

BHS Guidelines for the treatment of Burkitt's lymphoma

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Burkitt's lymphoma is a rare but very aggressive non-Hodgkin's lymphoma characterised by an isolated translocation t(8;14)(q24;q32). The sporadic form is the sub-entity most frequently encountered in Belgium. Diagnosis and initial work-up must be completed rapidly to start treatment as soon as possible. Positron emission tomography scan is useful for initial staging and to evaluate the chemosensitivity of the tumour during and after treatment. After debulking, it is recommended to add rituximab to chemotherapy. Currently intensive short-cycle and low intensity chemotherapies are two valuable options. Radiotherapy is not indicated except in case of central nervous system involvement. Patients achieving complete remission must be followed carefully during the first year to detect recurrence of the disease. More than 80% of patients sustain their remission one year following initial treatment and are considered cured. For patients in partial remission or with chemosensitive relapse, autologous stem cell transplantation is recommended following re-induction with non-cross-resistant polychemotherapy. Monitoring complete blood counts and cognitive functions is important to detect late toxicity of the applied therapies.

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Introduction

Burkitt's lymphoma (BL) is a rare but very aggressive non-Hodgkin's lymphoma (NHL) accounting for 0.8% of all B-cell lymphomas. Three different clinical subtypes of BL are recognised: *endemic BL (eBL)*, *sporadic variant (sBL)* and *immunodeficiency-associated BL (idBL)*.¹ Endemic BL, the most common form of BL with a geographical distribution identical to that of *Plasmodium falciparum*, mainly affects facial bones; typically the jaw. In sBL, the terminal ileum, caecum and intra-abdominal lymph nodes are the most commonly affected sites. Immunodeficiency-associated BL is mainly seen in human immunodeficiency virus (HIV) positive patients

and, to a lesser extent, in the context of immunomodulatory drugs in transplant patients or patients with auto-immune disease and in patients with primary immunodeficiency disorders (PID).¹

Endemic BL is almost exclusively encountered in the paediatric population, whereas PID and transplantation-related BL are very rare. Therefore these three subtypes will not be discussed in this article.

Pathology

For the histopathological diagnosis of BL, as for all lymphoproliferations, a surgical excision biopsy is preferred over a fine needle aspirate cytological evaluation

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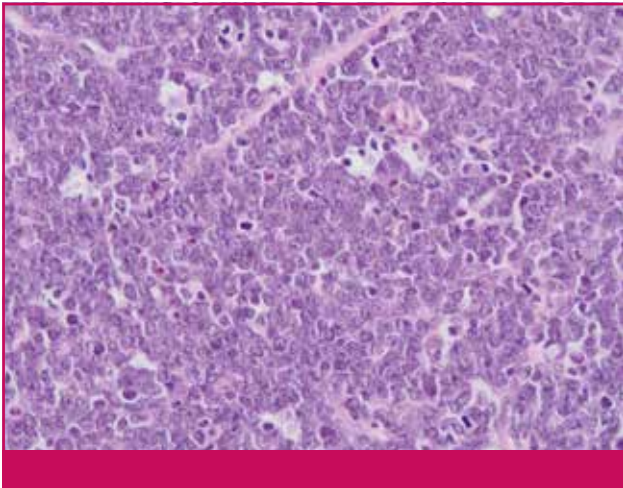


Figure 1. Illustration of a pathological preparation of Burkitt's Lymphoma (haematoxylin and eosin, 400x). Medium-sized cells with slightly irregular nuclei with coarsely dispersed chromatin often showing several nucleoli. Presence of numerous mitoses. Courtesy of Dr I. Scagnol, CHU, ULG, Liège.

or a core needle biopsy. However the latter two can be sufficient when the anatomical location is difficult to access or in case of recurrent disease.

BL cells are typically medium-sized lymphocytes with multiple small round nucleoli and little cytoplasm.¹ Their growth pattern is monotonous and diffuse, often with a 'starry sky' appearance due to a high amount of tingible body macrophages (Figure 1).

