key clinical features of these subtypes are summarised in Table 15.1.<sup>2</sup>

**Table 15.1 Lymphoma in children**

Histology	%	Immunophenotyping	Clinical presentation
Small non-cleaved (Burkitt and Burkitt-like)	40	B-cell 100%	Abdomen, head, neck, BM, CNS
Lymphoblastic	30	T-cell 90%	Mediastinum, lymph nodes
		B-cell 10%	CNS, BM, bone
Large cell	20	B-cell 100%	Mediastinum, abdomen
Anaplastic large cell	10	T-cell 70%	Skin, mediastinum, liver, spleen
		Null 20%	Abdomen
		B-cell 10%	

Source: Cairo<sup>2</sup>

Currently, there are several staging systems for childhood lymphoma: St. Jude, Children's Cancer Group, French Society of Pediatric Oncology (SFOP), and United Kingdom Children's Cancer Study Group (UKCCSG).<sup>2</sup> These reflect the diverse presentation, relatively small number of patients, and escalating cure rate in recent times.

#### **15.4 Management strategies**

Children with lymphoma uniformly have rapidly growing tumours with frequent visceral spread and involvement of the bone marrow and central nervous system. The high tumour burden places the child at high risk of serious metabolic complications even before therapy has commenced. The generally prompt response to therapy, although gratifying, can lead to serious life-threatening tumour lysis. The management of this issue and other complications arising during the early stages of therapy are discussed in Chapter 13. The complexity of current modern protocols, together with the need to have prompt and responsive teams to deal with acute complications, demands that children be managed in specialised units.

#### **15.5 Burkitt and Burkitt-like lymphomas**

In Burkitt lymphoma, short duration, intensive chemotherapy has been shown to be superior to less intensive, longer duration therapy as used in the treatment of ALL.<sup>3</sup> The mainstay of therapy in these protocols is cyclophosphamide, high-dose methotrexate, high-dose cytarabine, doxorubicin, vincristine, etoposide and steroids.

The role of surgery in modern treatment regimens is limited to obtaining adequate biopsy and management of acute emergencies (e.g. bowel obstruction). In selected patients, complete resection of small localised tumours (e.g. stage I or II abdominal masses) may be appropriate, providing it can be undertaken with minimal morbidity.<sup>4</sup>

The SFOP LMB 89 and the German BFM 90 protocols are the most effective reported. They have been used on large numbers of patients, with EFS rates of more than 90% for all patients; 80–90% for patients with stage IV Burkitt lymphoma and B-cell leukaemia, and 98–100% for stage I and II patients.<sup>5,6</sup> With such therapy, the significance of most prognostic factors has disappeared.

**Table 15.2 Results of various protocols in the treatment of paediatric B-cell lymphomas**

Study	Group	No. patients	3yr event-free survival (%)
Patte et al. 2001 <sup>5</sup>	LMB 89		
	Stage I and II patients	122	96±4
	Stage III patients	280	93±3
	Stage IV	97	95±4
	Leukemic patients	67	79±8
Reiter et al. 1999 <sup>6</sup>	Berlin-Frankfurt-Munster		
	Stage I	49	95±5
	Stage II	114	98±1
	Stage III	171	86±3
	Stage IV	23	83±8
	Leukemic patients	56	76±8
Link et al. 1997 <sup>7</sup>	Paediatric Oncology Group protocols		
Brecher et al. 1997 <sup>8</sup>	Stage I and II	>100	88
Bowman et al. 1996 <sup>9</sup>	Stage III	64	79±6
	Stage IV	59	79±9
	Leukemic patients	74	65±5
McGrath et al. 1996 <sup>10</sup>	US National Cancer Institute 89-C-41		
Adde et al. 1998 <sup>11</sup>	Low-risk patients	18	100
	High-risk patients	66	85
Gairo et al. 2003 <sup>12</sup>	Children's Cancer Group		
	Disseminated Disease		
	CCG 551, -503, -552	424	54 (4yrs)
	CCG 5911	46	80 (4yrs)

CNS prophylaxis is a crucial part of therapy. The use of high-dose systemic chemotherapy and intrathecal agents (MTX and Ara-C) has obviated the need for cranial or cranio-spinal radiotherapy. Indeed, some studies show that radiotherapy in Burkitt lymphomas is ineffective.<sup>13,14</sup>

Patients with completely resected stage I or II tumours (that are not in the head or neck, or epidural region) should not receive CNS prophylaxis, as the risk of CNS spread is very low.<sup>6</sup>

The prognosis for patients with CNS disease, previously poor, has dramatically improved with the above treatment approach.

