Profile of Predictive Factors of Response to Therapy in Patients with Diffuse Large B-cell Lymphoma in dr Soetomo General Teaching Hospital Surabaya

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Abstract

Despite the use of rituximab as a substantial treatment for Diffuse Large B-Cell Lymphoma (DLBCL), the survival rate remains low due to high incidences of relapse. Several predictive factors for relapse have been investigated however, still expensive and not applicable. Lymphocyte-monocyte ratio (LMR) reported as a predictor factor for treatment responses of DLBCL patients.

The aims of this study to know the profile of predictor factors include age, LDH, Ann Arbor stage, extranodal involvement and lymphocyte-monocyte ratio (LMR), with the treatment response of LNH type Diffuse Large B-Cell Lymphoma (DLBCL) patients in dr. Soetomo Surabaya.A retrospective observational descriptive study of 203 subjects undergoing R-CHOP chemotherapy during 2015-2017. Predictor variables were age, LDH, Ann Arbor stage, extranodal involvement and LMR. Elderly > 60 more unresponsive to chemotherapy 24 (46,2%) vs 28 (19%), high LDH more unresponsive 49 (94,2%) vs 3 (5, 8%). Ann Arbor stage III-IV more responsive to chemo than stage I-II, 24 (15,9%) vs 127 (84,155). In LMR< 2,6 subgroup, 84 (55,6%) subjects showed response to chemotherapy, while in LMR < 2,6 subgroup only 67 (44,4%) subgroups showed response.

The conclusion of this study are subjects ≥60 years old, high LDH ≥200 U/l, early stage of disease, extranodal involvement and LMR<2.6 had a higher risk of unresponsiveness to chemotherapy.

Clinical article (J Int Dent Med Res 2020; 13(2): 801-807)

Keywords: DLBCL, therapeutic response, predictive factors, LMR.

Received date: 25 March 2020 **Accept date:** 05 May 2020

Introduction

The cure rates of Non-Hodgkin Lymphoma (NHL) diffuse large B-cell lymphoma (DLBCL) subtype is still reportedly low despite rituximab as a substansial treatment; this is due to high rates of relapse after initial remission[1-2]. Response to therapy is often influenced by many factors including gender, race, age, lactate dehydrogenase (LDH) level, Ann Arbor staging, and extranodal involvement[3]. Some promising modern predictors have been investigated, such as gene expression profile evaluation and more advanced immunohistochemistry, but these tests require such an expensive molecular testing that it hinders its applicability and limits its widespread use[4-6].

On 2013, the number of people suffering from NHL of every histological subtype was approximately 2.96 million worldwide, with mortality of 226,000 patients[7]. It has been reported that 20-40% patients with DLBCL experience disease progression, relapse, and death after receiving standard chemotherapy[1,2,8]. A collection of data has reported several predictors to predict clinical outcome of patients with DLBCL. A study found that patients with DLBCL who relapsed had 5-year survival rate of only < 50%; thus it has been a challenge for the experts to find new, more applicable predictive factors[9].

In NHL, there are abnormalities of B lymphocyte functions that lead to damage and mutation of deoxyribonucleic acid (DNA), one of which is dysregulation of B-Cell Lymphoma 6 (BCL-6) which decreases expression of P53, a tumor suppressor, and increases antiapoptotic expression of B-Cell Lymphoma 2 (BCL-2)[10-11].

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B cell malignancy is divided based on the origin of differentiation into two types: germinal center and post germinal center[12].

Gen expression profiling can determine the characteristics, tumor differentiation origin, and interaction between tumor and non-tumor cells forming a tumor microenvironment (TME). Tumor-infiltrating lymphocyte and myeloid-derived suppressor cells have important roles on the pathogenesis of lymphoma, and is thought to be a promising predictive factor due to its significant role on natural and acquired immune response[13-15]. Several studies[16-18] have shown that lymphopenia, a marker of immune system suppression, is a poor prognostic factor of NHL, and also DLBCL. Recent studies suggest that macrophage (monocyte in tissues) is often associated with tumor growth, also known as tumor-associated macrophage (TAM), which plays a role in tumor angiogenesis, tumor cell proliferation, and immune evasion[19-21]. Lymphoma cells produce several cytokines such as interlukin-4 (IL-4), IL-10, and IL-13 which are thought to responsible in the increase and induction of lymphocyte to differentiate into TAM[22,23]

