Diffuse large B-cell lymphoma: concise review

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Diffuse large B-cell lymphoma (DLBCL) is the most frequent subtype of non-Hodgkin's lymphoma. At least two different subtypes are defined by gene expression microarray: germinal centre and activated B-cell post-germinal DLBCL. The International Prognostic Index remains the most useful in clinical practice. Biological prognostic factors should be discriminating when reproducible immuno-histological markers will be available. Standard treatment for DLBCL is the association of rituximab and CHOP chemotherapy. However young patients must be treated more aggressively. The treatment could be adapted according to early results of PET-CT scans. Prognosis of relapsing patients remains poor and stem cells transplantation (auto or allo) is indicated in sensitive relapses. Many new target treatments are available for refractory patients and, in the future, could be involved earlier in the treatment of DLBCL.
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Epidemiology

Diffuse large B-cell lymphoma (DLBCL) represents more than one third of all non Hodgkin's lymphomas (NHL). The annual incidence per 100,000 inhabitants of NHL in Belgium is 20.4% in males and 16.3% in females. There is no major difference between regions (*Table 1*), maybe except for a higher incidence in males in Flanders. NHL represents the seventh most frequent cancer in males, the sixth in females and is the second most frequent cancer in the young (between 15-29 year). It is the first in males between 30 to 44 years.[1] The incidence of NHL is higher in Western Europe and United States in comparison with Asia or Africa. The incidence of NHL increased during the second half of the twentieth century; however, since late 90's, this incidence is stable.[2]

Risk factors to develop DLBCL lymphoma are:

- Immunodeficiency (congenital, transplantation, immuno-suppressive drugs, auto-immune diseases, human immunodeficiency virus (HIV))
- Pesticides
- Infectious agents: (Epstein-Barr virus (EBV), human herpes virus (HHV)-8, human T-cell leukaemia virus type (HTLV)-1, helicobacter pylori, borrelia, chlamydia, campylobacter, plasmodium, hepatitis C, hepatitis B, HIV)
- Obesity
- Hair dyeing, tobacco?, benzene?

Immunodeficiencies related to congenital immunodeficiency, transplantation, autoimmune disease, immunosuppressive treatments and HIV infection represent the most important risk factors. HIV epidemic and increased use of immunosuppressive drugs could explain increased incidence in the late decades. Improvement of HIV treatment may explain in part the stabilisation of the incidence since 1995.[3]

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Pesticides used in agriculture explain the higher incidence of NHL in farmers.[4] However, some pesticides were now forbidden and this fact could also explain stabilisation of incidence. Obesity increases risk of NHL, especially DLBCL.[5] Viruses (HHV8, EBV, hepatitis C) are implicated in the genesis of several DLBCL. Other risk factors as hair dyeing, tobacco use and benzene are more debatable.

Pathology

In the chapter of mature B-cell neoplasms, the WHO classification of DLBCL in 2008 defined four categories (*Table 2*): diffuse large B-cell lymphoma not otherwise specified, DLBC subtypes, other lymphomas of large B-cells, and borderline cases.[6] These varieties represent multiple faces of DLBCL and probable different diseases with a relative common histology.

The immunophenotype of DLBCL is $CD19^+$, $CD20^+$, $CD22^+$ and $CD79a^+$, representing mature B-cells with expression of surface and/or cytoplasmic immunoproteins in 75% of cases. Other markers are rarely coexpressed: CD30, CD5. Others are used to define subtypes (cf. infra): CD10, BCL-6, MUM1, FOXP-1. The most frequent chromosomal abnormality involves 3q27 region (BCL-6 gene). The hallmark of follicular lymphoma, t(14;18), occurs in 20-30% of cases. MYC rearrangement is present in 15% of cases.

