Patient Safety & Quality Improvement Journal
http://psj.mums.ac.ir
PSQI

Evaluation of BCL6 and MUM1 Expression in Patients with Diffuse Large B Cell Lymphoma (DLBCL) and Their Correlation with Staging and Prognosis of the Disease

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ARTICLEINFO

Article type:
Review Article

Article history:
Received: 22-June-2014
Accepted: 14-July-2014

Keywords:
Diffuse large B-cell lymphoma
MUM1
BCL6

ABSTRACT

Diffuse Large B-Cell Lymphoma (DLBCL) is the most common type of Non-Hodgkin Lymphoma (NHL) which includes about (25%) of the cases.

Patients with DLBCL have a rapidly growing mass that is located in the neck or abdominal region. Multiple Myeloma Oncogene (MUM1) has an important role in lymphoid cell differentiation. MUM1/IRF4 is as oncogene related to myeloma and translocation (p25; q32), t (6; 14) and leads to a change in the heavy chain of Immunoglobulin (IGH). BCL6 exists in approximately (100%) of follicular cell cancer cases, (100%) of Burkitt lymphoma, (80%) of large B-cell lymphoma, and in more than (80%) of nodular lymphocytic Hodgkin lymphoma cases. BCL6 is related to cancers with a high proliferation cell index. In some studies BCL6 is expressed as a prognostic factor in LBCL patients

► ***Please cite this paper as*:**
Rahimi H, Jafarian AH, Samadi A, Meamar B. Evaluation of BCL6 and MUM1 Expression in Patients with Diffuse Large B Cell Lymphoma (DLBCL) and Their Correlation with Staging and Prognosis of the Disease. Patient Saf Qual Improv. 2015; 3(1):198-200.

Introduction

Diffuse Large B-Cell Lymphoma (DLBCL) is a high-grade neoplasm that has heterogeneous properties in clinical, morphological, and immunophenotypic aspects (1). DLBCL represent the most common type of adult non-Hodgkin's lymphomas in Western countries (2).

The prognostic importance of p53 and Bcl-2 protein expressions and Ki67 proliferation index in DLBCL, which has biological and clinical heterogeneity, can be understood in a large series of studies that have subclasses and immunohistochemical markers with optimal cut-off values (3). Recent investigations using cDNA and oligonucleotide microarrays have identified molecularly distinct groups of DLBCL with respect to the B-cell differentiation gene expression profile: the Germinal Center (GC) B-cell-like DLBCL, the activated B-cell-like DLBCL and the type three DLBCL (4). The GC B-cell-like DLBCL were characterized by the expression of genes of the normal GC B-cells, the activated B-cell-like DLBCL were characterized by the expression of genes that are normally induced luring in vitro activation of peripheral blood B-cells, while the type three DLBCL did not express either set of genes at a high level.

Patients with GC B-cell-like DLBCL had more favorable clinical outcome than those with activated B-cell-like or type three DLBCL (5).

Immunohistochemical studies have shown that the bc16/CD10/MUM1/CD138 B-cell differentiation immunophenotypes are prognostically relevant and may predict the cDNA classification in a sizable fraction of DLBCL (6). In the last few years, there has been accumulating molecular and immunohistochemical evidence indicating links between B-cell differentiation gene expression profiles and expression of apoptosis and cell cycle-associated genes in DLBCL (7). The present review summarizes data with respect to the relationships between Bcl_6 and Multiple Myeloma Oncogene (MUM1) and overall survival and prognosis in DLBCL.

Materials and Methods

Data sources: Electronic data bases were search with a detailed strategy to find relevant studies. We entered

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studies from Pub Med, Google scholar and SID up to 2014.Our key word and Medical Subject Headings (MESH) were diffuse large B-cell lymphoma and BCL-6 and MUM1. Retrieved articles were assessed to identify additional related articles from their reference list. We included articles with available abstract, full text with English language, human studies with participants aged more than 18.