Tests for gene expression profile is not avaible yet in every healthcare facility in general due to its high expertise and cost. Several predictors have been independently investigated such as age, LDH level, Ann Arbor staging, extranodal involvement, and performance status, which eventually gave way to the widely recognized international prognostic index (IPI). IPI is still currently used as predictive factor of response to therapy in NHL patients do to its simplicity and low cost[3,24]. Considering the cost and ease of use, recent studies have been seeking to find other predictors capable of reflecting host's circulating immune system status and predicting response to therapy in DLBCL[25]. Recent studies have showed that ALC / AMC (lymphocyte-monocyte ratio, LMR) is considered to reflect TME composition of DLBCL patients, which in turn, response to therapy[26-28]. The cost for LMR is considered relatively low in comparison to other new predictive factors, easy to perform, and does not require specific testing method. The author seeks to determine the profile of predictive factors of response to therapy in patients with DLBCL undergoing standard chemotherapy, such as age, Ann Arbor staging, extranodal involvement, and LMR.

Materials and methods

A retrospective, observational, and descriptive study to identify profiles of predictive variables of response to therapy in patients with NHL, DLBCL type. The study was conducted at the Oncology Outpatient Clinic Dr. Soetomo General Teaching Hospital Surabaya, from the medical records of patients visiting the clinic from 2015 to 2017. All patients fulfilling the inclusion and exclusion criteria were enrolled; the inclusion criteria were as follows: ≥ 18 years old at presentation, initial diagnosis being NHL, DLBCL subtype, and had completed standard chemotherapy regimen of R-CHOP for 4 cycles. Exclusion criteria were history of chemoradiation for NHL treatment, a documented infection 1 week before, patient with known hepatitis infection, patient with known chronic inflammation or autoimmune disease, history of malignancy other than NHL, lost to follow-up, and did not undergo chemotherapy according to schedule. All patients were enrolled into the study using consecutive sampling until at least 91 samples were collected (prespecified sample size). The data were obtained from the patients' medical record. The approval and ethical clearance from dr Soetomo Teaching Hospital number 452/Panke.KKE/VII/2017.

Results

General characteristic of subjects

There were 220 DLBCL patients undergoing chemotherapy for DLBCL during that time, of which 203 patients fulfilled the inclusion and exclusion criteria, thus were enrolled into the study. 17 patients were excluded due to incomplete medical record data (tabel 1).

Age subgroups compared with response to therapy profile in DLBCL patients

119 (78,8%) subjects younger than 60 years' old showed response to chemotherapy, while 28 (19 %) subjects showed no response. Among the older group (>60 years old), 32 (21,2%) subjects showed response to chemotherapy, while 24 (46,2%) subjects did not (figure 1).

Characteristic	Result (n = 203)
Gender:	
Male (n/%)	127 / 62,6
Female (n/%)	76 / 37,4
Age (years) /mean ± SD	51 ± 12,88
RLM – median / range	2,53 / 0,34-39,01
LDH – median / range	233 / 110-1863
Ann Arbor staging	
I	12 (6%)
II	18 (8,9%)
III	170 (83,7%)
IV	3 (1,5%)
Extranodal involvement	
Positive	29 (14,3%)
Negative	174 (85,7%)
Response	
Complete Response (n%)	115 (56,7 %)
Partial Response (n%)	36 (17,7%)
Stable Disease (n%)	3 (1,5 %)
Progressive Disease (n%)	49 (24,1%)

Table 1. General characteristic of subjects.

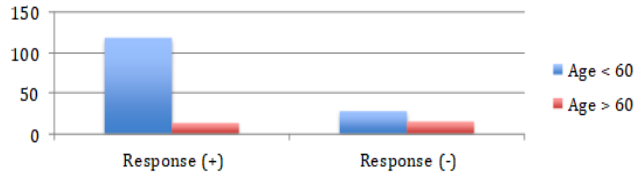

Figure 1. Age subgroups compared with response to therapy profile in DLBCL patients.

Lactate dehydrogenase level subgroups compared with response to therapy

Subjects in subgroup with LDH<200 U/l who showed response to therapy were 67 (44,4%), compared to 84 (55,6%) subjects in LDH≥200 U/l subgroup. 3 (5,8%) subjects showed no response to chemotherapy in LDH<200 U/l subgroup, while 49 (94,2%) showed no response in LDH≥200 U/l subgroup (figure 2).