Prognostic factors

In 1993, Shipp and others defined the International Prognostic Index based on five adverse prognostic factors: age over 60 years, Ann Arbor stage III-IV, 2 or more extranodal sites, performance status (ECOG scale) 2 or more, and elevation of LDH. IPI defined four groups: low risk (0, 1 factor), low-intermediate (2), high intermediate (3) and high risk (4-5).[7]

Many studies on patients treated before the rituximab era have demonstrated the validity of these categories.

The age-adjusted IPI (AA-IPI) was defined for young patients (below 61 years) in order to select patients with poor prognosis and thus candidates to receive more intense treatment. Three factors (stage, PS, LDH) remained to build AA-IPI. However in the elderly population, AA-IPI is not discriminatory for low risk and low intermediate. Cut off of 70 years appears more appropriate and could define elderly IPI (E-IPI).[8]

In the rituximab era, Sehn proposed a revised IPI with three categories: very good (0 factor), good (1-2) and poor (3-5).[9] However recently, a German group confirmed the validity of IPI for patients treated by R-CHOP elderly in the RICOVER trial.[10]

Gene expression analysed by microarray could define at least two different subtypes: the first one has the same gene expression as germinal centre B-cells (GCB-DLBCL) and the other the same gene expression as activated post-germinal B-cell (ABC-DLBCL).[11] GCB and ABC have different prognosis independently of IPI. The validity of these data were confirmed in large series and in patients treated with rituximab.[12,13] This method is expensive and requires frozen material. Immunohistology on fixed histological material was proposed to discriminate GCB and ABC.[14] The validation of this method was not confirmed probably due to the lack of reproducibility of different markers.[15-17] Prognostic impact of expression of some proteins (BCL-2, BCL-6) was abrogated with the use of rituximab.[18,19]

C-Myc rearrangements are seen in 15% of DLBCL and in 80% of DLBCL with similarities with Burkitt's lymphoma (BL) (grey zone DLBCL). By contrast to BL, c-Myc translocation in DLBCL is associated with other translocations. Expression of c-Myc is an independent poor prognostic factor.[20]

Dose-intensity (DI) has an important impact on survival and recently, a Belgian survey demonstrated that patients receiving more than 90% of average relative DI of CHOP had an improvement of survival.[21,22]

PET scan combined with CT is very useful for a better definition of initial staging and to define response at the end of treatment.[23] Moreover early evaluation of efficacy of treatment is an important prognostic factor. Patients with a PET negative after 1-3 courses had a better prognosis than patients with PET remaining positive.[24] However specificity and sensitivity of PET are not so good in DLBCL in comparison with Hodgkin's disease and false positive results occurred if low SUV positive scans are counted.[25,26] Quantitative analyses with percentage of SUV max reduction could be more accurate to define 2 populations with different prognosis.[27]

Treatment of first line

Limited stage

The previous standard 3 courses of CHOP followed by involved field radiotherapy (Miller) is no longer the standard. More intense chemotherapy

Table 1. Haematological cancers in Belgium: incidence (Belgian Cancer Registry - 2003).

Number of new cases/100,000 inhabitants/year				
		Flanders	**Walloon area**	**Brussels**
Non-Hodgkin's lymphomas	Men Women	18.8 14.8	13.1 11.1	18 15.5
Hodgkin's disease	Men Women	3 1.8	2.9 1.4	1.9 2.7
Myeloma	Men Women	8.3 5.6	5 3.2	5.4 4.3
Myeloid leukaemia	Men Women	5.7 4.6	3.5 2.2	4.9 4.8
Lymphoid leukaemia	Men Women	8 5.5	3.3 2.3	3.7 2.1

Table 2. Diffuse large B-cell lymphoma (DLBCL): variants, subgroups and subtypes/entities.