Guideline — Combination chemotherapy for Burkitt lymphoma	Level of evidence	Refs
Paediatric patients with Burkitt lymphoma require intensive combination chemotherapy of relatively short duration.	III	3

Guideline — CNS chemoprophylaxis — advanced lymphoma	Level of evidence	Refs
Central nervous system (CNS) chemoprophylaxis is mandatory for all patients with advanced-stage disease, and for those with localised head and neck disease.	III	13, 14

## 15.6 Lymphoblastic lymphomas

### 15.6.1 Chemotherapy

For children with T-LL, an ALL regimen is considered standard therapy. This principle arose from the results of a randomised Children's Cancer Group Study.<sup>3</sup>

Treatment intensity for children with LL is adapted to the risk of relapse. All children require prolonged therapy irrespective of their risk classification. Those with extensive disease are best treated with a high-risk ALL-type regimen for a prolonged period (two years). Those with limited-stage disease also benefit from a longer duration of treatment but with a regimen for low-risk ALL. Optimal duration of therapy for patients with localised LL has not yet been defined.<sup>7,15</sup> Survival rates for young patients with LL treated with ALL-based protocols ranges from 80% to 90%.<sup>16-22</sup>

### 15.6.2 Radiotherapy

Radiation therapy does not have a role in frontline therapy if effective combination chemotherapy is used. This applies to patients with localised or advanced and disseminated disease.<sup>7,15</sup> Radiotherapy might be indicated in certain selected situations such as spinal cord compression or thoracic outlet obstruction. However, even in such emergencies, initial treatment with chemotherapy is recommended given the unique chemosensitivity of LL (and the deleterious effects of external beam radiation on growing tissues). Local radiotherapy does not appear to benefit patients with overt testicular or bone disease.

Radiotherapy does have a role in the treatment of overt CNS disease. In certain centres and cooperative groups, it is also used for CNS prophylaxis. CNS prophylaxis is an integral component of therapy for children with T-LL. Intrathecal therapy with MTX and ARA C is considered standard therapy. In patients with extensive T-LL, cranial radiotherapy is currently used for prophylaxis, but the importance of its use is yet to be adequately established.<sup>21,22</sup> Patients with CNS disease at diagnosis require cranio-spinal radiotherapy.

### 15.6.3 Surgery

Surgical resection or debulking of lymphoma is no longer used or recommended. The main determinant of outcome is the tumour bulk at presentation, not the extent of surgical resection. This principle, first clearly established in Burkitt lymphoma, has been extended successfully to patients with LL.<sup>12,23,24</sup> Surgery has a clear role in selected patients who present with significant symptoms (GI obstruction/acute abdomen).

**Table 15.3 Treatment results in paediatric T-LL**

Study	Protocol/group	No. of patients	Results
Reiter et al. 2000 <sup>21</sup> Grenzebach et al. 2001 <sup>25</sup>	BFM 90	101	5yr EFS 92%
Anderson et al. 1993 <sup>3</sup>	LSA2L2/CCG	164 (advanced stage)	5yr EFS 64%
Hvizdala et al. 1988 <sup>26</sup>	LSA2L2/POG	76	3yr EFS 58%
Patte 1992 et al. <sup>19</sup>	LSA2L2 (Goustave-Roussy)	84	5yr EFS 78%
Amylon et al. 1999 <sup>27</sup>	POG 8691-8704	195(advanced stage)	4yr EFS 78%
Eden et al. 1992 <sup>22</sup>	UKCCG8503	95(advanced stage)	4yr EFS 65%
Reiter et al. 1995 <sup>20</sup>	BFM-85/BFM	77	7yrEFS 78%
Tubergen et al. 1995 <sup>28</sup>	CCG 502	281	5yr EFS 84% (localised) 67% (advanced)
Millot et al. 2001 <sup>29</sup>	EORTC 58881	60 (advanced stage)	6yr DFS 76%

