CHAPTER 14 HIGH-GRADE LYMPHOMA

14.1 Introduction

The high-grade lymphomas (HGL) are a small group of histologically diverse tumours with a number of biological and clinical features in common. The entities included in this chapter are:

- Burkitt lymphomas (BLs)
- lymphoblastic lymphomas (LLs) of precursor-T and B-cell types.

These are rare lymphomas, affecting predominantly younger people, and characterised by very high growth rates. Patients frequently present with rapidly growing tumours that interfere with or obstruct vital organ function. For example, the mediastinum is a common site of presentation of LL, leading to superior vena cava obstruction, tracheal compression, or pericardial effusion, frequently presenting as an acute medical emergency. Similarly, ureteric obstruction may result from a rapidly enlarging retroperitoneal mass due to BL. Efforts at diagnosis are often compromised or truncated because of the rapid development of medical complications from the underlying disease. The high-grade lymphomas have a high propensity to disseminate into bone marrow, central nervous system (CNS) and other sanctuary sites, a feature that shapes the treatment strategy for these patients.

The rarity of these lymphomas, the frequency of complications related to early disease and treatment, and the complexity of protocols for curative therapy, argue in favour of these patients being treated by experienced specialist teams.

14.2 Epidemiology

There are few epidemiological reports on the incidence of HGL in Western populations. Lymphoblastic lymphoma accounts for one third of lymphoma in children, but only 3–5% of lymphoma in adults. That equates to about 160 cases per year for the whole of Australia.[1]

In adults, the median age at diagnosis for precursor T-LL is in the early 20s, though some reports suggest that precursor B-LL occurs in older patients.[2–4] T-LL is much more common in males than females, with male:female ratios ranging from 2:1 to 4.5:1.[4,5]

14.3 Comments on diagnosis and staging

14.3.1 Burkitt and Burkitt-like lymphoma

Summary of clinicopathological features

Clinical	Rapid onset of bulky disease due to short doubling time. May present as acute leukaemia with blood and bone marrow involvement (L3/ALL). Tumour lysis syndrome seen in treatment of bulky disease. Clinicopathological variants: *Endemic*: African, 4–7 years, male predominance. Involves jaws, facial bones, orbit. Less often: ileum, caecum, ovaries, breast or kidneys. *Sporadic*: children and young adults, male predominance. Ileocaecal mass. Less often: ovaries, breast or kidneys. *Immunodeficiency associated*: usually HIV associated.
Morphology	Monotonous, intermediate to size cells with multiple nucleoli, basophilic, often vacuolated cytoplasm. High turnover with apoptosis, tingible body macrophages and abundant mitoses. *Variants*: BL with plasmacytoid differentiation; atypical Burkitt/Burkitt-like.
Immunophenotype	IgM, CD19+, CD20+, CD22+, CD79a+, CD10+, *bcl-6*+, CD5-, CD23-, *bcl-2*-, TdT-. Endemic: CD21+, sporadic CD21-. A high-growth fraction (Ki-67) of 100% is required, but not specific.
Genetics	Somatic Ig VH rearrangement t(8;14). *Variants*: t(2;8), t(8;22) EBV+ in virtually all endemic cases, 25–40% of immunodeficiency-related cases. A diagnosis of Burkitt-like lymphoma requires specific evidence for *c-myc* dysregulation.

Burkitt and Burkitt-like lymphoma have been and to some extent remain a source of confusion in relation to clinicopathological definitions, pathological characteristics (both at light and ultrastructural levels), and clinical behaviour. Burkitt lymphoma is defined pathologically by the t(8;14), t(2;8), or t(8;22) chromosomal translocations involving the *c-myc* gene, whereas the diagnosis of Burkitt-like lymphoma (BLL) has been considerably less precise.[6]

From the epidemiological standpoint, Burkitt lymphoma exists as three distinct variants:

- *endemic BL*, which occurs in equatorial Africa and New Guinea
- *immunodeficiency-associated BL*, which occurs most frequently in association with human immunodeficiency virus infection
- *sporadic BL*, which accounts for approximately 2% of all lymphomas in developed countries.