Diffuse large B-cell lymphoma, not otherwise specified (NOS)

- Common morphologic variants
  - centroblastic
  - immunoblastic
  - anaplastic
- Rare morphologic variants
- Molecular subgroups
  - germinal centre B-cell-like (GCB)
  - activated B-cell-like (ABC)
- Immunohistochemical subgroups
  - CD5-positive diffuse large B-cell lymphoma (DLBCL)
  - GCB
  - non-GCB

DLBCL subtypes

- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL of the elderly

Other lymphomas of large B-cells

- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- ALK-positive LBCL
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma

Borderline cases

- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

(ACVBP) is superior to CHOP + radiotherapy in young patients.[28] Chemotherapy alone (CHOP) is equivalent to CHOP + radiotherapy in elderly patients.[29] Results of rituximab combined with chemotherapy are so good in this situation (MINT trial) with a 90% overall survival that radiotherapy has no place in first line treatment in localised DLBCL.[30]

Elderly patients

The GELA trial demonstrated that rituximab + CHOP chemotherapy is superior to CHOP in response rate (*Figure 1*), event free survival, progression free survival and overall survival and 10 years follow-up confirmed these results (*Figure 2*).[31-33]

Other prospective randomised trials and registry data demonstrate that not only in elderly patients

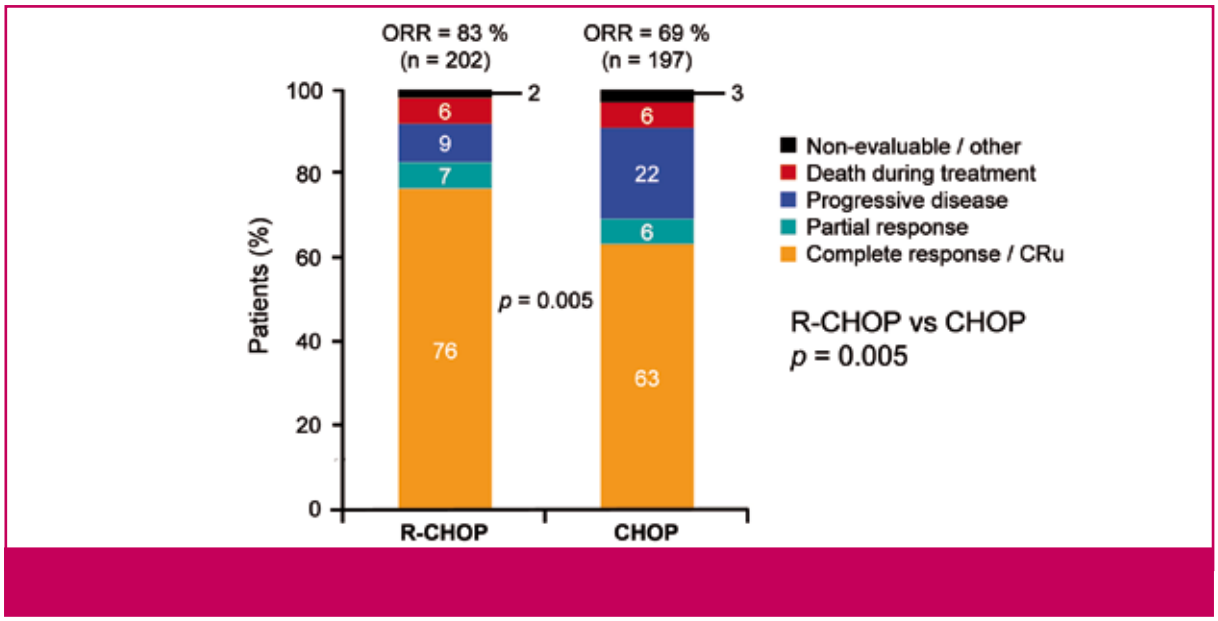

Figure 1. LNH98-5: Improved response rate and quality of response with R-CHOP.

