PROGNOSTIC VALUE OF AGE-ADJUSTED INTERNATIONAL PROGNOSTIC INDEX IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA – A SINGLE CENTRE EXPERIENCE

Summary
Introduction. The research aimed to evaluate the impact of age-adjusted international prognostic index and time to the first relapse on overall survival and progression-free survival from the beginning of the second line of treatment in patients with relapsed/refractory diffuse large B-cell lymphoma. Material and Methods. The research included 36 patients with relapsed/refractory diffuse large B-cell lymphoma treated at the Oncology Institute of Vojvodina, Serbia, from January 2013 to December 2015. Patients were stratified according to age-adjusted international prognostic index score at the time of relapse into patients with low risk (score 0–1) and patients with high risk (score 2–3), as well as according to the time of the first relapse: early relapse (<12 months) and late relapse (>12 months). Results. In the group of patients with a score of 0–1, the median overall survival was 44 months compared with 6 months in patients with score of 2–3, hazard ratio 0.4 (confidence interval 0.16–0.99), p = 0.03. In patients with early relapse, the median overall survival was 7 months compared with 25 months in patients with late relapse, hazard ratio 0.55 (confidence interval 0.25–1.19), p = 0.12. In patients with early relapse, median progression-free survival was 0 months compared with 10 months in patients with late relapse, hazard ratio 0.34 (confidence interval 0.12–1.00), p = 0.0017. Conclusion. The impact of age-adjusted international prognostic index score significantly affects overall survival in patients with relapsed diffuse large B-cell lymphoma. The time to the first relapse impacts progression-free survival calculated from the time of the second line of treatment initiation.

Key words: Prognosis; Indexes; Lymphoma, Large B-Cell; Diffuse; Recurrence; Disease-Free Survival; Lymphoma, Non-Hodgkin; Age Factors

Sažetak
Uvod. Cilj ovog istraživanja je procena uticaja Age-adjusted International Prognostic Index i vremena do pojave prvog relapsa na ukupno preživljanje i vreme do progresije bolesti kod bolesnika sa relapsnim ili refrakternim difuznim B-krupnoćelijskim limfomom. Materijal i metode. U istraživanje je uključeno 36 bolesnika koji su u periodu od januara 2013. do decembra 2015. godine lečeni u Institutu za onkologiju Vojvodine zbog relapsnog ili refrakternog difuznog B-krupnoćelijskog limfoma. Bolesnici su grupisani prema vrednosti Age-adjusted International Prognostic Index skora u relapsu na bolesnike sa niskim rizikom (skor 0-1) i bolesnike sa visokim rizikom (skor 2-3) i vremenu do pojave prvog relapsa. Rezultati. Mediјana ukupnog preživljanja u grupi bolesnika sa niskim rizikom (skor 0-1) iznosila je 44 mесеца у односу на групу бoлесника са високим rизиком (skor 2-3) gde je medijana ukupnog preživljanja iznosila 6 месеци, однос hazarda 0.4 (interval poverenja 0.16–0.99), p = 0.03. Mediјana ukupnог preživljanja у групи бoлесnika са rаним relapsom iznosila je sedam месеци у односу на medijanu ukupног прeživljanja бoлесника сa касним relapsom коja je iznosila 25 месеци, однос hazardа 0.55 (interval poverenja 0.25-1.19), p = 0.12. U групи bolesnika сa ranim relapsom medijana vremena до прogresije bolesti iznosila je 0 месеци у односу на групу бoлесника сa касnim relapsom код kojих je medijana vremena до progresije bolesti iznosila 10 месеци, однос hazardа 0.34 (interval poverenja 0.12–1.00), p = 0.0017. Zaključak. Vrednost relapsnog Age-adjusted International Prognostic Index skora značajno utičе на ukupно preživljanje bolesnika sa relapsnim difuznim B-krupnoćelijskim limfomom, dok vreme do prvog relapsa značajno utičе на vreme до progresije bolesti nakon započinjanja druge linije lečenja kod bolesnika sa relapsnim ili refrakternim difuznim B-krupnoćelijskim limfomom. Ključne reči: prognoza; indeksi; difuzni B-krupnoćelijski limfom; relaps; preživljanje bez bolesti; ne-Hočkinov limfom; uzrast