Guideline — Management of lymphoblastic lymphoma	Level of evidence	Refs
Children with lymphoblastic lymphoma should be treated with a chemotherapy regimen designed for the therapy of acute lymphoblastic leukaemia (ALL).	III	3
The duration of treatment may be able to be adjusted, based on risk factors.	III	3, 7, 15
Treatment must include central nervous system (CNS) prophylaxis.	III	21, 22
Patients with central nervous system (CNS) disease at diagnosis require cranio-spinal radiotherapy.	IV	7, 15

## 15.7 B-lineage lymphoblastic lymphoma

This uncommon subtype accounts for 15% of lymphoblastic lymphoma in children. ALL-type therapy is the optimal treatment.<sup>16,30</sup>

## 15.8 Large-cell lymphoma (LCL)

### 15.8.1 B-cell LCL

#### *Limited stage*

Children with localised B-cell LCL have an excellent (90–95%) five-year event-free survival as demonstrated by cooperative group regimens.<sup>5,6,15,31</sup>

**Table 15.4 Treatment and outcome of limited-stage (localised) B large-cell lymphoma in children and adolescents**

Variable	CCG <sup>31</sup>	POG <sup>15</sup>	SFOP <sup>5</sup>	BFM <sup>6</sup>
Subjects (n)	52	27	52	71
Treatment	COMP	COMP	COPAD	CP, DX, FROS, MTX, Ara-C, VP-16, DX, MTX, CTX, DOX
Length (months)	6	8	1.5	3
5-year EFS (estimated)	95%	88%	99%	100%

These studies established that cure in the majority of children with limited-stage disease can be achieved with therapy that is intensive, of short duration (2–6 months), and does not require radiotherapy, surgery, or extensive CNS prophylaxis. Although several effective regimens have been identified, randomised comparison trials have not been undertaken to define a standard treatment.

#### *Advanced stage*

Event-free survival of 90% is achieved using intense regimens originally developed for patients with small non-cleaved cell (Burkitt's) lymphoma.<sup>5,6,32,33</sup>

**Table 15.5 Treatment and prognosis of advanced B large-cell lymphoma in children and adolescents**

Variable	CCG <sup>32</sup>	POG <sup>33</sup>	SFOP <sup>5</sup>	BFM <sup>6</sup>
Subjects (n)	18	33	62	56
Treatment	Orange	APO +	LMB	BFM
Length (months)	6	12	6	5
3-year EFS (estimated)	90%	78%	90%	95%

Guideline — Management of localised large-cell lymphoma and advanced-state disease	Level of evidence	Refs
Children with localised large-cell lymphoma require intensive short-term therapy.	III	1, 5, 6, 15, 31
Children with advanced-stage disease require intensive Burkitt-style therapy.	III	5, 6, 15, 32, 33

#### **15.8.2 Anaplastic large-cell lymphoma (ALCL)**

The optimum therapy for this subtype of NHL has not been defined for children. Recommended regimens are based on high-grade peripheral B-cell (SNCL [Burkitt's]) lymphoma protocols.<sup>34–36</sup>

**Table 15.6 Anaplastic large-cell lymphoma — results of treatment with Burkitt cell regimens**

Study group	Number of patients	CCR %	EFS %	S %	Ref	Median follow up (yrs)
High-grade B-cell regimen	82	95	66 (3yrs)	83 (3yrs)	34	4.1
BFM high-grade B-cell regimen	89		76 (all) 100% (localised) 73–79% (advanced)		35	5.6
UKCCSG high-grade B-cell regimen	72	82	59 (5yrs)	65 (5yrs)	36	4.3