The accompanying recommendations apply only to sporadic BL and BLL.

Within the defined pathological group of Burkitt lymphoma, BLL, and B-cell acute lymphoblastic leukaemia (ALL) (L3) is a clinical entity characterised by a short history of rapidly developing symptoms and signs, and which without treatment, results in life-threatening complications within days to weeks. This clinical entity has now been most reliably defined pathologically as a malignant lymphoma exhibiting essentially 100% positivity for the proliferation marker Ki-67.

The pathological diagnosis can be made on biopsy of nodal or extra-nodal tissue, or on bone marrow aspirate and trephine biopsy in leukemic patients. For the purpose of these guidelines, the finding of 100% Ki-67 positivity on immunostaining is required for the diagnosis of BL or BLL.[7] All such cases should be referred to a specialist lymphoma histopathologist for diagnostic confirmation.

With regard to staging investigations, patients with suspected or confirmed BL or BLL should have full staging procedures preferred, including a complete blood count, bone marrow aspiration and

trephine biopsy, full biochemical profile, including LDH and uric acid, and serum protein electrophoresis. Viral serology for HIV, hepatitis B and C, and EBV should be performed. CAT scans of neck, chest, abdomen and pelvis should be carried out. A CSF sample should be obtained by lumbar puncture, and where clinically indicated, CNS imaging by CAT scans or MRI may be necessary.

14.3.2 Lymphoblastic lymphomas

Summary of clinicopathological features: precursor T lymphoblastic leukaemia/lymphoma

Clinical	Mediastinal mass, respiratory embarrassment, pleural effusion, +/- high WCC and marrow involvement. Other sites of predilection — CNS and gonads in addition to lymph nodes, spleen, liver, skin, Waldeyer's ring. Outcome similar to B-ALL.
Morphology	Diffuse nodal involvement +/- follicular sparing; 'starry-sky' appearance; medium-sized lymphoblasts; nuclei round or convoluted; finely granular chromatin; nucleoli typically inconspicuous.
Immunophenotype	TdT+; variably express CD1a, CD2, CD3, CD4, CD5, CD7, CD8; CD4/8 may be co-expressed; CD10 variable; pan-B antigen negative; high proliferation index (Ki-67+).
Genetics	Clonal rearrangements of TCR genes; IgH clonally rearranged in up to 20% cases; TAL-1 microscopic deletion 25% cases; del(9p) 30% cases; one third have rearrangements involving TCR genes and a variety of partner genes.

Summary of clinicopathological features: precursor B lymphoblastic leukaemia (B-ALL) or lymphoma (B-LBL)

Clinical	B-ALL: predilection for CNS, lymph nodes, spleen, liver and gonads. Present with bone marrow failure. B-LBL: skin, bone, soft tissue and lymph nodes.
Morphology	B-ALL: small to intermediate-sized cells with dispersed, fine chromatin, multiple, variable nucleoli, blue–grey cytoplasm. Occasionally hand-mirror cells, coarse azurophilic granules (t(9;22)(q34;q11.2)). B-LBL: diffuse, rarely partial effacement. Small to intermediate-sized cells with rounded, variable convoluted nuclei, dispersed chromatin, moderate mitotic activity. Often 'starry sky' appearance. Resembles T-precursor neoplasms. May form 'Indian file' pattern resembling lobular carcinoma of breast.
Immunophenotype	TdT+; HLA-DR+; CD19+, cCD79a+. CD10+ and CD24+ except in variant (4;11)(q21;q23). CD20, CD22 and CD45 variable. CD13 and CD33 may be expressed in B-ALL/LBL. CD10 and cIg expression define level of maturation. SIg usually absent except some cases of pre-BALL/LBL. CD43 often positive. Moderately high proliferation index (Ki-67).
Genetics	*Good prognostic groups:* Hyperdiploid >50 (DI 1.16 to 1.6) t(12;21)(p13;q22) (*TEL/AML1* fusion) *Intermediate prognostic groups* Hyperdiploidy<51 Near triploidy del(6q); del(9p); del(12p) *Poor prognostic groups:* t(9;22)(q34;q11.2) (*BCR/ABL* fusion with age-related variants) t(4;11)(q21;q23) (*AF4/MLL*) t(1;19)(q23;p13.3) (*PBX/E2A*) Hypodiploidy