Introduction
Diffuse large B-cell lymphoma (DLBCL) is the most common Non-Hodgkin lymphoma (NHL) and accounts for 30–40% of all NHLs [1]. Since 1970, the standard therapeutic option in the treatment of DLBCL has been a chemotherapy regimen with cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP)
which is associated with a 50% complete remission (CR) [2]. The current standard is immunochemotherapy with rituximab plus cyclophosphamide, adriamycin, vincristine, and prednisone (R-CHOP) which is associated with a 60% CR [3]. Even after achieving a CR, 30 – 40% of patients relapse [4]. Among patients who relapse or who are refractory to first-line treatment, 40% are eligible for high-dose chemo with autologous stem cell transplantation (ASCT) [5]. After ASCT, 50% of patients relapse [6] with a median survival of 3 months [7]. The treatment of choice in patients who are not eligible for high-dose chemo with ASCT (60%) [5] is GemOx (gemcitabine-oxaliplatin), bendamustine, gemcitabine, dexamethasone, and cisplatin (GDP), lenalidomide (activated B-cell - non–germinal center B-cell [GCB] and ibrutinib (non-GCB) [8–12].

This research aimed to estimate the overall survival (OS) and progression-free survival (PFS) in patients with relapsed DLBCL. We have also examined the impact of age-adjusted International Prognostic Index (aaIPI) and time to the first relapse on the OS and PFS after the beginning of the second line treatment; the impact of time to disease relapse after the first line of treatment (early or late relapse) on OS, and time to disease progression after the second line of treatment.

**Material and Methods**

The research included patients with relapsed DLBCL who were treated at the Oncology Institute of Vojvodina, Serbia from January 2013 to December 2015. The data were obtained from the medical histories of patients and the following characteristics were analyzed: sex, age at the time of diagnosis, germinal center B-cell (GCB)/non-GCB subtype [14], initial treatment, time of disease relapse (early relapse ≤ 12 months from the end of the first-line treatment, late relapse > 12 months from the end of the first line of treatment). The same parameters were evaluated at the time of the first and the second relapse. The OS was calculated from the time of initiation of the second-line treatment until death or the last follow-up visit. The PFS was calculated from the start of the second-line treatment until disease progression.

The primary endpoint of our study was to estimate OS and PFS from the initiation of treatment post-relapse using Kaplan–Meier curves. The statistical data analysis was performed by using MedCalc statistical software (version 18.10).

**Results**

The research included 36 patients, with average age of 56 years, ranging from 22 to 78 years. Sixteen out of 36 (44%) were male, 20 (55%) were female. According to Ann Arbor classification at the time of diagnosis, the patient's age-adjusted International Prognostic Index (aaIPI) and time to the first relapse on the OS and PFS after the beginning of the second line treatment; the impact of time to disease relapse after the first line of treatment (early or late relapse) on OS, and time to disease progression after the second line of treatment.
4 patients had stage I (11%), 6 had stage II (16%), 13 had stage III (36%) and 13 stage IV (36%). Thirteen patients had GCB subtype, while 11 had non-GCB. According to aaIPI at the time of initial diagnosis: 13 patients were low risk (0 - 1), while 19 were high risk patients (2 - 3). All patients were treated with R-CHOP regimen in the first line of treatment, 15 (41%) with six cycles, whereas 21 (58%) received eight cycles. After the first line of treatment, 23/36 (33%) had a CR, 18 (50%) had a partial response (PR), 1 (2.7%) patient had a stable disease (SD), while 5 (13.8%) had a progressive disease (PD).

At the time of the first relapse, Ann Arbor stage was available for 33 patients, 6 (18%) had stage I, 7 (21%) had stage II, 7 (21%) had stage III, while 13 (39%) had stage IV. AaIPI score at the time of relapse was available for 26 patients; 13 were low risk (0 - 1) while the remaining 13 (50%) were high risk patients (2 - 3). Late relapse occurred in 21/36 (58%), while 14 (42%) patients had an early relapse. In the second-line treatment, 12/32 (37.5%) patients were treated with platinum-based regimen, 12 (37%) with ifosfamide-based regimen, while 8 (25%) patients were treated with one of various CHOP-like regimens. Data on response to treatment were collected for 30 patients: CR and PR were achieved in 9 (30%) and 10 (33%) patients, respectively; SD was not registered in any patient, while PD occurred in 11 (36.6%). Among patients who achieved CR or PR, 3 eventually received ASCT.

Data on Ann Arbor stage were available for 18 patients after the second relapse staged from I to IV: 2 (11%), 3 (16.6%), 2 (11.1%) and 11 (61.1%), respectively. AaIPI score was collected for 18 patients with second relapse: 10 (55.5%) were low risk (0 - 1), while 8 (44.4%) were high risk (2 - 3). In the third-line treatment 4 (22%) out of 18 patients were treated with ifosfamide-based regimen, 8 (44.4%) received one of CHOP-like regimens, 3 (16.6%) platinum-based regimen, while 2 (11.1%) received cyclophosphamide, vincristine sulfate, adriamycin, dexamethasone (hyper CVAD). Response to treatment was collected for 16 patients: CR, PR, SD and PD occurred in 6 (37.5%), 1 (6.25%), 1 (6.25%), 8 (50%) patients, respectively.

