



# Other T- and B-Aggressive Lymphomas and Lymphomas Associated with HIV

# 87

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## 87.1 Burkitt Lymphoma (BL)

### 87.1.1 Definition and Epidemiology

BL accounts for around 2% of all adult NHL with a higher incidence in patients with immunodeficiency and in patients who are HIV positive. There is an endemic pediatric subtype in Equatorial Africa which is strongly associated with EBV. The clinical course of BL usually is highly aggressive with a Ki67 expression of nearly 100% requiring prompt institution of therapy.

### 87.1.2 Diagnosis

A tissue biopsy/cytology sample is mandatory for the diagnosis. The hallmark of the tumor is the rearrangement of a gene encoding MYC, but the diagnosis requires a combination of morphology, immunophenotype, and genetic analysis.

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### 87.1.3 Risk Factors

Several studies have identified risk factors for poor outcome. Beside older age, advanced stage, and comorbidities, such risk factors are an elevated serum LDH, failure to achieve CR, anemia, CNS involvement, and BM infiltration.

### 87.1.4 First-Line Treatment

The optimal first-line therapy in BL has not been defined yet. To achieve a fast and stable remission, an intensive regimen combining several compounds is used in most centers. Combinations of RTX, doxorubicin (DOX), alkylators, VCR, and VP with direct therapy to prevent CNS disease are highly active.

The HOVON CODOX-M/IVAC regimen (CY, DOX, VCR, MTX, IFO, Ara-C, and VP) achieved a 2-year EFS of 65% and a 2-year OS of 73% and is very active especially in high-risk patients (Mead et al. 2002).

The B-ALL protocol (MTX, Ara-C, CY, VP, IFO) of the German GMALL study group achieved a CR in 88% of patients, with a 5-year PFS of 71% and a 5-year OS of 80% (Hoelzer et al. 2014). This means that a significant portion of patients have a chance to get cured with first-line therapy.

Recently, using modifications of R-EPOCH (RTX, VP, VCR, CY, DOX), high activity in BL was reported (Roschewski et al. 2017).

### 87.1.5 Autologous HSCT

There are several studies exploring the role of auto-HSCT in first remission. In a prospective trial, the HOVON group treated 27 patients with 2 cycles of intensive induction followed by BEAM-conditioned auto-HSCT for those patients achieving at least a PR (van Imhoff et al. 2005). The 5-year EFS and OS was 73% and 81%, respectively. In a retrospective analysis of 117 patients receiving auto-HSCT as part of first-line therapy between 1984 and 1994, patients in CR at time of transplant had a 3-year OS of 72% (Sweetenham et al. 1996). In the relapse situation, patients who were chemotherapy-sensitive had a 3-year OS of 37% following auto-HSCT compared to just 7% for those who were chemotherapy resistant (Sweetenham et al. 1996). In summary, auto-HSCT in BL is feasible, but there is no documented advantage compared to standard combination chemotherapy for patients responding sufficiently to first-line treatment. Auto-HSCT may be used to optimize remission in patients with insufficient response or as bridging to allo-HSCT. In the relapse setting, given the intensive regimens usually used as first-line treatment, the difficulty lies in achieving a response good enough to proceed to auto-HSCT and to collect HSC; hence, auto-HSCT is rarely used in BL.

### 87.1.6 Allogeneic HSCT (Peniket et al. 2003)

Indicated in	CR $\geq$ 2
Donor	MRS > MUD > MMUD
Conditioning	RIC > MAC
TRM (1 year)	30%
OS (5 year)	30–40%
DFS	35%

## 87.2 Lymphoblastic Lymphoma (LBL)

### 87.2.1 Definition and Epidemiology

LBL is an aggressive neoplasm of precursor B cells (B-LBL) or T cells (T-LBL) with features of

acute leukemia. It accounts for approximately 2% of all NHL. In adults, around 90% of all LBL are T-LBL.

### 87.2.2 Diagnosis

The diagnosis is based on a LN biopsy. T-LBL is usually TdT-positive with a variable expression of other T-cell markers (CD7 and CD3 are often positive).

### 87.2.3 Risk Factors

At this time, no convincing prognostic model for these patients is available. Several studies tried to identify risk factors; the following may be associated with an unfavorable outcome: elevated LDH, BM or CNS involvement, and stage IV disease. The role of MRD in LBL has not been defined yet, but as we learned from acute leukemias and other lymphomas, persisted MRD positivity might be a predictor of poor outcome.

### 87.2.4 First-Line Treatment

Standard approaches for patients with LBL are adapted to ALL protocols. These regimens contain multiple drugs, such as CY, MTX, VCR, Ara-C, thioguanine, L-asparaginase, VP, nitrosoureas, and anthracyclines. With these protocols, a CR rate of 80% and a DFS of 56% have been reported (Estey et al. 2008).

### 87.2.5 Autologous HSCT

There are only very few studies evaluating the role of auto-HSCT in LBL. In CR1, the use of auto-HSCT as a consolidation may improve relapse-free survival but has no effect on OS (Sweetenham et al. 2001). In another study in 128 patients with LBL receiving auto-HSCT, RR at 5 years was 56% (Levine et al. 2003). No documented role in more advanced disease >CR1 is reported either. In

conclusion, data for auto-HSCT in LBL are too scarce to come to firm conclusions.