Comments on diagnosis and staging

The lymphoblastic lymphomas form a second group of high-grade NHL with discrete cytological, histological, and clinical features. The predominant type is T-cell lymphoblastic lymphoma (T-LL), a tumour derived from immature thymocytes and closely related to the T-cell variant of acute lymphoblastic leukaemia (T-ALL). B-cell LL is a very rare and clinically more heterogeneous syndrome that requires separate consideration.

The defining pathological features of T-LL are the cytological findings of medium to large lymphoblasts, often with convoluted nuclei, and the characteristic immunophenotype, with expression of early T lineage antigens. In certain circumstances, the finding of these two characteristics on needle biopsy may be sufficient to make a confident diagnosis of T-LL.

Patients with T-LL frequently present with rapidly progressive supra-diaphragmatic lymphadenopathy, or with symptoms relating to superior vena caval obstruction, tracheal compression, or pleural or pericardial effusions. These clinical symptoms may rapidly evolve into medical emergencies, requiring rapid diagnosis, staging and management. Early involvement of bone marrow and/or CNS is a frequent event.

The distinction between T-LL and T-ALL is often contentious. Both disease entities are closely related, being derived from malignant transformation of cortical thymocytes. While the genetic and cytogenetic abnormalities observed in T-ALL and T-LL are more diverse than in the Burkitt

lymphomas, there is a similar distribution of these molecular changes, and overlapping cytological and immunophenotypic findings. Both diseases involve the bone marrow. A consensus cut-off of 25% has been applied, therefore, to distinguish T-LL (<25% marrow blasts) from T-ALL (>25% blasts).

Aside from the issue of marrow involvement, it is recommended that where possible, patients with suspected or confirmed T-LL have full staging procedures carried out, including complete blood count, biochemical profile including LDH and uric acid, radiological staging with chest X-ray and CAT scans of chest, abdomen and pelvis, and CSF examination by lumbar puncture. A formal tissue biopsy of nodal or extra-nodal tissue should be performed unless precluded by clinical circumstances.

Guideline — High-grade lymphoma — specialist pathologist, bone marrow and cerebrospinal fluid assessment	**Level of evidence**	**Refs**
Biopsies of tissues suspected to be Burkitt or other high-grade lymphoma should be referred for review by a pathologist skilled in lymphoma diagnosis.	IV	3
Patients with newly diagnosed high-grade lymphoma should have mandatory assessment of bone marrow and cerebrospinal fluid.	IV	8

General comments on management

In general, the same management principles apply to high-grade NHL as to all other lymphomas: accurate diagnosis based on adequate tissue biopsy, full staging of the disease clinically, pathologically and radiologically, and appropriate treatment delivered by an experienced clinical team. There are, however, a number of special circumstances that warrant the management of cases of high-grade NHL within clinical teams with particular expertise in the treatment of high-grade haematological malignancies. These factors include:

- the relative youth of these patients compared to the average age of onset of other forms of NHL
- the relatively high potential of curability with appropriate care
- the frequent difficulty in obtaining an adequate diagnostic biopsy
- the rapid pace of the disease and the frequency of serious medical complications related to intra-thoracic, abdominal, CNS and bone marrow involvement
- the risk of serious metabolic complications, such as hyperuricemia, hyperkalemia, and acute renal failure early after commencing chemotherapy, due to tumour lysis
- the complexity of combined chemotherapy and radiation therapy protocols.