BL has a characteristic immunophenotypic profile: CD10+, CD20+, Ki67+ in nearly 100%, TdT-, Bcl2-, Bcl6+, c-MYC+. The hallmark cytogenetic aberration involves the overexpression of c-MYC oncogene, mostly due to a t(8;14)(q24;q32) or less frequently a t(8;22)(q24;q11) or t(2;8)(q24;p12) translocation, and can be detected in 90% of cases by classical karyotyping or fluorescence *in situ* hybridisation (FISH). Cytogenetic analysis is recommended to allow a clear distinction between BL and other c-MYC-driven B-NHL, especially diffuse large B-cell lymphoma. BL is mostly characterised by a simple karyotype including a t(8;14)(q24;q32) translocation with few additional abnormalities such as gain of chromosome 1q while other c-MYC-driven B-NHL will exhibit a complex karyotype with multiple chromosomal gains and/or losses (Table 1). Fifteen to thirty percent of sBL and 25-40% of idBL are EBV+, in contrast with eBL where >90% of cases are EBV+.¹ Microarray-based gene expression profiling can identify a molecular Burkitt's signature but this is not yet used in daily clinical practice.²⁻⁴

The differential diagnosis with "B-cell lymphoma, un-



Figure 2. High avidity for ¹⁸F-FDG of BL-cells. Illustration of the avidity of Burkitt's Lymphoma-cells for the ¹⁸F-FDG. PET scan at initial staging (girl, 19 years old, post transplant t(8,14)(q32;q21) pos BL, stage IV with elevated LDH serum level).

Courtesy of Prof Dr O. Gheysens, UZ Leuven.

classifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt's lymphoma", previously named 'Burkitt's-like lymphoma (BLL)' is essential (Table 1), as the outcome is poor with bad response to the classical regimens used for BL or DLBCL.^{1,5-8} This provisional histological sub-entity encompasses several aggressive B-cell lymphomas that do not entirely reflect the morphological, immunohistochemical, cytogenetic or clinical characteristics of a typical BL.

Initial work-up

Staging must be completed rapidly in order to avoid delay of therapy, which must start within 48 hours after diagnosis.

A personal history and clinical examination must be performed with attention to B symptoms (fever, night sweats and weight loss), performance status (PS) and neurological symptoms and signs.

Laboratory tests must include complete blood counts, liver and renal function, electrolytes, uric acid, lactate dehydrogenase (LDH) and serology for HIV, EBV, hepatitis B and C.

Table 1. Differential diagnosis between Burkitt's lymphoma and "B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt's lymphoma".¹

	BL	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL
CD10	+	+
BCL6	+	+/-
BCL2	-	+
Ki67	>98%	<90%
MYC	Simple	Complex
EBV	+/-	-

DLBCL: diffuse large B-cell lymphoma, BL: Burkitt's lymphoma

Contrast-enhanced chest and abdominal/pelvic CT scans are mandatory. Although BL are 18FDG-avid (Figure 2), PET scan is not formally indicated in this situation and, in clinical practice, cannot always be performed immediately.^{9,10} A bone marrow aspiration with biopsy and a lumbar puncture with flow cytometry of the cerebrospinal fluid are mandatory.

Before starting treatment, cardiac evaluation (transthoracic echocardiography), pregnancy testing in women of child-bearing age and discussion about fertility issues must be done.

Staging

Two staging systems are used: the Murphy and Hustu staging system and the Ann Arbor classification (Table 2).^{11,12} The first has been developed for paediatric BL and is now also used in protocols including adolescent and young adults (AYAs). It takes into account the frequently observed extranodal involvement and incompletely resected intra-abdominal or intra-thoracic masses. This staging system is not validated in adult BL and no comparison of the prognostic value with the Ann Arbor classification is available.

Prognostic factors and treatment stratification

Prognostic factors used to stratify patients into different treatment groups vary from one co-operative group to another. Age, PS, LDH, bone marrow and central nervous system (CNS) involvement are the most frequently used.¹² The LYSA-GRAALL Intergroup recognises three different prognostic groups. Group A comprises patients with completely resected stage I or abdominal stage II

disease (Murphy and Hustu classification). Group C encompasses patients with CNS infiltration and/or bone marrow involvement. Other patients are classified as group B.

The Dana Farber Intergroup distinguishes two prognostic groups.¹³ Patients with normal LDH, good PS (ECOG 0 or 1) and a tumour mass <10 cm are allocated to the low-risk group. Other patients are considered high-risk.

