Impact of Central Nervous System International Prognostic Index on the treatment of Diffuse Large B Cell Lymphoma

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Abstract

Background

The central nervous system international prognostic index [CNS-IPI] is being used widely for the identification of patients with diffuse large B cell lymphoma [DLBCL] with high risk of CNS relapse. The aim of our study is to confirm the value of the CNS-IPI in predicting CNS relapse in our young study population and to evaluate the impact on selection of patients for CNS prophylaxis.

Methods

We retrospectively reviewed patients with pathological diagnosis of DLBCL who were treated with R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone] regimen from January 2004 till December 2016 with no evidence of CNS involvement on diagnosis. Different demographic, disease characteristics and treatment given including the use of intrathecal chemotherapy prophylaxis were collected. Correlation between CNS-IPI and CNS relapse was examined through chi square test. Median time to CNS relapse and median overall survival [OS] after CNS relapse were estimated using the Kaplan-Meier plots.

Results

354 patients were included. Median age was 46 years. 52 [15%] patients were given intrathecal chemotherapy [ITC] prophylaxis, of whom CNS-IPI was high in 7[13%]. Overall, 5% of the patients [n = 17] developed CNS relapse. The median survival after CNS relapse was 7 months. The rate of CNS relapse in patients with low, intermediate and high risk CNS-IPI was 0.6%, 3% and 22% respectively [p = < 0.001]. On multivariate analysis, involvement of bone marrow [p = 0.039] and renal or adrenal glands [p = 0.023] significantly correlated with CNS relapse. Considering the CNS-IPI and high risk anatomical sites [breast, uterus, testis and epidural space], 26% of our patients with DLBCL would have needed prophylaxis.

Conclusion

Although CNS-IPI helps in better selection of DLBCL patients for CNS prophylaxis, it will significantly and possibly unnecessarily increase the number of patients exposed to prophylaxis. More investigational biomarkers and methods are necessary to better refining high risk patients.

Introduction:

Diffuse large B cell lymphoma [DLBCL] is the most common lymphoma in adults, representing about one third of newly diagnosed cases [1, 2]. Using the standard combination chemo-immunotherapy RCHOP regimen [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone], 70% of cases are
expected to be cured, while 30% will have refractory or relapsed disease [3.4]. Although relapse in the central nervous system [CNS] is relatively rare, occurring in about [2–4%] [5, 6], it is a devastating event with a median survival of usually less than 6 months [7.8].

Many studies have attempted to identify risk factors for CNS relapse, with inconsistent results due to the heterogeneity in patient population, limited sample size and the fact that many were performed in the pre-rituximab era [9–11]. Accordingly, patients were variably selected for administration of CNS prophylaxis, mostly based on anatomical location [breast, testis, bone, cranial sinuses and epidural space] and disease stage [12].

In 2016, Schmitz et al developed the CNS-IPI using data of 2164 patients treated on prospective German High-Grade Non-Hodgkin Lymphoma Study Group [DSHNHL] studies, and was validated in 1597 patients treated with RCHOP in British Columbia Cancer Agency [BCCA] [13]. Since then, the CNS-IPI has been adopted to evaluate the risk of CNS relapse by several national and international guidelines [14, 15].

An accurate selection of the patients who need administration of various treatments to prevent CNS relapse is crucial, given the associated toxicities and the demand it causes on hospital services. The impact of CNS-IPI in selecting patients for screening of CNS involvement and administration CNS directed prophylaxis is not well studied. Our study aims to validate CNS-IPI in our patient population and to evaluate the indications for intra-thecal chemotherapy [ITC] prophylaxis before the adoption CNS-IPI to estimate the impact of using CNS-IPI on the treatment of DLBCL.

### Patients And Methods:

We retrospectively analysed medical records of adult patients diagnosed with DLBCL without evidence of CNS involvement at diagnosis and treated with RCHOP regimen at Medical Oncology Department, King Hussein Cancer Centre in Jordan from January 2004 till December 2016.

The following variables were retrieved from patients charts and electronic medical records; age, gender, Eastern Cooperative Oncology Group [ECOG] performance status, lactate dehydrogenase [LDH], albumin, alkaline phosphatase [ALP], stage, extranodal sites involved, the use of ITC, indications for ITC, systemic and CNS relapse.