Guideline — High-grade lymphoma — multidisciplinary care	**Level of evidence**	**Refs**
Patients with newly diagnosed high-grade lymphoma should ideally be managed in specialist units experienced in treating these disorders.	IV	9, 10

14.4 Burkitt lymphoma

Standard treatment programs in use for intermediate-grade NHL have been demonstrated to be unsuitable for the curative treatment of patients with BL and BLL.

Due to the relative rarity of these tumours, large randomised trials have not been conducted in BL and BLL. However, a small number of phase II studies have been reported in the past decade, demonstrating high response rates and improved cure rates with short-term high-intensity regimens.[8,11–15]

Table 14.1 Treatment results in adult Burkitt's lymphoma

Study	Protocol	Number of patients	Results
McGrath et al. 1996[11]	CODOX-M/IVAC NCI 89-C41	41 (20 adults)	2yr EFS 92%
Mead et al. 1996[12]	CODOX-M/IVAC (UKLG)	52 (all adults)	2yr EFS Low risk 83.3% High risk 59.5%
Patte et al. 1991[8]	LMB	34 (some stage IV DLCC)	35-month DFS 68%
Schwenn et al. 1991[13]	HiC-COM	20	2yr EFS 75%
Thomas et al. 1999[14]	Hyper-CVAD	26 (all adults)	3yr OS 49%
Reiter et al. 2000[16]	BFM 86	151 (all children, some large-cell NHL)	7yr EFS 81%

The general principle behind these studies is the intensified use of several chemotherapeutic agents, particularly methotrexate, cyclophosphamide, an anthracycline, and cytarabine, used in repeated short courses, with treatment lasting less than six months and not followed by maintenance therapy. The selection of drugs with excellent CNS penetration, such as methotrexate and cytarabine, appears to obviate the need for prophylactic CNS radiation therapy.

Guideline — Intensive treatment of Burkitt lymphoma	Level of evidence	Refs
Adults with Burkitt lymphoma should be treated, where possible, with intensive combination chemotherapy of relatively limited duration, according to one of the recently published treatment regimens.	III	8, 11–15

14.5 Lymphoblastic lymphoma

The optimal treatment for adults with T-LL has not been defined.

Early assessment of the results of combination chemotherapy protocols originally designed for treatment of intermediate-grade lymphoma, incorporating an anthracycline, vincristine and prednisone, plus other drugs, produced unsatisfactory results. In one study, the complete response rate was only 53%. Almost half of the patients not receiving CNS prophylaxis developed CNS disease, and only 20% were long-term survivors.[17] Although no randomised clinical trials have been conducted, CHOP-like regimens without CNS treatment and longer-term maintenance therapy appear to be inadequate therapy for T-LL.[4,17–20]

Following improved results in paediatric patients with protocols designed for management of ALL (intensive multi-drug induction and consolidation therapy, prophylactic CNS treatment, and prolonged maintenance therapy), similar treatment strategies have been applied in adults with T-LL.[19,21–35] The results from larger, recently reported phase II studies are shown in Table 14.2.

Table 14.2 Results of ALL-like regimens in adults with T-lymphoblastic lymphoma

Study	Number of cases	Regimen	CNS therapy	% CR	% DFS	% Survival
Slater et al. 1986[24]	51	L2 L10 or modified L17 or modified	IT	78	75 at 5yr (60 if leukemic)	45 at 5yr
Coleman et al. 1986[25]	44	Cy, Dox, VP, Lasp, MP, MTX	CNS RT, IT	95	35	40 at 5yr
Morel et al. 1992[19]	30	LNH-84	IT	83	44	60
	22	FRALLE	CNS RT, IT	91	52	65
	7	LALA	CNS RT, IT	86	33	57
Bouabdallah et al. 1998[33]	50	LALA or BFM	CNS RT, IT	89	45 at 5yr	49 at 5yr
	12	Various NHL		58		
Thomas et al. 1999[34]	24	Hyper CVAD	CNS RT, IT	96	72 at 3yr	80 at 3yr
Hoelzer et al. 2002[35]	45	GMALL 04/89, 05/93	CNS RT, IT	93	62 at 5yr	51 at 5yr