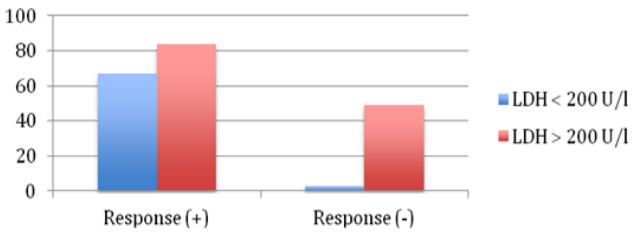

Figure 2. LDH level subgroups compared with response to therapy profile in DLBCL patients.

Ann arbor staging subgroups compared with response to therapy profile

Among subjects with stage I-II disease (Ann Arbor staging), 24 (15,9%) showed response to chemotherapy, while 46 (88,5%) did not. 127 (84,1%) subjects with stage III-IV disease showed response to chemotherapy, while 6 (11,1%) did not (figure 3).

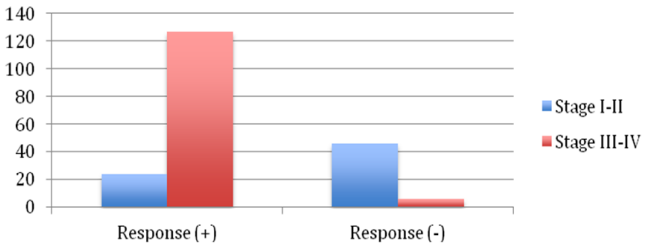

Figure 3. Ann Arbor staging subgroups compared with response to therapy profile in DLBCL patients.

Extranodal involvement subgroups compared with response to therapy

136 (90,1%) subjects with no extranodal involvement showed response to chemotherapy, compared to 15 (9,9%) subjects with extranodal involvement. 38 (73,1%) subjects with no extranodal involvement did not show response, compared to 14 (26,9%) subjects with extranodal involvement (figure 4).

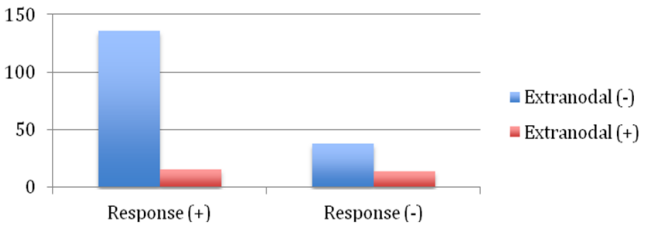

Figure 4. Extranodal involvement subgroups compared with response to therapy profile in DLBCL patients.

Lymphocyte-monocyte ratio (LMR) subgroups compared with response to therapy

In LMR ≥ 2,6 subgroup, 84 (55,6%) subjects showed response to chemotherapy, while 8 (15,4%) did not. In LMR < 2,6 subgroup, 67 (44,4%) subgroups showed response, while 44 (84,6%) did not (figure 5).

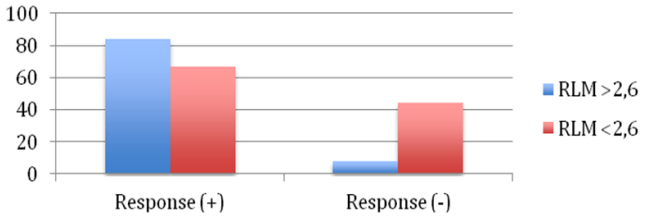

Figure 5. Lymphocyte-monocyte ratio subgroups compared with response to therapy.

Discussion

Study subjects' general characteristics

In this study, most of subjects were male (62,6% vs 37,4%), with mean age 51 ± 12,88. Several previous studies in the epidemiology, non-responder as well as mortality predictor after R-CHOP chemotherapy in DLBCL patients also showed similar demographic characteristics of male predominance[29]. Males have poorer response to chemotherapy due to pharmacokinetic difference between male and female body, and its association with rituximab level in the serum[30,31]. A study in Korea reported that the level of Glutathione-S-transferase (GST) in male might increase the toxicity caused by R-CHOP chemotherapy, while estradiol level in female might be a protective factor[32]. The median age in this study is different from other studies in the UK (70 years old)[33], while the median age in studies conducted in Europe and the US was between 60-70 years old[34]. In Indonesia, a survey conducted by Dharmais Cancer Hospital between 2010 to 2011 found that patients with NHL ranged from 50 to 54 years old, similar to this study (52 years old)[35]. There has been no clear explanation regarding this rather significant difference. In this study, non-responders to R-CHOP chemotherapy in patients with DLBCL were 25.6%, with 1.5% achieving stable disease and 24.1% having their disease progressed.