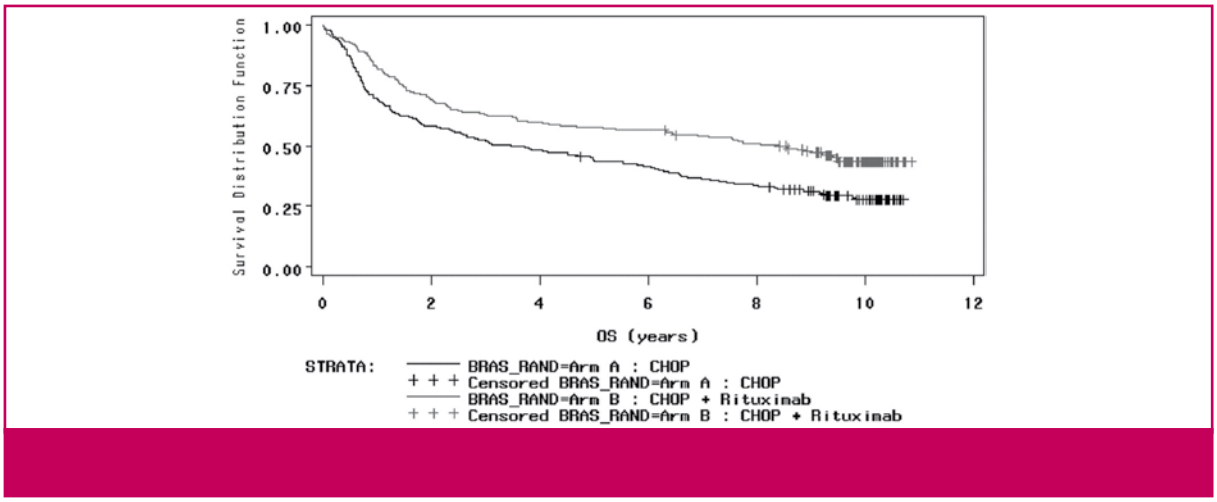

Figure 2. Overall survival in patients treated with CHOP and R-CHOP (10 years FU).
This Figure is reproduced by permission of the American Society of Hematology.[33]

but also in young patients, rituximab associated with chemotherapy increases survival (*Table 3*).

The German group has previously demonstrated that increase in DI by given CHOP every 2 weeks instead of 3 weeks improves survival.[34] The Ricover study demonstrated that R-CHOP 14 was superior to CHOP 14 suggesting that R-CHOP 14 may be better than R-CHOP 21.[35] Two prospective randomised trials do not support this hypothesis.[40,41]

Young patients with adverse prognosis

In these patients, prognosis is poor, even with R-CHOP. Attempts to increase results were more intense chemotherapies like R-CHOEP, R-EPOCH, R-ACVBP.[42-44] In these 3 situations where chemotherapy is more intense than CHOP, rituximab increases the efficacy.

A prospective randomised trial in young patients with one adverse prognostic factor in AAIPI has demonstrated superiority of R-ACVBP over R-CHOP.[45]

Many studies were performed to test more intensive chemotherapies followed by autologous stem cell transplantation in first line treatment in poor prognosis DLBCL. Meta-analysis does not support the recommendation of these treatments.[46]

Recently, Glass in the German group compared R-CHOEP-14 to R-megaCHOEP with PBSC infusion and showed no difference in results.[47]

Table 3. Improved event free survival (EFS) and overall survival (OS) with R-CHOP is consistent in clinical trials and clinical practice.

	n	Chemo	Response (%)	Rituximab benefit	
				EFS or PFS	OS
GELA[31-33]	399 Elderly (60-80)	CHOP-21 x 8	76 vs 63 P=0.005	0.00002	0.0073
RICOVER-60[35]	1222 Elderly (61-80)	CHOP-14 x 6 CHOP-14 x 8	78 vs 68 76 vs 72	<0.001	0.003*
HOVON/NORDIC[36]	199 Elderly (65-80)	CHOP-14 x 8	ND	<0.01	0.05
Intergroup USA[37] (Habermann)	632 Elderly (>60)	CHOP-21	77 vs 76	0.003	0.05
MInT[30]	Young (18-60) Low risk	CHOP-21 or others	86 vs 68 P <0.0001	<0.0001	0.0001
British Columbia[38]	292 All ages	CHOP-like	ND	0.002	<0.0001
Czech Republic[39]	376 Young	CHOP-like	ND	0.0001	0.0007

*p-values for R-CHOP-14 x 6, †Secondary analysis without maintenance.