While initial complete response rates of up to 96% have been reported, systemic and CNS relapse rates have been high, and long-term disease-free survival rates of 45–72% have been described. These results are equivalent to those observed in ALL. Important prognostic factors reported in adult T-LL include age, serum LDH, and presence of bone marrow involvement. Differences in results reported in different series may reflect variability in patient composition based on these prognostic factors.

Although no comparative clinical trials have been conducted, the balance of opinion would favour the use of one of the ALL regimens, using at least four-drug-combination induction chemotherapy with prophylactic intrathecal treatment, intensive consolidation chemotherapy, further prophylactic treatment to the CNS with intrathecal therapy, high-dose systemic methotrexate, or cranial irradiation, followed by prolonged maintenance treatment with antimetabolite agents.

Guideline — Lymphoblastic lymphoma — intensive treatment	Level of evidence	Refs
Adults with lymphoblastic lymphoma should be treated with a regimen designed for therapy of acute lymphoblastic leukaemia.	III	19, 21
This must include CNS prophylaxis.	III	36

14.5.1 Prophylaxis and treatment of sanctuary sites

There is a high rate of relapse in the CNS during or after systemic treatment with chemotherapy for high-grade NHL (HGNHL). Patients with a high LDH or involvement of head and neck sites have been reported to be at greater risk.[36] Prophylactic treatment of the CNS is mandatory.

Radiotherapy and chemotherapy give equivalent results in terms of survival, but in one study, irradiated patients had significantly fewer episodes of CNS relapse.[37] Prophylaxis given early in the course of systemic treatment may be more effective.[25] In order to avoid late complications, chemotherapy is preferred in children. In adults, the risks of late complications are much less and radiotherapy is an alternative when there is a contraindication to chemotherapy.

The combination of radiotherapy and chemotherapy is used to treat established CNS involvement.

There is no role for prophylactic treatment of the testes.

14.5.2 Management of early treatment complications

Tumour lysis

Because of the high cellular proliferation rate, patients may present with hyperuricaemia and hyperphosphatemia, or develop it after the first dose of chemotherapy due to rapid tumour lysis. All patients should be assessed for hyperuricaemia and renal impairment prior to treatment. Prophylaxis with allopurinol and double maintenance fluids should be given before commencing chemotherapy.

Therapy with urate oxidase (now available) should be considered in patients with large tumour burden, as this agent rapidly decreases uric acid to undetectable levels by converting it to allantoin — a very high water-soluble compound. The use of urate oxidase dramatically reduces metabolic complications of tumour lysis. Hyperuricaemia should be corrected with hydration and alkalinisation and a good urine flow established before chemotherapy is given, to reduce the risk of renal failure from tumour lysis.

Hyperphosphataemia is managed with parenteral fluids, diuresis and oral calcium carbonate. (Note that sevelamer hydrochloride as a new oral intestinal phosphate-binding agent may become available.) Excessive alkalinisation of urine should be avoided. If hypophosphatemia is profound there is usually coexistent hypocalcaemia. Calcium replacement is *not* recommended unless the patient is symptomatic. In acute tumour lysis, there is a substantial risk of hyperkalaemia and risk of death. Potassium replacement must be avoided. If, despite supportive measures, metabolic disturbances or fluid balance cannot be controlled, haemodialysis will be necessary. The calibre and type of monitoring needed for patients with acute tumour lysis requires management in critical care units.