The MD Anderson Cancer Centre and the Cancer and Leukaemia Group B (CALGB) do not distinguish different prognostic groups.^{14,15}

These stratifications determine the intensity, length and type of regimen (combination and number of cycles of systemic and intrathecal chemotherapy and the need for radiotherapy). However, it seems increasingly clear that the best prognostic marker is the chemosensitivity of the tumour.

Treatment

General considerations

Unfortunately, given the low incidence of the disease, available studies include only a limited number of patients and published randomised studies are not available. Comparing studies is difficult because disease definition, stratification and median age of included patients vary.

Treatment must be started promptly (ideally within 48 hours after diagnosis) including prevention of the tumour lysis syndrome (TLS) by forced diuresis and the use of rasburicase.¹³ The unavoidable first step of treatment is the application of prephase with low-dose cyclophosphamide (e.g. 200 mg/m²/day(d), d1-5) and

Table 2. Murphy and Ann Arbor classifications.¹²

	Murphy system	Ann arbor system
Stage I	Single nodal or extranodal site <i>excluding mediastinum or abdomen</i>	Single nodal or extranodal site
Stage II	Two or more nodal areas on one side of diaphragm	Two or more nodal areas on one side of diaphragm or Localized involvement of an extralymphatic site and of one or more nodal sites on the same side of the diaphragm (IIE)
Stage IIR	<i>Completely resected intra-abdominal disease</i>	
Stage III	Two or more nodal areas on opposite sides of the diaphragm or <i>Primary intrathoracic tumour Paraspinal or epidural tumours Extensive intra-abdominal disease</i>	Two or more nodal areas on opposite sides of the diaphragm which may include/involvement of the spleen (IIIs) or localized involvement of an extranodal site (IIIE)
Stage IIIA	<i>Localized non resectable abdominal disease</i>	
Stage IIIB	<i>Widespread multiorgan intra-abdominal disease</i>	
Stage IV	<i>Central nervous system or bone marrow involvement</i>	
Favourable	Stage I or IIR	Diffuse or disseminated involvement of one or more extralymphatic sites Two single extranodal tumours on opposite sides of diaphragm <i>Also A + B depending on symptoms</i> Stage IA and IIA Stage I, II and III

Italics identify differences between the two systems.

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prednisone (e.g. 60 mg/m²/d, d1-5). In comparison with standard dose of chemotherapy, the application of this prephase limits the risk of TLS by decreasing the release of cytokines, particularly in case of high tumour burden, a situation that can be lethal given the aggressiveness and chemosensitivity of the tumour. Moreover, this procedure allows finalising the staging process.

Intensive short-cycle chemotherapies (ISCC) that include alkylating agents such as cyclophosphamide and cell-cycle phase-specific agents that cross the blood-brain barrier (i.e. cytarabine and methotrexate) are frequently combined but are associated with a high rate of haematological and non-haematological toxicities. These regimens further aim to prevent CNS extension by the administration of intrathecal therapy consisting of methotrexate, cytarabine and prednisone.^{14,15}

Low intensity chemotherapies (LIC), such as Dose Adjusted (DA)-EPOCH-R (etoposide, vincristine, cyclophosphamide, doxorubicin, prednisone and rituximab) or Short Cycle (SC)-EPOCH-R, kill tumour cells by prolonged low-concentration drug exposure.¹⁶ This type of regimen seems as efficient and less toxic compared to ISCC and may be more suitable for frailer patients (elderly or HIV+ patients). As these regimens have no drugs that cross the blood-brain barrier, they cannot be used in case of CNS involvement.

The interval between cycles of chemotherapy must be

as short as possible and a new cycle must start as soon as haematological recovery has occurred. In this setting, the use of granulocyte-colony stimulating factors is essential.

Rituximab gives sufficient promising results to recommend its adjunction to chemotherapy and it may even erase the prognostic difference between young and elderly patients. However, its administration is avoided during the debulking phase given the high risk of TLS. Involved-field radiotherapy has no place in BL, except for patients with CNS involvement. In this situation, either pancranial or craniospinal irradiation (in case of leptomeningeal disease) can be applied, taking into account the high neurological and myelosuppressive toxicity rates. The recommended dose is 40 Gy, varying between 36 and 45 Gy and depending on the clinical condition. Boost radiotherapy is possible in case of localised intracerebral disease.

In case of initial CNS invasion, the number of intrathecal chemotherapy administrations is increased.