### 87.2.6 Allogeneic HSCT

There is also no established role for allo-HSCT in patients with LBL. Compared to auto-HSCT, allo-HSCT is associated with a higher TRM but lower RR. In 76 patients receiving allo-HSCT, 5-year RR was 34% (Levine et al. 2003). In this retrospective study, there was no significant difference in OS at 1 year and 5 years between auto-HSCT and allo-HSCT. In general, the indication for allo-HSCT should be based on risk factors, remission, and MRD.

## 87.3 Peripheral T-Cell Lymphomas (PTCLs)

### 87.3.1 Definition and Epidemiology

PTCLs are a very heterogeneous group of lymphomas originating from the T-cell lineage. They account for approximately 10–15% of all NHL. Because of this low incidence, large randomized studies are difficult to perform.

### 87.3.2 Diagnosis

The diagnosis, as in any NHL, should be based on a LN biopsy. The differential diagnosis between PTCL and other types of T-NHL is crucial for the outcomes, and in some specific cases, the treatments are very different.

### 87.3.3 Risk Factors

The IPI is the most commonly used prognostic tool in PTCL. The following factors are associated with worse outcome: age >60 years, ECOG >1, elevated LDH, stages II–IV, and extranodal involvement >1 site. In anaplastic large cell lymphoma (ALCL), the tumors are categorized in ALK+ or ALK- with better prognosis for ALK+ lymphomas.

### 87.3.4 First-Line Treatment

The primary goal of first-line treatment is to get a deep and continuing remission. Standard regimens are anthracycline-containing combinations like CHOP or CHOEP, achieving a 3-year EFS of 50–70% and a 3-year OS of 75–80% (Schmitz et al. 2010). In the relapse situation, the overall prognosis of PTCL is dismal, and the optimal treatment for these patients has not been defined yet. Relapse patients not able to receive intensive treatment including HSCT may be offered single-agent therapy, e.g., gemcitabine, or in case of CD30 expression, brentuximab vedotin.

### 87.3.5 Autologous HSCT (Kyriakou et al. 2008; d'Amore et al. 2012; Kewalramani et al. 2006; Wilhelm et al. 2016)

Indicated in	CR1 (IPI > 1), CR ≥ 2
Conditioning	BEAC, BEAM, LEAM, CBV
TRM (1 year)	5–7%
REL (3 years)	40–50%
OS (5 years)	70% (CR1), 50% (CR≥2)
PFS (5 years)	50 % (CR1), 20–35% (CR≥2)

### 87.3.6 Allogeneic HSCT (Schmitz et al. 2014, 2018; Doderio et al. 2012)

Indicated in	CR ≥ 2, relapse post auto-HSCT
Donor	MRS > MUD > MMUD
Conditioning	RIC > MAC
GVHD prophylaxis	CSA, CSA-MTX, CSA-MMF
Graft failure	<10%
TRM (1 year)	20–25%
REL (3 years)	20–40%
OS (3 years)	40–60%
PFS (3 years)	30–50%

## 87.4 HIV-Associated Lymphomas

### 87.4.1 Definition and Epidemiology

Patients infected with HIV have an increased risk of developing NHLs as compared to the general population. The most frequent subtypes are

DLBCL and BL. Both are AIDS-defining illnesses, while HL is one of the non-AIDS-defining malignancies.

### 87.4.2 Risk Factors

In the era of combined antiretroviral therapy (cART), the risk factors that determine prognosis in patients with HIV-related lymphoma are the same as in the general population and, hence, depend on the subtype of lymphoma, rather than on HIV-related factors.

### 87.4.3 First-Line Therapy

The optimal therapy for these patients has not been defined yet, but since the availability of cART, the outcome of HIV-lymphoma has considerably improved. The consequent use of cART during therapy is of major importance for successful treatment. In first-line treatment, patients will receive treatment comparable with HIV-negative patients. The indication for HSCT has to be discussed in the relapse situation.

### 87.4.4 Autologous HSCT (Hübel et al. 2017; Diez-Martin et al. 2009; Balsalobre et al. 2009)

Indicated in	CR $\geq$ 2; same indications as in the general population with the same type of lymphoma
Conditioning	BEAC, BEAM, LEAM, CBV
TRM (1 year)	5–7%
REL (3 years)	30–40%
OS (5 years)	50–60%
PFS (5 years)	50–60%

### 87.4.5 Allogeneic HSCT

Experience on the use of allo-HSCT in patients with lymphoma and HIV infection is very limited, and no definitive recommendation can be

given at this time. There are some case reports or small retrospective analysis showing that allo-HSCT in HIV-positive patients using MRD, MUD, or CB is feasible, but application of cART and viroimmunological reconstitution is a matter of debate. In a recent report of five HIV-positive patients who underwent allo-HSCT with various hematologic malignancies, there was no TRM or major infections (Mulanovich et al. 2016). HIV virus load remained undetectable with continuous cART. Three patients relapsed 6, 7, and 13 months after transplant, and two were alive and well after 42 and 55 months.

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