14.5.3 Complications caused by lymphoma

Airways obstruction, SVC obstruction, cardiac tamponade

Large mediastinal masses may cause severe airways obstruction at presentation. The problem may be acute because of the very rapid cell turnover in HGNHL. Appropriate respiratory support and cytotoxic treatment should be given as an emergency measure. Because of the unique chemosensitivity of T-LL, rapid responses are seen with chemotherapy. Radiotherapy may also give rapid tumour response and small doses may achieve significant tumour shrinkage. However, all patients will need to start chemotherapy within a few days and the concurrent use of mediastinal radiotherapy and anthracycline chemotherapy may cause severe mucosal reactions.

Cardiac tamponade requires prompt initiation of specific therapy together with pericardial paracentesis. SVC obstruction, although not uncommon in this setting, is not usually life threatening.

Abdominal complications

Massive abdominal involvement (commonly with ascites) is most usually due to Burkitt's lymphoma, and may be responsible for perforation and/or obstruction of bowel (including intussusception), GI haemorrhage, obstruction of ureters, IVC and lymphatics. GI haemorrhage or obstruction may require surgical intervention. Initial treatment should also include specific treatment for the lymphoma.

Ureteric obstruction may require initial management with surgical stents or nephrostomy tubes and the prompt institution of therapy. Such obstruction carries added significance in the presence of a high tumour burden, as treatment will require the establishment of diuresis, and management of hyperuricemia and hyperphosphatemia to avoid or minimise acute renal failure.

Neurological complications

Neurological emergencies include paraplegia, cranial nerve palsies, meningeal disease and intracerebral tumour. In general, excellent responses are obtained with chemotherapy. Extradural disease is the cause of paraplegia and responds promptly to systemic therapy. Delay in institution of treatment can lead to irreversible paraplegia due to compromise of the external blood supply to the cord.

Guideline — Lymphoblastic lymphoma — specialist care	Level of evidence	Refs
Patients with lymphoblastic lymphoma should be managed in units with experience in dealing with the early complications of the disease and its treatment.	IV	19, 21
Prophylaxis with fluids and allopurinol should be given before starting therapy.	IV	36

14.5.4 Assessment of response

Janicek et al. reported that early restaging gallium scans can be predictive of outcome in patients treated on CHOP regimens.[38] This may not apply to children, who have vastly superior outcome with current intensive therapy. Monitoring response with gallium scans is not recommended.

Second-look surgery is not recommended, based on the evidence presented by the Berlin-Frankfurt-Munster (BFM) Group.[15] For patients with high-risk disease who are already receiving intensive regimens, the identification of residual disease late in therapy is of limited value, as few therapeutic options remain (but might include high-dose therapy and stem cell rescue).

The early identification of slow responders with second-look surgery may be beneficial if the patient was initially assigned to a low-risk regimen because it would provide an opportunity to intensify therapy.

The role of surveillance scanning at the end of therapy is questionable because early detection of relapse is unlikely to affect outcome.

The role of new imaging modalities such as PET scanning in the follow-up surveillance of patients treated for HGNHL remains to be determined.

14.5.5 Role of adjuvant radiotherapy for sites of bulky disease

While radiotherapy improves survival in bulky intermediate-grade lymphoma, there is no evidence that it improves outcome in HGNHL. A randomised trial in children showed no survival benefit and increased acute toxicity when radiotherapy was given to large mediastinal masses.[39] The combination of radiotherapy and anthracycline-based chemotherapy increases the acute side effects of radiotherapy, particularly skin and mucosal reactions within the radiation field.

Radiotherapy may be considered in the management of residual gallium avid masses, but given the small number of such cases, there is no strong evidence of benefit. Radiotherapy may also be considered when there is airways compromise at presentation, although there is no evidence that the response to radiotherapy is any faster than that to chemotherapy.