Guideline — Treating anaplastic large-cell lymphoma	Level of evidence	Refs
Therapy for anaplastic large-cell lymphoma should be based on SNCL (Burkitt's) protocol until optimum therapy is defined.	III	34–36

## 15.9 Low or intermediate-grade lymphomas

Such lymphomas are rare in childhood, making incidence and frequency estimates unreliable.<sup>37,38</sup> Most patients present with localised disease, often in the cervical legion, respond promptly to therapy, and have an excellent five-year event-free survival (greater than 90%). There is a male predominance. Histologically, both follicular and diffuse patterns of lymph node involvement are relatively common. This is referred to in Chapter 12. Optimum therapy is not defined. Conservative therapy for localised disease may be appropriate, but cannot yet be recommended.<sup>39</sup>

### 15.10 Late effects: follow up and management — a multidisciplinary approach

End-of-treatment surveillance and late effects are discussed in Sections 15.12.10 and 15.12.12 respectively.

### 15.11 Salvage therapy

Children within initially localised lymphoma who subsequently experience a local recurrence can be rescued with intensive re-treatment programs. However, relapses in children are generally systemic and rarely localised. Salvage therapy with intensive chemotherapy regimens is usually not successful. High-dose chemotherapy regimen with stem cell rescue offers a small but significant chance of long-term disease-free survival for children with large-cell lymphoma.

## 15.12 Hodgkin lymphoma

### 15.12.1 Introduction

Hodgkin lymphoma in children is a highly curable malignancy. Biologically, there is little to distinguish the behaviour of the disease and its response to therapy between adults and children. The earliest paediatric treatment regimens were modelled on those developed for adults. The recognition that the quality of long-term survival could be severely compromised by the late sequelae of therapy led to significant modifications of treatment strategies for children. There remains, however, considerable overlap with adult practice in the way paediatric patients are evaluated and in the

principles of therapy that are applied. This reflects the common basic biology of the disease (see also Chapter 11).

### 15.12.2 Epidemiology

Each year in Australia, approximately 30–40 children under the age of 15 years are diagnosed with Hodgkin lymphoma.<sup>40</sup> The incidence in the 10–15 year age group is more than double the rate under ten years of age.<sup>41</sup> The bimodal age distribution in Australia is typical of developed countries, with an early peak in the incidence of the disease between 20 and 30 years. Within this peak there is variability in the features of the disease. For example, there is a marked male predominance (4:1) under the age of ten years, which gives way to an equal male and female incidence in adolescents and young adults.<sup>42,43</sup> Although the nodular sclerosis variant is the most common histological subtype in children overall, this is not the case for those under ten years of age, for whom mixed cellularity is the predominant variant. There is also significant ethnic and geographical variation in the distribution of histological subtypes.<sup>44</sup>

Lower socioeconomic status is associated with children presenting under the age of ten years. Conversely, a higher socioeconomic background is associated with Hodgkin lymphoma in older children and adolescents.

### 15.12.3 Pathogenesis and aetiology

Hodgkin lymphoma is a B-cell malignancy. The strong association of Epstein Barr virus (EBV) with HL in adults is also present in the children. Distinctive features of the association with EBV in the paediatric age group include a high incidence in Asian children, in those with the mixed cellularity variant, and in the younger age group (less than ten years). Children with genetic (e.g. ataxia telangiectasia) and acquired (e.g. HIV) immunodeficiency disorders have a higher incidence of HL. The influence of genetic factors is also seen in the increased risk faced by first-degree relatives and especially, identical twins.<sup>45,46</sup>

Malignant cells in involved nodes or tissue in HL account for less than 1% of the total cell population. This feature that makes it imperative that adequate tissue (by excision or open biopsy) is obtained for diagnostic purposes. Core biopsy is usually inadequate for this purpose.

Disease classification is the same for children and adults.