Autologous stem cell transplantation (SCT) has no place for patients in complete response (CR) and must be reserved for patients in first partial response (PR) or in chemosensitive relapse. Due to the high proliferation rate of BL, graft-versus-tumour effects observed after allogeneic SCT are too slow to appear and to be efficient and therefore this type of transplant is not recommended.^{17,18}

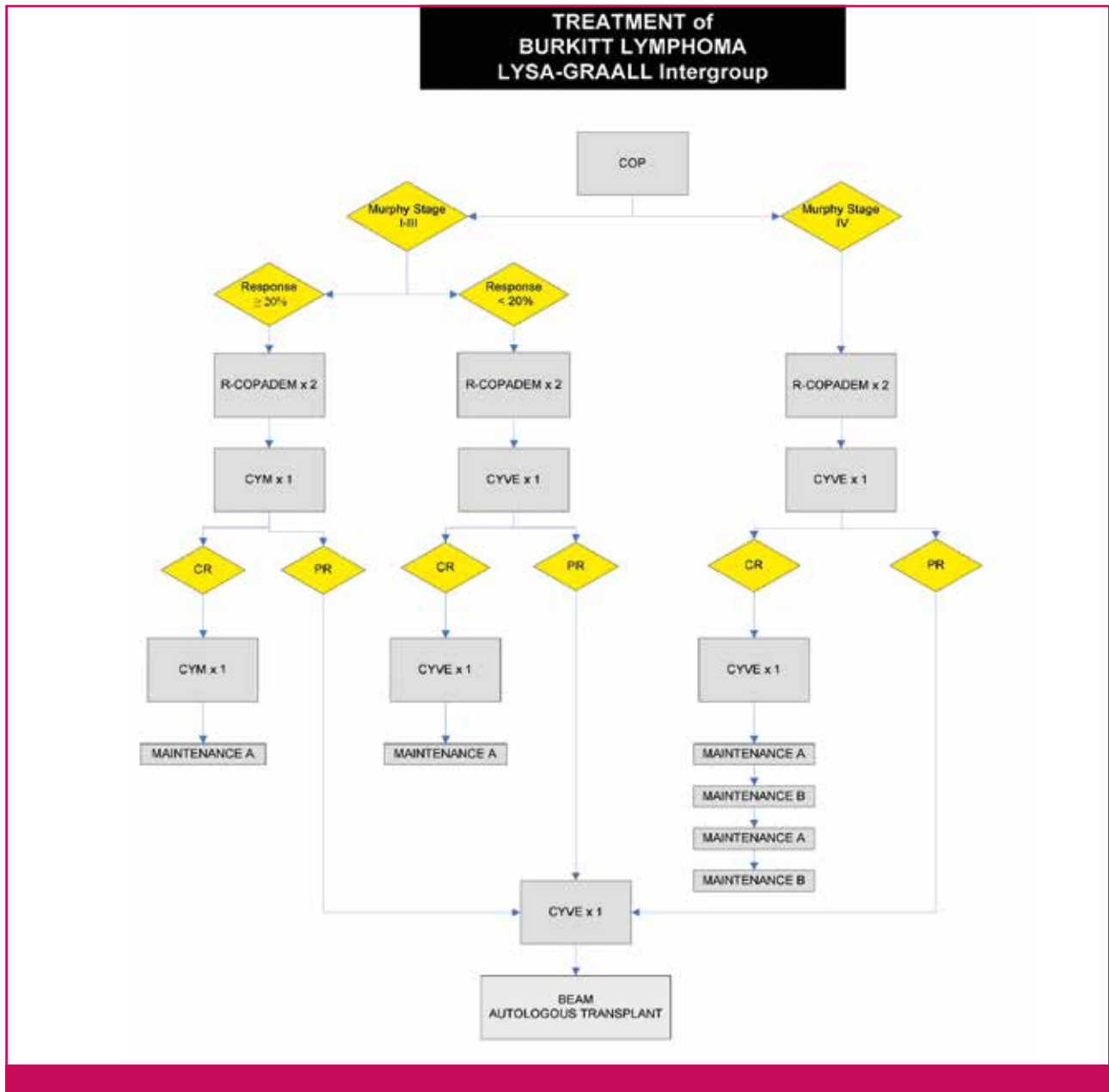


Figure 3. The LYSA-GRAALL Intergroup regimen.¹⁵

CR: complete remission; **PR:** partial remission; **COP:** cyclophosphamide, vincristine, prednisone; **R-COPADM:** rituximab, cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate; **CYM:** HD methotrexate, cytarabine; **CYVE:** cytarabine, etoposide; **MAINTENANCE A:** prednisone, vincristine, methotrexate, cyclophosphamide, adriamycin; **MAINTENANCE B:** aracytine, etoposide. **IT²:** methotrexate & solu-medrol intrathecal; **IT³:** methotrexate, cytarabine & solu-medrol intrathecal; *: dosage of methotrexate depending on age and CNS infiltration; **: number of IT injections depending on CNS infiltration; °: dosage of cytarabine depending on age; °°: dosages of cytarabine and methotrexate depending on age.

Recommended treatment schedules for first line treatment

Given the rarity of the disorder, it is highly recommended to include patients in clinical trials conducted by international co-operative groups.

Localised disease

In the rare cases of completely resected localised disease,

a short multi-agent chemotherapy program (e.g. CO-PADM x2) without CNS prophylaxis gives very good results and avoids toxicities associated with longer chemotherapy.¹⁹

