Integral Transformation Index Indicating the Probability of High-Grade B-Cell Lymphoma Development From Transformed Low-Grade Lymphoma

Anna Misyurina PhD[1*], Sergey Kravchenko PhD[1], Aminat Magomedova PhD[1], Alla Kovrigina PhD[1], Tatiana Obukhova PhD[1], Ksenia Sychevskaya PhD[1], Vsevolod Misyurin PhD[2], Fatima Babaeva PhD[1]

1- National Research Center for Heamatology, 2 - N.N. Blokhin National Medical Cancer Research Center, Moscow, Russian Federation

*Corresponding author: Anna Misyurina, during the period of collecting, analyzing data and writing the publication, worked as a hematologist in chemotherapy of hemablastosis department in National Research Center for Hematology

Abstract

We suggested Integral Transformation Index to distinguish cases of low-grade lymphoma transformation into high-grade.

Background

In the revised version of WHO classification of 2017th the group of high-grade B-cell lymphoma double-hit (HGBL DH) was distinguished from high-grade B-cell lymphoma not otherwise specified (HGBL NOS) based on revealing of rearrangements of genes *c-MYC* and *BCL2* and/or *BCL6* [1]. Nowadays we have more data telling us that these provisional entities are represented by different types of lymphomas which can develop from low-grade: follicular (FL) or marginal zone lymphoma (MZL). This is confirmed by the fact that ***c-MYC/BCL2*** **HGBL DH, HGBL TH (triple-hit),** ***c-MYC/BCL6 HGBL DH*** **and HGBL NOS differ by molecular and mutational profile [2-5].**

Objective

To characterize clinical features of HGBLs and to estimate the count of HGBLs developed from low-grade-lymphomas (LGLs).

Materials & Methods

We have analyzed the data of 99 patients with HGBLs that have been treated since 2010 till 2022 years in National research Center for Hematology, Moscow, Russian Federation.

Twenty-six patients had *c-MYC/BCL2* HGBL DH, 6 - HGBL TH, 16 - *c-MYC/BCL6 HGBL DH* and 51 pts - HGBL NOS. Classically the diagnosis was confirmed by histological and immunohistochemical study in all cases. FISH was performed for all patients to reveal translocation of genes **c-MYC** (8q24), ***BCL2*** (18q21) and ***BCL6*** (3q27). In some cases, we could estimate ***TP53*** mutation and deletion status by Sanger sequencing and/or FISH.

We suggested an INTEGRAL TRANSFORMATION INDEX (ITI) indicating the probability of HGBL development from LGL (FL or MZL).

It included following:

- histologically confirmed transformation (by two consequent biopsies or morphological signs of high- and low-grade lymphomas in one biopsy sample),
- lymphoma history longer than 4 months,
- discordant bone marrow involvement (infiltration by small B-cells),
- paraprotein secretion,
- leukemic blood count or minimal disseminated disease, submitted by flow cytometry.

Statistical analysis was performed using STATISTICA 12.0. Compassion between groups was carried out using χ2 test, Kaplan-Meier method and log-rank test. Differences were considered as significant at p-value < 0,05.

Results

Clinical features	c-MYC/BCL2, HGBCL DH, n=26	HGBL TH, n=6	c-MYC/BCL6 HGBCL DH, n=16	HGBL NOS, n=51	p
Morphological signs of transformation	11/26 (42%)	3/6 (50%)	6/16 (38%)	4/51 (8%)	0,003
History of lymphoma longer than 4 months	7/25 (27%)	2/6 (33%)	8/16 (50%)	17/49 (35%)	>0,05
Monoclonal paraprotein secretion	0	0	2/11 (18%)	9/46 (20%)	NA
Bone marrow involvement	9/24 (38%)	3/6 (50%)	9/16 (56%)	22/51 (43%)	>0,05
Discordant bone marrow involvement	4/24 (16%)	0	5/16 (31%)	11/51 (22%)	>0,05
Circulating tumor cells in peripheral blood	4/9 (44%)	1/2 (50%)	0/3 (0%)	2/3 (75%)	0,08
ITI score at least 1 point	16/26 (62%)	5/6 (83%)	13/16 (81%)	34/51 (67%)	>0,05
Non-GCB-subtype	2/22 (9%)	0	9/16 (56%)	10/40 (25%)	0,03
GCB-subtype	20/22 (91%)	5/5 (100%)	7/16 (44%)	30/40 (75%)	
CNS involvement at the time of disease onset or relapse/progression	6/25 (24%)	2/6 (33%)	4/15 (27%)	16/50 (32%)	>0,05
Spleen involvement	4/24 (16%)	3/6 (50%)	9/16 (56%)	12/51 (24%)	0,009
TP53 del/mut	3/16 (19%)	4/6 (67%)	2/12 (17%)	13/33 (39%)	0,03

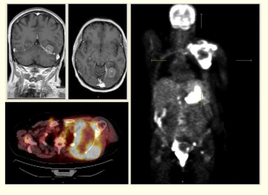


Figure 1 *Clinical portrait of patient with c-MYC/BCL2 HGBL DH with multiple extranodal sites of involvement, including CNS and two lymphoma clones in bone marrow*

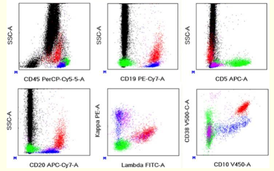


Figure 2 *Several tumour clones in bone marrow according flow cytometry results. The first population (43,6% from lymphocytes) with immunophenotype* ***SSChi CD19+Lambda+CD20bright+CD10+CD38+CD5- (red colour)****; the second population (24,5% from lymphocytes) with immunophenotype* ***CD19+Kappa+CD20+CD10+CD38-CD5- (blue colour)***

Summary

c-MYC/BCL2 HGBL DH and HGBL TH are more homogenous group of GCB-lymphomas in majority of cases represented by transformation of FL.

c-MYC/BCL6 HGBL DH can be represented by transformation of LGLs with paraprotein secretion and spleen involvement.

HGBL NOS is represented by lymphomas with aggressive morphology and clinical manifestation but has more illegible profile.

Discussion

Although the detection of transformation of high-grade B-cell lymphoma from low-grade B-cell lymphoma did not reveal an association with disease outcome, this fact may be important in determining the therapeutic strategy.

References

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