Age and response to therapy in DLBCL patients

This study found that amongst subjects aged ≥60 years old, 32 (21,1%) showed response to chemotherapy, compared to 24 (46,2%) who showed no response. Immunosenescence, a natural decline of immune response in the elderly, is thought to be responsible for the decline of lymphoid progenitor function that plays a role in growth of B-lymphocyte, T-lymphocyte, and NK (natural killer) cells[36]. Other physiological changes occur in elderly, such as accumulation of reactive oxygen species (ROS) which causes direct damage on nuclear DNA. In addition,telomere shortening in elderly disrupts DNA replication, and is thought to play a role in the blunted response to therapy in elderly, as well as poorer prognosis[37]. Age is always a poor prognostic factor in advanced-stage DLBL patients, since it is usually accompanied by other ilnessess and/or comorbids, which will influence therapeutic decision, as reported by Shipp and colleagues, who conducted a multicenter study of 3273 NHL patients in the US, Europe, and Canada, where 510 (38%) subjects aged more than 60 years old did not show response to chemotherapy, with OR 1,96 times more than those who were under 60 years old[3, 38]. A similar Italian study by Rambaldi found that amongst 355 subjects aged more than 60 years' old, 186 (50%) failed to show response to R-CHOP chemotherapy, with OR 1,70 (CI: 1,22-2,36)[39]. Dixon and colleagues suggested that the low overall survival in elderly is caused by their inability to receive the full dose of chemotherapy due to certain comorbids[40]. In addition, the alteration of drug pharmacokinetics and pharmacodynamics, decrease metabolism of certain chemotherapy agents such as anthracyclin, thus increasing its toxicity[41].

Lactate dehydrogenase (LDH) and response to therapy in DLBCL patients

Our study showed that amongst the high LDH group (LDH ≥200 U/l) 84 (55,6%) subjects showed response, while in low LDH group only 67 (44.4%) did not. Similar study conducted by Rambaldi and colleagues using LDH level more than 440 U/l as cutoff found that 68 of 373 subjects in high LDH group did not show response to therapy, while 36 of 327 subjects in low LDH group did nt show response (OR 3.44; CI: 2.34-5.06)[39]. Li and colleagues, using LDH > 200 U/l as cutoff, found that 105 of 163 subjects in high LDH group did not show response to therapy, compared to 58 of 163 subjects in low LDH group (OR 1.218; CI: 0.376-3.945)[42]. LDH is a tetrametric enzyme which converts lactate into pyruvate and elevated where certain tissue is damaged. High level of LDH in NHL patient is commonly found in bulky tumor, also a poor prognostic factor independent of histopathology subtype[43]. On the other hand, several other studies showed that LDH is not a poor prognostic

factor of DLBCL patients, especially those with extranodal involvement[44-46].

Ann Arbor staging with response to therapy in DLBCL patients

This study showed that among subjects with advanced DLBCL (Ann Arbor stage III-IV) having treated with RCHOP chemotherapy, 127 (84,1%) showed response to chemotherapy, while 46 (88,5%) did not. Li and colleagues showed that advanced Ann Arbor staging (III-IV) - besides other predictors such as age, gender, ECOG performance status, LDH level, extranodal involvement, and LMR - was a predictor of response to therapy with p<0.001, in which 56 of 199 subjects did not show response[27]. A multivariate analysis done by Wilcox and colleagues in a study of 366 patients evaluating several predictor variables reported a p of 0.006 for Ann Arbor staging variable[26]. A study by Wang and coleagues of 355 patients reported a p of 0.18 for Ann Arbor staging variable, based on multivariate analysis[47]. Another study conducted by Tomita using 10 predictive variables found that LDH was the only significant one, while Ann Arbor was not significant as predictive variable in DLBCL involving the CNS (p>0.05)[44]. The diversity of result from various studies is thought to be caused by several factors such as varying demographic characteristics, sample size, and most importantly extranodal involvement in early stage of the disease (stage I-II) which may confound the staging variable [48].