Selection of patients for administration of CNS prophylaxis was done based on decision of the team in the lymphoma multidisciplinary meeting. Previous guidelines didn’t specify specific indications. ITC was the only treatment given to prevent CNS relapse.

Staging was done according to Lugano staging system [16] depending on computed tomography [CT] scan and positron emission tomography [PET-CT] scan [in patients diagnosed after 2010] [16]. Bulky disease was defined as tumor bulk more than 10 centimetres. Breast, testis, uterus and epidural space were considered high risk anatomical sites [9]. Refractory disease was defined as radiological evidence of disease progression during or within 3 months after finishing the last cycle of chemotherapy or
radiotherapy, whereas relapsed disease was defined as radiological evidence of disease progression beyond 3 months after completion of therapy.

Patients were followed every 3 months in the first two years, then every 6–12 months thereafter, with clinical examination as well as CT scans for total of 5 years after which, they were followed with clinical examination of a yearly basis. Lumbar puncture or brain imaging (CT or MRI) were done only in patients who developed symptoms of CNS relapse.

CNS relapse was diagnosed based on either the radiological findings, cerebrospinal fluid cytology or brain biopsy.

The rate of relapse was calculated by dividing on the number of patient with CNS relapse by the whole number of the patients included.

The CNS-IPI was calculated using age, stage, ECOG performance status, LDH, number of extranodal sites and renal and adrenal gland involvement, and patients were classified as low risk, intermediate or high risk, as previously described [13].

The correlation between different clinical and laboratory variables with CNS-IPI risk groups and CNS relapse was assessed by univariate and multivariate analysis utilizing the backward stepwise Cox-regression model.

The median time from diagnosis to CNS relapse and survival after CNS relapse were calculated and plotted by the Kaplan-Meier method and compared by the Log-Rank test.

Results:

Patients' characteristics and treatment:

A total of 354 patients were included, 193 [54.5%] were males, with a median age of 46 [range, 18-90]. CNS-IPI was low in 148 [41.9%] patients, intermediate in 161 [45.5%] and high in 45 [12.7%] patients [table 1], whereas 30 patients [8.5%] were considered to have high risk anatomical sites [15 paraspinal, 8 breast, 4 testicles, 3 uterus]. In these patients, CNS-IPI was low in 8 [26.6%], intermediate in 20 [66.7%] and high in 2 [6.7%].

All patients were treated with RCHOP. The number of chemotherapy cycles was based on the initial disease stage and interim radiological response, with a median of 6 cycles [range, 3-8].

Two-hundred and eighty-eight patients [81.3%] achieved a complete response [CR], and the rest were considered to have refractory disease. After a median follow-up of 27.7 months, 39 [11%] patients developed relapse and 249 [70.3%] patients remained disease free.

Intrathecal chemotherapy:
Intrathecal methotrexate [IT MTX] with each cycle of chemotherapy was given to prevent CNS relapse to 52 [14.6%] patients. A median of 4 doses [range, 2-8] was given. The characteristics of the patients and the indications for IT MTX are detailed in table 2. Sixteen patients [53%] with high risk anatomical sites were given IT MTX.
| Feature                        | Number [%] |
|-------------------------------|------------|
| **Age >60**                   | 98 [27.7%] |
| **Gender**                    |            |
| Male                          | 193 [54.5%]|
| Female                        | 161 [45.5%]|
| **B symptoms**                | 143 [41%]  |
| **ECOG performance status**   |            |
| 0-1                           | 316 [89.3%]|
| >1                            | 38 [10.7%] |
| **High LDH**                  | 207 [59.3%]|
| **Albumin <3.5 g/dl**         | 53 [15.5%] |
| **High Alkaline phosphatase** | 62 [18.3%] |
| **Bulky disease**             | 114 [32%]  |
| **Stage**                     |            |
| I-II                          | 140 [39.5%]|
| III-IV                        | 214 [60.5%]|
| **Extranod al involvement**   | 230 [65.3%]|
| **Number of extranodal sites**|            |
| <2                            | 266 [75%]  |
| ≥2                            | 88 [24.9%] |
| **Selected high risk anatomical sites** | |
| Renal or adrenal gland involvement | 26 [7.3%] |
| Epidural mass                 | 15 [4.3%]  |
| Bone marrow                   | 32 [9%]    |
| Breast                        | 8 [2.2%]   |
| Stage IE                      | 3 [0.8%]   |
| Advanced stage                | 5 [1.4%]   |
| Uterus                        | 3 [0.8%]   |
| Testis                        | 4 [1.1%]   |
| **CNS-IPI**                   |            |
|       |        |                  |
|-------|--------|------------------|
| 0-1   | [low]  | 148 [41.8%]      |
| 2-3   | [intermediate] | 161 [45.5%]    |
| 4-6   | [high] | 45 [12.7%]       |