Disseminated disease

Figures 3 to 6 show different treatment schedules used

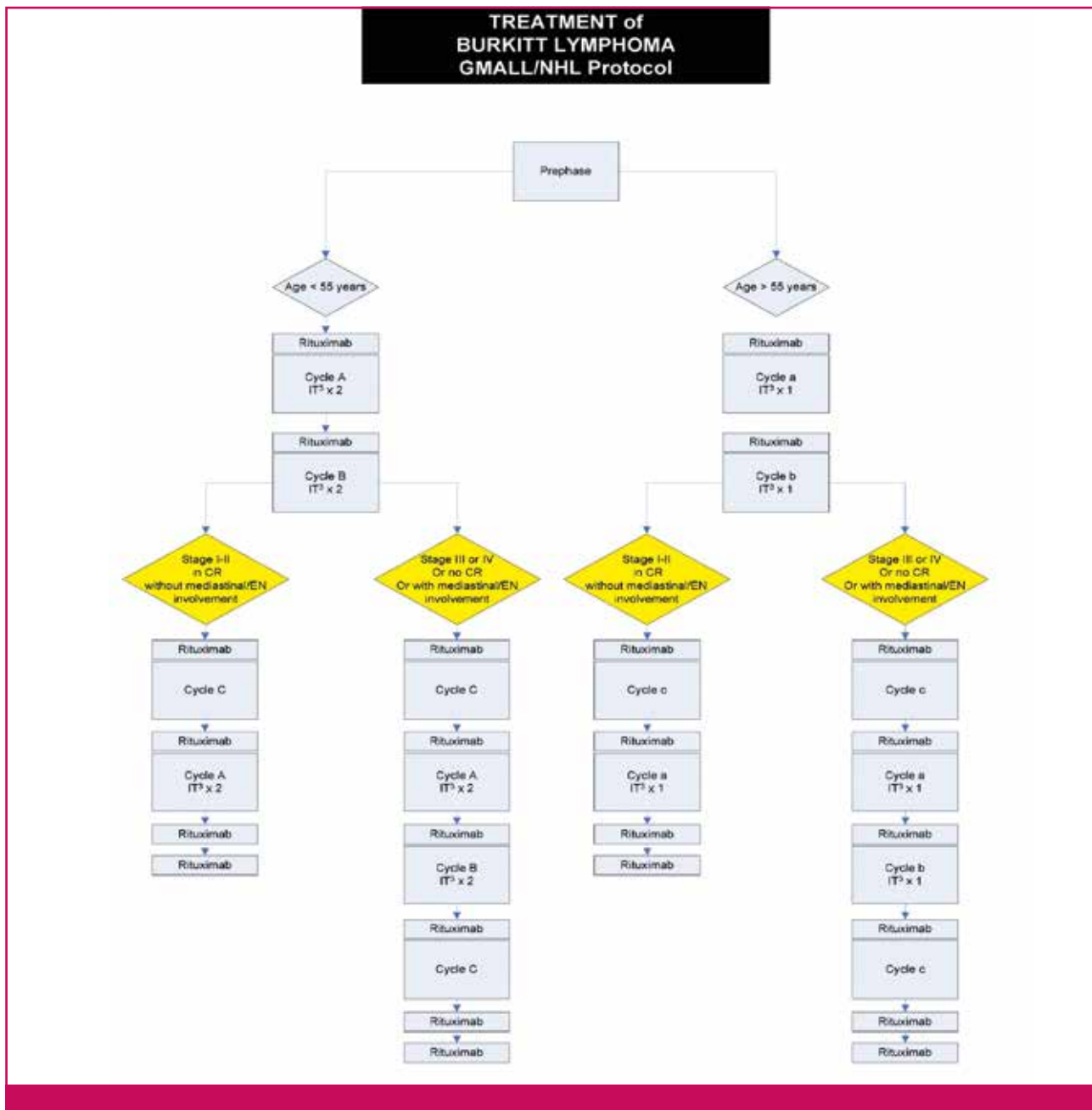


Figure 4. The GMALL/NHL protocol.¹⁴

CR: complete remission; **A:** dexamethasone, vincristine, ifosfamide, HD-methotrexate, etoposide, cytarabine, intrathecal triple therapy; **B:** dexamethasone, vincristine, cyclophosphamide, HD-methotrexate, adriamycin, intrathecal triple therapy; **C:** dexamethasone, vindesine, HD-methotrexate, etoposide, HD-cytarabine; **a:** dexamethasone, reduced ifosfamide, reduced HD-methotrexate, reduced etoposide, reduced cytarabine, methotrexate intrathecal; **b:** dexamethasone, reduced vincristine, cyclophosphamide, reduced HD-methotrexate, adriamycin, methotrexate intrathecal; **IT³:** methotrexate, dexamethasone & cytarabine intrathecal.

by the main co-operative groups. ISCC used by the LYSA-GRAAL Intergroup, the German Multicentre Study Group for Adult ALL (GMALL) or the Dana Farber Institute are very efficacious with an acceptable benefit/toxicity ratio.^{15,20-22}