Overall in children, the nodular sclerosis variant is the most common, accounting for 60% of cases (40% of diagnoses under the age of ten years, and 70% of older children and adolescents). Children with the mixed cellularity subtype make up 30% of the total, and these patients are more likely to present with advanced disease. Lymphocyte predominant subtypes are relatively uncommon, making up about 10% of the total. Lymphocyte-depleted HL is rare in childhood.

### 15.12.4 Clinical features

The most common presentation is with cervical and/or supraclavicular masses that are otherwise asymptomatic. Two thirds of children have mediastinal involvement. Subdiaphragmatic presentation is rare. Rarely, patients present with signs of auto-immune haemolytic anaemia or thrombocytopaenia.

### 15.12.5 Staging

The staging system is the same as used in adults. Modern treatment and imaging modalities have virtually eliminated staging laparotomy.

### 15.12.6 Evaluation

Patient evaluation is essentially similar to that recommended for adults: bone marrow biopsy (bilateral) in any patient with B symptoms, or those with stage III or IV disease. The yield in children with localised disease (without B symptoms) is very low. Marrow biopsies will require a general anaesthetic in children.

Malignant cells in involved nodes or tissue in HL account for less than 1% of the total cell population. This makes it imperative that adequate tissue (by excision or open biopsy) is obtained for diagnostic purposes. Core biopsy is usually inadequate for this purpose. Twenty per cent of core biopsies give false negative results.<sup>47</sup>

It is important to consider fertility preservation after diagnosis is confirmed, by either sperm storage (pubertal) or ovarian biopsy and storage (any age).

PET scan detects more sites than gallium, and is better to assess residual disease. PET scan, however, can be too sensitive and positive regions might need to be assessed by biopsy, especially when the scan is performed to assess early response or after completion of therapy.<sup>48-51</sup>

Guideline — Open biopsy to ensure less diagnostic error	Level of evidence	Refs
Open biopsy to ensure sufficient tissue for analysis is the procedure of choice to minimise diagnostic errors (see Chapter 10 — Surgical biopsy in lymphoma).	III	47

### 15.12.7 Principles of therapy

All patients should be treated at paediatric oncology centres and entered into clinical trials where possible. This is feasible, as all centres in Australia are associated with the United States Children's Oncology Group (COG).

1. With modern treatment, overall survival of children with HL is 90%.<sup>52</sup> However, the late effects of therapy (second malignancies) are directly responsible for a large proportion of patient deaths.<sup>53</sup> Newer therapies developed over recent years focus on preventing long-term toxicity.<sup>54</sup> Late sequelae of full-dose radiotherapy has resulted in a shift to using combined therapy (chemotherapy with lower-dose radiotherapy).

High cure rates can be achieved with programs ranging from single modality radiotherapy to varying combined modality regimes. These options vary in terms of rates of relapse, chance of salvage therapy, and toxicity. Parents, as well as older children when adequately informed, may express a preference for the type and style of therapy.

### 15.12.8 Treatment of localised disease

In selected (but not all) centres in Australia, therapy with chemotherapy alone for all patients has been the standard treatment for many years. Such protocols were established to avoid the effects of radiotherapy, and in a desire to eliminate staging laparotomy as a diagnostic/prognostic tool. However, there are few studies that demonstrate the value or superiority of this approach for all patients. Both the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG) have conducted randomised studies comparing chemotherapy alone with combined modality treatment (chemotherapy reduced dose, involved-field radiotherapy) in patients with intermediate to advanced disease stages.<sup>55,56</sup> In these two sets of studies, the overall survival was equivalent in both treatment arms. However, in the CCG study, low-dose involved-field radiotherapy improved the event-free survival (EFS). In the POG study, the addition of radiotherapy made no difference, but both groups

received a heavy chemotherapy schedule. Similarly, the German paediatric cooperative group evaluated a chemotherapy-alone approach in patients who achieved a complete remission (CR), and compared this to patients who had not achieved CR after the same chemotherapy and who went on to receive involved-field radiotherapy. Again, both groups had equivalent overall survival, but the group receiving chemotherapy alone had a lower EFS (81% versus 92%,  $P=0.01$ ).<sup>57</sup>

Chemotherapy-only programs for patients with localised or bulky disease have not yet been adopted as standard therapy by larger national cooperative children's cancer groups in the United States or Europe. Rather, such groups continue to explore in randomised studies the selected use of chemotherapy alone in discrete, well-defined cohorts of children. This approach highlights the clear move by the groups towards limiting radiotherapy as well as reducing chemotherapy exposure, particularly in patients with localised disease. In addition, these clinical studies are evaluating 'response-based' therapies with the aim of limiting treatment exposure in children.