**Intrathecal chemotherapy**

|       |        |                  |
|-------|--------|------------------|
| Yes   |        | 52 [14.6%]       |
| No    |        | 302 [85.4%]      |

**CNS relapse**

|       |        |                  |
|-------|--------|------------------|
| Yes   |        | 17 [4.8%]        |
| No    |        | 337 [95.2%]      |

Table [1] patients' characteristics
| Feature                          | Number [%] |
|---------------------------------|------------|
| **Age > 60**                    | 8 [15.4%]  |
| **Median age**                  | 46.5 years |
| **Gender**                      |            |
| Male                            | 24 [46.1%] |
| Female                          | 28 [53.9%] |
| **ECOG performance status**     |            |
| 0-1                             | 47 [90.4%] |
| >1                              | 5 [9.6%]   |
| **High LDH**                    | 32 [61.5%] |
| **Albumin <3.5 g/dl**           | 7 [13.4%]  |
| **High Alkaline phosphatase**   | 11 [21.2%] |
| **Bulky disease**               | 12 [23%]   |
| **Stage**                       |            |
| I-II                            | 19 [36.6%] |
| III-IV                          | 33 [63.4%] |
| **Extranodal involvement**      | 44 [84.6%] |
| **Number of extranodal sites**  |            |
| < 2                             | 33 [63.5%] |
| ≥ 2                             | 19 [36.5%] |
| **Indications for IT chemotherapy** |        |
| **One high risk anatomical site** |        |
| Skull bones and nasal sinuses   | 17 [32.7%] |
| Tonsils                         | 5 [9.6%]   |
| Epidural mass and spine         | 7 [13.5%]  |
| Testicles                       | 3 [5.8%]   |
| Kidneys                         | 2 [3.8%]   |
| Bone marrow/bone                | 6 [11.5%]  |
| **Multiple extranodal sites [including high risk anatomical sites]** | 12 [23.1%] |
Table [2]: IT chemotherapy patients.

**CNS relapse:**

Four of 52 patients [7.6%] who received intrathecal chemotherapy [n=52], presented CNS relapse, amongst them CNS-IPI was intermediate in 1 patient and high in 3 patients.

The CNS-IPI significantly correlated with the risk of CNS relapse as the rate of relapse was [1/148] 0.06%, [6/161] 3.7% and [10/45] 22.2% among patients with low, intermediate and high scores [p = <0001].

ECOG performance status of >1, advanced stage [III or IV], high LDH, bulky disease, renal or adrenal involvement, and bone marrow involvement were associated with an increased risk of CNS relapse in univariate analysis [table 3]. Bone marrow and renal or adrenal involvement were significantly associated with CNS relapse in multivariate analysis [table 4].

Among patients with high risk anatomical sites [n=30], 2 patients [6.6%] developed CNS relapse; one with breast involvement who didn’t receive ITC and the other with epidural mass who received ITC.

The median survival of patients with no CNS relapse was not reached, while for patients with relapse/refractory disease who had CNS vs. no CNS relapse was 14 vs 29 months, respectively [p =0.444][Figures 1,2].

Table [3]: Univariate analysis
|                          | Total | No CNS relapse | CNS relapse (%) | P value |
|--------------------------|-------|----------------|-----------------|---------|
| Sex [male/female]        | 193/161 | 183/149        | 10(5.1%)/7(4.3%) | 0.724   |
| Age >60 years            | 98     | 95             | 3(3%)           | 0.823   |
| B symptoms               | 143    | 134            | 9 (6.2%)        | 0.205   |
| ECOG PS 2 or more        | 38     | 32             | 6 (15.8%)       | 0.001   |
| High LDH                 | 207    | 202            | 15 (7.2%)       | 0.004   |
| Albumin <3.5             | 53     | 49             | 4 (7.5%)        | 0.189   |
| High ALP                 | 62     | 57             | 5(8%)           | 0.083   |
| Bulky disease            | 114    | 104            | 10 (8.7%)       | 0.013   |
| Stage III or IV          | 214    | 197            | 17(7.9%)        | 0.001   |
| 2 or more extranodal sites | 88      | 75             | 13 (14.7%)      | <0.001  |
| Renal or suprarenal gland | 26      | 14             | 12 (46.1%)      | <0.001  |
| Bone marrow involvement  | 32     | 27             | 5(15.6%)        | 0.003   |
| Liver involvement        | 33     | 31             | 2(6%)           | 0.685   |