In 2012 the LYSA-GRAAL intergroup reported the preliminary results of the LMBA02 protocol (R-COPADM

x2 and R-CY(M)VE x2). With a median follow-up of 38 months, the 3 year EFS and OS of 128 young patients with HIV- BL were 76 and 82%, respectively.¹⁵ At the same time, the GMALL protocol reported rates of PFS and OS at 7 years of 83 and 88%, respectively, for 134 BL patients younger than 85 years.²⁰ The Dana Farber protocol (R-CODOX-M x2 and R-IVAC 2x) observed

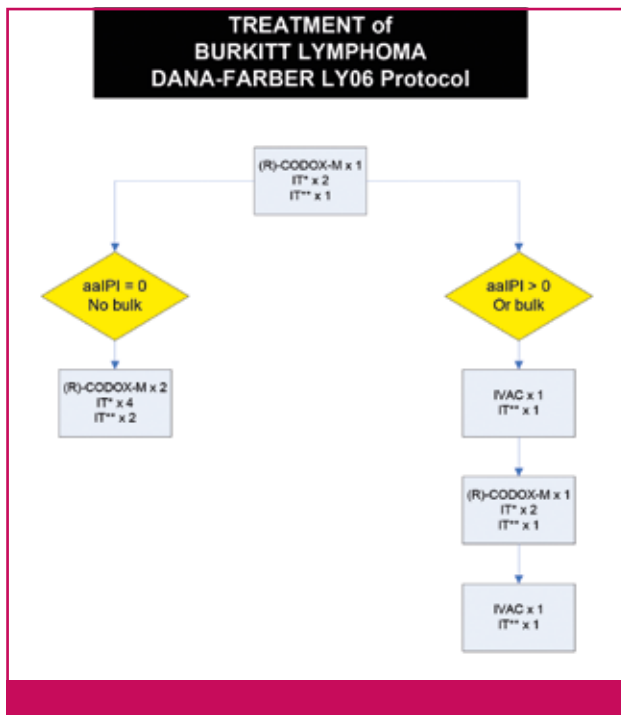


Figure 5. The DANA-Farber regimen.^{21,26}

aa-IPI: Age-adjusted International Prognostic Index; **R:** rituximab; **CODOX-M:** cyclophosphamide, doxorubicin, vincristine, methotrexate; **IVAC:** ifosfamide, cytarabine, etoposide; **IT*:** cytarabine intrathecal; **IT**:** methotrexate intrathecal.