Extranodal involvement with response to therapy in DLBCL patients

This study showed that amongst DLBCL patients presenting with extranodal involvement who underwent RCHOP chemotherapy, 15 (9,9%) subject showed response, while 14 (26,9%) subjects did not. Data obtained from SEER from 2004 to 2013 showed that amongst 25992 patients, extranodal involvement was found in 31.6% of patients. Gastrointestinal tract, head and neck and skin are the three most common site of extranodal involvement[29]. Shipp and collaegues found that 47% of 646 DLBCL patients with extranodal involvement did not show response to therapy, compared to 28% in patients without extranodal involvement (OR 1.48)[3]. This result by Li and coleagues who found that among 163 subjects, 132 with extranodal involvement did not show response, compared to 32 subjects without extranodal involvement (OR 2.41; CI: 1.05-5.48)[42]. An Italian study found that among 90 subjects, 25 with extranodal involvement did not show response, compared to 21 without extranodal involvement (OR 1.68; CI: 1.18-2.38)[39].

There are other factors believed to be influencing the prognosis of patients with extranodal involvement, such as age, gender, race, and the site of extranodal manifestation. Data from the SEER showed that 62% patients with extranodal involvement were elderly[29]. In males, the most common extranodal sites are the important tissues such as gastrointestinal tract, airways, liver, and pancreas, while in females are the thyroid gland and breast[29].

Lymphocyte-monocyte ratio (LMR) with response to therapy in DLBCL patients

This study showed that among DLBCL patients undergoing R-CHOP chemotherapy with LMR< 2.6, 67 (44.4%) subjects showed responose to chemotherapy, while 44 (84,6%) did not. This is similar to previous studies, which generally found that patients with low LMR had higher probability of showing no response to chemotherapy. Lymphocyte is known to act as part of immunosurveillance against NHL. Several observational studies showed that low absolute lymphocyte count (ALC) was a poor predictive factor of NHL regardless of histological subtype, including DLBCL. Although the exact mechanism is still unknown, the low ALC is thought to be the result of immunosuppression, an indication that he host's immune response is not adequate; the low ALC is caused by lympholytic cytokines origated from lymphoma cell, which may induce resistance against certain chemotherapy, or both, and other possibilities[16,18]. Lymphocytic cytokines are interleukin-4 (IL-4), IL-10, IL-13, which will induce lymphocytes to differentiate into tumor associated macrophage (TAM) which is considered to be a surrogate for tumor environment, which has been recently reported as one of predictive factor in DLBCL, as TAM possesses the ability to suppress anti tumor factors, and induces tumor angiogenesis[19,20, 48]. A Chinese study by Li and colleagues of 276 patients using LMR<2.6 as cut-off showed that 25 (9.2%) subjects did not respond, with OR 1.699 (CI 1.071-2.702) compared to subjects in LMR>2.6 group[27]. In 2014, Wei and collegues showed an OR of 2.789 using the same LMR cut-

off[49]. Another study in Italia by Rambaldi and colleagues of 373 patients using LMR<2.6 as cut-off found that 62 (19%) subjects did not respond to therapy with OR 2.25 (CI: 1.58-3.19) compared to subjects wih LMR>2.6[39]. A study by Jelicic and colleagues of 182 patients using LMR≤2,8 as cut-off showed that 39 (24.9%) subjects did not respond; while in LMR>2.8 group of 154 patients, 28 (18.2%) subjects did not respond (OR 0.73; CI: 0.381-1.406)[50]. A study by Yan-Li and colleagues of 163 patients using LMR<2.0 as cut-off showed 57 subjects did not respond; while in LMR>2.0 group of 163 patients, 37 subjects did not respond (OR 3.65; CI: 1.18-11.20)[42]. These studies on LMR and response to therapy yielded various OR; this can be caused by several factors such as diverse race and ethnic group, age, histopathology type.

Conclusions

Predictive factors of several variables on response to R-CHOP chemotherapy in DLBCL patients were investigated in this study. In this study, it appeared that subjects ≥60 years old, high LDH≥200 U/l, early stage of disease, extranodal involvement and LMR<2.6 had a higher risk of unresponsiveness to chemotherapy.

Declaration of Interest

The authors report no conflict of interest.

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