|                          | P value | Odds ratio [95% confidence interval] |
|--------------------------|---------|--------------------------------------|
| ECOG PS 2 or more        | 0.195   | 2.367 [0.642-8.798]                  |
| High LDH                 | 0.274   | 3.399 [0.379-30.480]                 |
| Bulky disease            | 0.375   | 1.743 [0.51-5.955]                   |
| Stage III or IV          | 0.996   | ................                     |
| 2 or more extranodal sites | 0.221  | 2.594 [0.563-11.945]                 |
| Renal or suprarenal gland | 0.023  | 4.995 [1.253-19.914]                 |
| Bone marrow involvement  | 0.039   | 4.156 [1.074-16.079]                 |

Table [4]: Multivariate analysis
Table 5
Candidates for CNS prophylaxis according to CNS-IPI and high risk anatomical sites

| Indication                                                                 | Number [%] |
|----------------------------------------------------------------------------|------------|
| High CNS-IPI                                                               | 45 [12.7%]|
| Bone marrow involvement with low-intermediate risk CNS-IPI                  | 18 [5%]   |
| Renal and adrenal gland involvement with low-intermediate risk CNS-IPI      | 1 [0.2%]  |
| Breast, epidural space, testis and uterine involvement with low-intermediate risk CNS-IPI | 28 [7.9%] |
| Total                                                                      | 92 [25.9%]|

Discussion:

Analysing the risk CNS relapse in DLBCL is challenging as this is a rare event. The selection of patients for CNS prophylaxis is even more complex and depends on clinical and biological factors with varied indications in most of the published trails.

In 5 of the DHSNHL trials, prophylaxis was mandated for patients with bone marrow, testicular or head and neck lymph nodes involvement [13] while in the United Kingdom National Cancer Research Institute [UK NCRI] trial, prophylaxis was given to patients with bone marrow, peripheral blood, nasal/paranasal sinuses, orbit and testicular involvement [6].

In our study, 12.7% of patients had high risk CNS-IPI, which is consistent with the data reported by Schmitz et al. Among this group, the rate of CNS relapse in our study was relatively high [22% compared to 12% in Schmitz et al]. Although we included a smaller number of patients, the risk of CNS relapse was variable even in the high risk group; in our study, 15% and 32.5% of patients with CNS-IPI of 5 and 6 respectively developed CNS relapse [13].

We confirmed the value of CNS-IPI in predicting CNS relapse in a relatively younger age group as the median age of our patients is 15–20 years less than patients included in most of the studies published in this regard [6, 11, and 13].

In our study, bone marrow involvement was associated with an increased risk of CNS relapse, which was observed in several trials [17, 18] and in the BCAA confirmation cohort of Schmitz et al trial, and explained by exclusion of patient with >25% bone marrow involvement from DSHNHL trials [13].

In addition to high CNS-IPI, involvement of certain anatomical sites [breast, uterus, testis and epidural space] may increase the risk of CNS relapse irrespective of the CNS-IPI [19, 22]. Given the fact that involvement of these sites is rare, they were underrepresented or even excluded from many prospective trials [9]. Guidelines vary in selecting these patients for CNS prophylaxis. For example, National Comprehensive Cancer Network [NCCN] guidelines recommend prophylaxis for patients with testicular,
breast and cutaneous DLBCL [14], while Spanish Lymphoma group recommends that patients with testicular, breast, kidneys or adrenal glands and epidural space involvement should receive prophylaxis [15]. In our study 30 [8.4%] patients had high risk anatomical sites, among which CNS-IPI was high in 2 [6.6%] patients and CNS relapse occurred in 2 [6.6%] of the 30. Involvement of the tonsils and paranasal sinuses were associated with increased risk of CNS relapse [6%] in pre-rituximab era, but this risk decreased to 1.6% when rituximab was incorporated in the primary therapy [23].