PFS and OS rates of 64.6% and 72.8%, respectively in a group of 60 young patients. The 2 year EFS and OS were 83.3 and 81.5% for low-risk patients and 59.5 and 69.9% for high-risk patients.²¹ The National Cancer Institute (NCI) recently published promising results obtained with the LIC DA-EPOCH-R regimen in a small cohort of 19 patients. With a median follow-up of 86 months, the PFS and OS rates were 95% and 100% respectively. The SC-EPOCH-RR regimen, reserved for HIV+ patients, was associated with PFS and OS rates of 90 and 100% respectively.²² To date, no direct comparison between ISCC and LIC is available.

Particular situations

Elderly patients

Fit elderly patients, until the age of 75, can be treated with the ISCC regimens as long as the doses of cytarabine and methotrexate are adjusted. The DA-EPOCH-R regimen could be an alternative for elderly BL patients.¹⁶ With the association of rituximab and chemotherapy, the worse prognosis of older patients is less apparent.^{12,20}

HivBL

It is recommended to use the same ISCC protocols for

patients with hivBL.²³ The SC-EPOCH-RR is alternative but the results need validation in a larger cohort.²² In addition to chemotherapy, the use of highly active anti-retroviral therapy (HAART) has clearly improved response and survival rates of these patients.^{16,24,25} However, given the possibility of interactions between anti-retroviral and chemotherapeutic drugs, close cooperation between haematologists and infectiologists is mandatory.

Treatment recommendation BHS Lymphoproliferative Group

The Belgian Hematological Society (BHS) lymphoproliferative subcommittee recommends an ISCC regimen for young patients with a newly diagnosed BL. These regimens can also be applied in elderly patients up to the age of 75 who are fit, as long as the doses for cytarabine and methotrexate are adjusted. A LIC as DA-EPOCH-R can be an alternative in patients older than 75 or patients less than 75 with comorbidities as long as CNS involvement is excluded. For HIV+ patients without important comorbidities, ISCC remains the first choice of treatment. SC-EPOCH-R can be an alternative in patients with a bad PS as long as the CNS is not involved.

Re-evaluation

The BHS lymphoproliferative subcommittee recommends performing a CT-scan in the middle and at the end of treatment. A PET scan is only indicated in case of residual masses.

Follow-up

After treatment, CT-scans are repeated every six months during the first year. A patient with sustained CR one year after treatment can be considered cured and therefore, imaging procedures can be omitted from the second year on. Given the risk of late toxic effects, physicians must continue to follow complete blood counts and cognitive functions at regular intervals.

Relapse

Usually, relapses occur during the first year following treatment. In patients with relapsed disease, autologous SCT can result in a PFS of 30-40%. Allogeneic SCT is also an option in relapsing patients with a sibling or matched related donor; however, the role of reduced intensity conditioning (RIC) and T-cell depletion is not well defined.^{17,18}