In overall patients, median OS (5-year follow-up) was 18 months (7 - 44) (Graph 1). Median OS in patients with late relapse versus early relapse (Graph 2) was 10 months (5 - 31) versus 25 months (10 - 37). In overall patients, median PFS was 4 months (0 - 9) (Graph 3). In early-relapse subgroup of patients, median PFS was 0 months, versus 10 months in late-relapse subgroup, HR 0.34 (CI 0.12 - 1.00).
p = 0.0017 (Graph 4). Median PFS of patients who were treated with third-line treatment was 0 months (0 - 4) (Graph 5).

Discussion

Patients with refractory or relapsed DLBCL after first-line treatment are candidates for salvage treatment [15]. The overall response rate to various salvage protocols is 42–64% [16–20]. Patients who achieve a response to salvage therapy receive high dose chemo with ASCT [21]. All our patients were treated with R-CHOP as the first-line regimen. At first relapse, different salvage protocols were used. The median OS from the beginning of salvage treatment was 18 months, while survival at 5 years was 27%, regardless of the salvage protocol used. The (CORAL) study reported 62% of patients treated with R-CHOP protocol. At first relapse, patients were treated with R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-DHAP (rituximab, dexamethasone, cisplatin, and cytarabine) and after achieving a response they proceeded to ASCT. The OS at 3 years was 49% [22]. Paul et al. performed a study where all patients were treated with CHOP regimen at first-line and ICE salvage protocol; the OS at 4 years was 34% [23]. Rachel et al. reported that 5-year OS (38%) in patients treated with various salvage protocols and eventually ASCT [24]. We observed a significant difference in OS among our patients with low-risk aIPI 0 - 1 (45%, median OS 44 months) in comparison to patients with high-risk aIPI 2 - 3 (10% - median OS 6 months). Three-year OS in low-risk patients in CORAL trial was 62%, versus 32% in high-risk patients (p < .001) [22]. Another trial also reported a significant difference in 4-year OS in patients with low, intermediate and high risk, (74% v 49% v 18%, respectively) [23]. Rachel et al. reported that median OS in low-risk patients was 27 versus 5 months in high-risk patients (p < .001) [24]. According to our data, after a 3-year follow up, PFS was 16%, calculated from the start of the second-line treatment. There was a significant difference in PFS after initiation of the second-line treatment. Three-year PFS in patients with late relapse was 22%, median PFS 10 months, compared to early-relapsed patients with a second relapse in the first months of the second-line treatment (median 0 months). The CORAL trial reported 3-year PFS, post-second-line treatment initiation, to be 37% in overall patient population, and it did not differ in the subpopulation with late relapse. In early-relapse patients, PFS was 23% [22].

Our results are comparable to the data reported by above mentioned authors and confirm the fact that patients with relapsed/refractory DLBCL have a very poor prognosis [22–24]. SCHOLAR-1 trial reported that OS of patients who relapsed in less than 12 months post ASCT, with all treatments available, was 6.3 months [25]. Chimeric antigen receptor (CAR)-T cell therapy proved effective in patients with relapsed/refractory DLBCL [25]. ZUMA trial treated patients with refractory DLBCL with axi-cabtagene ciloleucel (anti-CD19 CAR T-cell) [26]. The treatment response rate was 82% and CR was achieved in 54% patients. After 15.4 months follow up, 42% of patients still responded to the treatment, while 40% still had CR [26]. In JULIET trial, patients with relapsed/refractory DLBCL were treated with tisagenlecleucel [27]. The overall response rate was 54%, 40% had CR, while 13% had PR. The median duration of response was not achieved after 19 months of follow up [27]. Polatuzumab vedotin (anti-CD79 antibody-drug conjugate) in combination with bendamustine and rituximab vs. bendamustine alone in relapsed/refractory DLBCL patients who were not eligible for ASCT accomplished significantly longer OS and PFS [28]. A CR was achieved in 40% of patients who were treated with polatuzumab vedotin in combination with bendamustine and rituximab in comparison to 13% of patients who were treated with bendamustine and rituximab [28].

Conclusion

The age-adjusted international prognostic index score calculation significantly influences the overall survival in patients with relapsed/refractory diffuse large B-cell lymphoma. Time to the first relapse significantly impacts the time to disease progression after the second-line treatment initiation in these patients, so this subpopulation warrants novel therapeutic options in the future.

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