Critical appraisal: In the first step, abstracts were reviewed by two independent researchers. First search was started with 93 abstract, 70 were excluded due to no relevancy. Full texts of remained articles were evaluated regard to exclusion criteria. And finally ten studies were entered.

We used a structural data extraction tool. But due to heterogeneity in outcome measurements, a Meta analysis was not performed.

Results

Diffuse Large B-cell Lymphoma (DLBCL), the most common type of lymphoma in adults, accounts for 30–(40%) of new lymphoma diagnoses in the Western world. Its incidence is increasing among all age groups and both sexes (8). Table-1 showed the summery of previous studies result. It is a clinically, morphologically and genetically heterogeneous disease.

A significant proportion (20–40%) of patients cannot be cured with current chemotherapeutic regimens (3).

Table 1: Selected articles summery

First author	Prognostic factor	Major finding
Küçükzeybek (9)	Bcl-2, p53	Bcl-2 and p53 protein expressions had no effect on overall survival of patients with DLBCL.
Chung (10)	Bcl-6	Bcl-6 expression was associated with poorer outcome.
Chen (11)	MUM1/ Bcl-6	Expression of bcl-6 and MUM1 correlates with survival.
De Mello (12)	MUM1	MUM1 expression was associated with poor prognosis.
Nyman (13)	MUM1/ Bcl-6	Expression of bcl-6 and MUM1 correlates poor prognosis
Chuang (14)	MUM1/ Bcl-6	Expression of bcl-6 and MUM1 correlates poor prognosis
Uccella (15)	Bcl-6	Bcl-6 expression was associated with poorer outcome
Muris (1)	MUM1	MUM1 expression was associated with poor prognosis.
Sundram(16)	MUM1/ Bcl-6	Expression of bcl-6 and MUM1 correlates with survival.
Braaten (17)	Bcl-6	Expression of BCL-6 was significantly associated with longer overall survival.

Gene Expression Profiling (GEP) is the gold standard for defining the molecular DLBCL subtypes, but is currently not applicable to the routine diagnostic work-up of lymphoma cases (9). Therefore, several groups have tried to develop a substitute involving Immunohistochemistry (IHC).

Discussion

Previous series have identified various clinical prognostic parameters such as early-stage detection, younger age, and radical surgery in patients with Primary Gastric (PG) lymphoma (18). In these studies, however, patients with diseases with low-grade component (MALT lymphoma) and/or with high-stage disease had been included.

The survival probability for patients with gastric MALT lymphomas is significantly better than patients with secondary high-grade transformation or de novo PG-DLBCL; whereas the survival of the latter two high-grade tumor groups is usually not significantly different (19).

In the other retrospective study involving a total of 423 consecutive DLBCL patients t was revealed that bcl-6 protein expression is a favorable prognostic factor (p=0.017; multivariate Cox proportional hazard regression model) in addition to age (2).

Determining the gene profile using an array-based technology provided the assessment of thousands of genes. This technology leads to the possibility of identifying patterns in gene incidence with diagnostic importance, prognosis, and establishment of new treatment goals. The goal of this study was the identification of new prognostic factors in diffuse large B-cell lymphoma.

MUM1/IRF4 is made by means of interferon and related to cell proliferation, survival, and resistance to viral infection.

Evidence shows that MUM1 in the last stage the plasma cell's change to B lymphoma plays an important role. MUM1 is expressed in (50%-70%) of DLBCL cases (12). BCL6 is one of the regulators in a multi-functional cell cycle and plays a role in many of the various processes like differentiation of lymphocytes and immune response.

Conclusion

In most studies, a cutoff level of the MUM1 and BCL6 gene expression equal to (75%) was considered, but our study showed that a cutoff level of (25%) is linked with the stage of disease. A MUM1 gene expression more than (25%) is linked with patient mortality. However, these two genes with a cutoff level of (25%) play a role in determining the survival of patients.

Acknowledgment

We would like to thank Miss Koleini for helping us.

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