Conclusion

Sporadic BL and hivBL are two BL subtypes encoun-

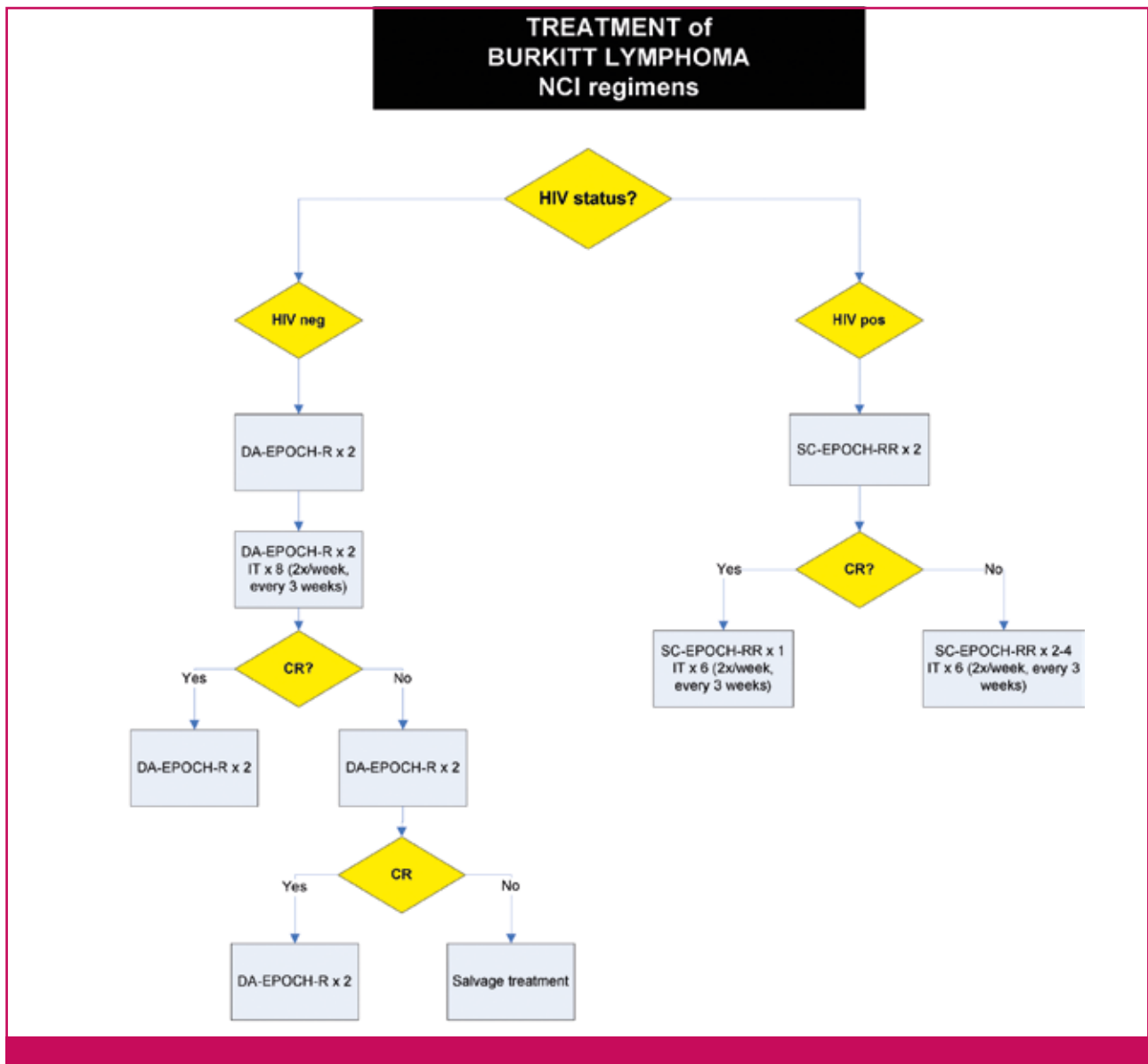


Figure 6. The NCI regimens.^{16,22}

DA-EPOCH: Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; **R:** rituximab; **SC-EPOCH:** Short-cycle etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; **HIV:** human immunodeficiency virus; **CR:** complete remission.

tered in Belgium. Although rare, BL is a very aggressive NHL due to its high proliferation rate. Pathological and cytogenetic analyses are necessary to exclude a BLL and staging procedures must be completed rapidly to avoid delay of treatment initiation. A prephase with low-dose steroids and cyclophosphamide allows finishing initial staging, establishing chemosensitivity of the tumour and avoiding TLS. Following prephase, 'ISCC' or 'LIC', with the administration of rituximab leads to survival rates of more than 80%. However, without available randomised studies, it is quite difficult to recommend one specific therapeutic regimen above another and therefore it is highly recommended to enrol

patients in clinical studies. After treatment, patients must be followed to detect late side effects.

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Key messages for clinical practice

1. **BL, characterised by an isolated translocation t(8;14)(q24;q32), is a rare but very aggressive NHL due to the extremely high proliferation rate.**
2. **Diagnosis and staging must be completed rapidly and treatment started within 48 hours.**
3. **After debulking, to avoid TLS, it is recommended to add rituximab to ISCC or LIC. Involved-field radiotherapy has no place in BL, except for patients with CNS involvement.**
4. **Patients achieving CR must be followed carefully during the first year to detect recurrence of the disease. More than 80% of patients sustain their remission one year following initial treatment and are considered cured.**
5. **Prolonged monitoring of complete blood counts and cognitive functions are important to detect late toxicity of the applied therapies.**
6. **For patients in PR or with chemosensitive relapse, autologous SCT is recommended following re-induction with non-cross-resistant polychemotherapy.**

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