Treatment of relapsing patients

Comparative and randomised trials have demonstrated that high dose treatment with autologous stem cells transplantation improves survival in relapsing patients.[48,49]

Recently, the CORAL international trial compared R-ICE to R-DHAP followed by BEAM and ASCT in relapsing/refractory DLBCL and showed that OS was 50% at 3 years with no difference between the 2 arms.[50]For patients receiving ASCT, PFS is 50% at 3 years. Two important bad prognostic factors were previous treatment with rituximab and early relapse (less than one year). For this population, an alternative treatment must be proposed to patients and probably allogeneic transplantation (after reduced intensity conditioning regimen) could obtain better results. Patients refractory to salvage regimen have a very poor prognosis and are not good candidates for allogeneic transplantation.[51]

New treatments

New monoclonal antibodies or new drugs exploring different pathways of action are tested in phase I-II trials (*Table 4*).[52] Lenalidomide is one of the more active drugs in relapsing patients (ORR=32% and CR 12% in heavily pretreated patients) and is now tested as consolidation of treatment in a phase III trial in the international REMARC study in elderly patients where, despite the efficacy of R-CHOP, 30% of patients died during the first 2 years.[53] There is a necessity to improve response quality and duration. Only new treatments could improve the prognosis in elderly patients for whom increasing the dosis of chemotherapy is not possible.

Conclusion

DLBCL is the most frequent NHL and is not a unique disease. From a molecular point of view three different diseases are characterised.[54] However, a simple reproductive method remains to be determined. Rituximab associated to chemotherapy can cure 60% (elderly) to 90% (localised disease) of patient with DLBCL. Improvement of these results especially in elderly patients can be obtained in the future by new treatments.

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Table 4. New treatments.

New monoclonal antibodies

- Novel anti-CD20 antibodies: ofatumumab, GA101, veltuzumab
- Anti-CD22 antibodies: epratuzumab
- Anti-CD80 antibodies: galiximab
- Anti-CD40 antibodies: SGN-40
- Antiangiogenic antibodies: bevacizumab

New therapeutical agents in B lymphomas (other than monoclonal antibodies)

1. Agents targeting tumoural microenvironment:
   - immunomodulators (imids): lenalidomide
   - T-reg depletion: Denileukin Diftitox
2. Action pathways inhibitors:
   - B-cell receptors: SYK inhibitor (fostamatinib), Btk inhibitor (PCI-32765)
   - JAK/STAK pathway: SB 1518
   - PI3 kinase/AKT/mTOR pathways: PIK3 kinase inhibitor (CAL-101), AKT inhibitor (Perifosine), mTOR inhibitor (temsirolimus, everolimus : RAD001)
   - RAS pathway: RAS inhibitor (tipifarnib, sorafenib)
   - PKC pathway: PKC inhibitor (enzastaurin)
   - NFkB modulation: proteasome inhibitor (bortezomib)
3. Apoptosis promoters:
   - HDAC inhibitors: vorinostat, romidepsine, parabinostat, MGCD0103
   - Bcl-2 inhibitors: ABT-263, obatoclax
4. New agents targeting ADN synthesis:
   - bendamustine
   - pralatrexate

New drugs and rational combinations

- rituximab: bendamustine, IMIDS, temsirolimus
- bortezomib (+ RCVP, R-CHOP, Fluda R, Cy Dexa R, RCAP)
- lenalidomide + R-CHOP (R2 CHOP)
- lenalidomide + everolimus
- sorafenib + everolimus
- everolimus/temsirolimus + perifosine
- everolimus + parabinostat

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