Guideline — Radiation therapy and bulky disease	Level of evidence	Refs
Adjuvant radiotherapy is not indicated in treatment of sites of original bulk disease in high-grade lymphoma.	II	39

14.5.6 Bone marrow and stem cell transplantation

High-dose chemotherapy with autologous stem cell rescue

A number of studies have examined the role of early high-dose therapy with chemotherapy and/or total body irradiation for patients with T-LL in first complete response, followed by hematopoietic stem cell rescue with cryopreserved bone marrow or peripheral blood stem cells. Initial results suggested durable responses in up to 75% of cases, while a large series of cases collected by the EBMT showed a 63% probability of DFS at six years. One small randomised trial comparing standard chemotherapy with autologous stem cell transplantation has been reported.[42] A total of 65 patients were randomised, 31 to transplant and 34 to chemotherapy. The three-year relapse-free survival figures of 24% for chemotherapy and 55% for transplant arm were not significantly different. Other smaller phase II studies are listed in Table 14.3.[33,40,41,43–46]

Table 14.3 Results of high-dose therapy and autologous stem cell transplantation in adults with T-lymphoblastic lymphoma in first remission

Study	Number of cases	% TRM	% DFS	% survival
Milpied et al. 1989[43]	13	0	70	80 at 4yr
Santini et al. 1989[44]	12	0	75	NR
Verdonck et al. 1992[40]	9	0	67	NR
Baro et al. 1992[45]	14	9	77	85
Sweetenham et al. 1994[46]	21	14	NR	63
Jost et al. 1995[41]	12	0	42	NR
Bouabdallah et al. 1998[33]	18	0	NR	50 at 5yr
Sweetenham et al. 2001[42]	31	3	50 at 2yr	NR

At present, high-dose therapy with stem cell rescue for adult T-LL in first complete response appears to be effective therapy, but it has not been demonstrated to be superior to maintenance chemotherapy.

Allogeneic bone marrow transplantation

The role of allogeneic bone marrow transplantation in the early phases of therapy for adult T-LL has not been defined. Several small phase II studies have been reported.[33,43,47,48]

Although toxicity appears to be higher for patients receiving allografts, long-term results do not appear different from those of patients receiving autografts.

Table 14.4 Results of allogeneic bone marrow transplantation for adults with T-lymphoblastic lymphoma in first remission

Study	Number of cases	% TRM	% DFS	% survival
Phillips et al. 1986[47]	2	0	NR	NR
Ernst et al. 1986[48]	8	23	NR	69
Milpied et al. 1989[43]	12	17	67	80
Bouabdallah et al. 1998[33]	11	17	NR	78 at 5yr

Guideline — High-dose chemotherapy and autologous stem cell support	Level of evidence	Refs
High-dose chemotherapy with autologous stem cell support is effective therapy for patients with lymphoblastic lymphoma in first remission, but it has not been proven to produce superior disease-free survival. Ideally, it should be used only in the context of a clinical trial.	III	40, 41

14.5.7 Follow up and management of late effects of therapy: importance of multidisciplinary approach

Long-term follow up requires (a) that the patient eventually takes responsibility for his or her medical care and (b) the identification of a regular/consistent family medical practitioner supported by a specialist centre.

Specific issues

- fertility
- puberty delayed — rare
- growth — if CNS prophylaxis includes radiotherapy, more marked if includes spine/pituitary
- second malignant neoplasms — brain tumours cranial irradiation; myelodysplasia, AML
- hypothyroidism — scatter effect of radiotherapy
- IQ performance and psycho-social adjustment
- cardiac-anthracyclines — long-term follow up shows cardiac failure even with low doses of anthracycline

Treatment of relapse

The prognosis for patients with systemic relapse of HGNHL is poor. Responses to intensive salvage chemotherapy may be achieved, but rarely will be durable. Small case series of successful treatment of relapsed HGNHL with either autologous or allogeneic stem cell transplantation have been reported, although the proportion of long-term disease-free survival in these patients is low.

Isolated CNS or other extramedullary site relapse may be treated with local radiotherapy, but subsequent systemic relapse is usual.

14.5.8 Management of B-lineage lymphoblastic lymphoma

This accounts for 15% of lymphoblastic lymphomas in childhood. ALL-type therapy is regarded as optimal treatment.[49,50]

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