Our data showed that 15% of the whole DLBCL patients were given IT chemotherapy, which is similar to previously published trials [24–26]. However, if we included patients with bone marrow, renal or adrenal glands involvement and low-intermediate risk CNS-IPI [19 patients; 5.3%] and patients with high risk anatomical sites with low-intermediate risk CNS-IPI [28 patients; 7.6%] as candidates for CNS prophylaxis, as some guidelines or trials recommend [9, 29], a total of 92 [25, 9%] of DLBCL patients would have been considered for CNS prophylaxis [Table 5].

Despite the high correlation of CNS-IPI with risk of CNS relapse, its positive predictive value is low [12%], resulting in a significant proportion of patients that may unnecessarily receive prophylaxis.

The use of biomarkers may further help to identify high risk patients. Two large studies evaluated the impact of the cell of origin [defined by gene expression profiling] on CNS relapse with conflicting results [27, 28]. High grade lymphomas with MYC and BCL 2 translocation [double hit] represent about 5% of all large B cell lymphomas with CNS involvement at diagnosis or at relapse approaching 50% [29, 30]. On the other hand, expression of MYC and BCL2 [double expressor] without translocation occurs in about 30% of DLBCL, the risk of CNS relapse appears to be increased in patient with activated B cell subtype and intermediate or high risk CNS-IPI [31].

Another emerging approach is the use of pre-treatment PET-CT scan total lesion glycolysis [TLG]. In one study, among different predictive factors, TLG of more than 2000 was the only factor that significantly correlated with CNS relapse [22% vs 0.8%] [32]. These findings may need to be confirmed in larger studies.

The best approach for prevention of CNS relapse is still controversial because of lack of well randomized prospective trials, conflicting evidence and potential toxicity. Although IT chemotherapy is commonly used, evidence of efficacy is conflicting. Some studies showed that it is effective [24, 33] but many failed to demonstrate a benefit, especially in high risk patients [34, 35]. The lack of efficacy of IT chemotherapy may be due to the uneven distribution in the neuro axis as well as failure of significant penetration to the brain parenchyma as most relapses in the rituximab era are parenchymal rather than leptomeningeal [6, 36]. Systemic high dose methotrexate produces more equal concentration in the subarachnoid space and has been shown to be effective in high risk patients [36, 37]. However, there is still a debate regarding the optimal schedule and dose to be used [9]. Due to the small number of patients with high CNS-IPI given IT chemotherapy in our study, we could not conclude on the efficacy of IT chemotherapy. However, among patients with high CNS-IPI, relapse rate appears to be high [3 out 7 patients developed relapse].
Conclusion:

Inclusion of CNS-IPI in the evaluation of all DLBCL for deciding on CNS prophylaxis may help in better selection of patients with high risk for CNS relapse, but it can result in exposure of many patients to unnecessary treatments. Further studies using different biomarkers including the cell of origin, double hit or expressor subtypes and TLG on PET-CT scan are needed to help in more proper selection of patients.

Abbreviations

CNS-IPI: central nervous system international prognostic index, DLBCL: diffuse large B cell lymphoma, R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, ITC: intrathecal chemotherapy, DSHNHL: German High-Grade Non-Hodgkin Lymphoma Study Group, BCCA: British Columbia Cancer Agency, ECOG: Eastern Cooperative Oncology Group, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, CT: computed tomography, PET-CT: positron emission tomography, CR: complete response, IT MTX: intrathecal methotrexate, UK NCRI: United Kingdom National Cancer Research Institute, NCCN: National Comprehensive Cancer Network, TLG: total lesion glycolysis.

Declarations

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate:

This study was approved by our institutional review board in King Hussein Cancer Centre. Consent for publication: Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Authors’ contributions:

All authors have read and approved the manuscript, and ensure that this is the case. MM: Project development, Data Collection, Data analysis, Manuscript writing. FT: Project development, data analysis.
AA: Project development, Data Collection, Data analysis, LA: Data collection. OS: Data collection. RK: Data Collection, BF: Data collection, MR: Project development, Data analysis, KH: Project development, Manuscript writing.

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**Figures**

**Figure 1**

Survival of patients with no CNS relapse vs CNS relapse.
Figure 2

Survival of relapsed/refractory patients with no CNS relapse vs CNS relapse.