Guideline — Low or intermediate-risk disease — combined-modality therapy	Level of evidence	Refs
Children with localised low-risk or intermediate-risk disease (that is, they have adverse prognostic factors, for example, mediastinal mass, bulky disease, B symptoms) are best treated with combined-modality therapy.	II	55, 56

### 15.12.9 Treatment of advanced disease

The treatment regimens adapted from adult trials (MOPP<sup>1</sup>, ABVD<sup>2</sup>) have been shown to have significant late sequelae. Over the past 15 years, concerted attempts have been made through clinical trials to diminish this late toxicity yet still maintain the excellent cure rate.<sup>52</sup> There are now numerous highly effective chemotherapy regimens for patients with advanced disease.<sup>54</sup> No one regimen is clearly superior. Recent results from the German-Austrian Hodgkin Lymphoma Group are amongst the best reported.<sup>58</sup> Regimens developed for adults such as BEACOPP<sup>3</sup> or escalated BEACOPP are dose-intensive programs that may offer further improvements in outcome for children with advanced high-risk disease.<sup>59</sup>

It is recommended that radiation alone is not a treatment option for children with classical HD, even for those with localised disease. For adults (and hence for children), radiation therapy alone is no longer the treatment of choice in most centres in the United States and Europe.<sup>60</sup>

Most children with nodular lymphocyte predominant HD present with localised disease. They have an excellent prognosis. Whether patients with stage I-A need therapy beyond surgical excision is not yet known. In patients for whom growth of tissues is not an issue (adolescents), local radiotherapy for this unique subgroup might be appropriate.

Aspects of radiotherapy are discussed in Sections 11.14–17.

<sup>1</sup> MOPP: nitrogen mustard, vincristine, prednisone, procarbazine.

<sup>2</sup> ABVD: adriamycin, bleomycin, vincristine, OTIC

<sup>3</sup> BEACOPP: bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, prednisone, procarbazine.

Guideline — Multidisciplinary treatment for advanced lymphoma	Level of evidence	Refs
For patients with advanced disease, intensive risk-adapted chemotherapy represents standard therapy. Patients who achieve prompt complete remission may not require radiotherapy. For patients who have a partial response, involved-field radiotherapy to areas of bulk disease is of benefit.	II	55, 56

### 15.12.10 Post treatment surveillance

Most children who relapse do so within two years of completing treatment. It is not known whether the early detection of recurrent disease alters outcome. Nevertheless, it is standard practice in many units to follow patients with serial CT and gallium scans (PET scans in the future) every three months for two years. Thereafter, follow up is designed to monitor the patient for late effects of therapy.

### 15.12.11 Salvage therapy

Determining appropriate salvage therapy depends very much on factors such as the nature of therapy the patient received previously, the duration of remission, the site of relapse, and changes to the underlying histology. Conventional treatment programs may prove effective in patients who have had minimal prior therapy. However, standard care for most patients who experience an early relapse associated with B symptoms, or have a stage II or greater late relapse, is autologous stem cell transplantation.<sup>61,62</sup>

### 15.12.12 Late effects

All paediatric oncology units in Australia have a comprehensive program of following children and adolescents who are long-term survivors of childhood cancer. Specific late effects for long-term survivors of HL include:

- soft tissue and bone growth abnormalities including avascular necrosis (steroid effect)
- pulmonary complications (bleomycin, radiation)
- cardiovascular sequelae (anthracyclines, radiation)
- endocrine abnormalities including hypothyroidism, infertility
- second malignant neoplasms

## 15.13 References

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