Stand-alone intrathecal CNS prophylaxis provide unclear benefit in reducing CNS relapse risk in elderly DLBCL patients treated with R-CHOP and is associated increased infection-related toxicity

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Abstract

DLBCL CNS relapse following R-CHOP occurs in 2-5%. Many patients ≥70 years are unsuitable for high-dose methotrexate (HDMTX) prophylaxis and therefore often receive stand-alone intrathecal prophylaxis. The CNS international prognostic index (CNS-IPI) is a clinical CNS relapse risk score which has not specifically been validated in elderly patients. The value of CNS prophylaxis in patients ≥70 years remains uncertain. Data on 690 consecutively R-CHOP-treated DLBCL patients ≥70 years were collected across 8 UK centres (2009-2018). CNS prophylaxis was administered per physician preference. Median age was 77.2 years and median follow-up 2.8 years. CNS-IPI was 1-3 in 60.1%, 4 in 23.8%, 5 in 13.0% and 6 in 3.3%. Renal and/or adrenal (R/A) involvement occurred in 8.8%. 2-year CNS relapse incidence was 2.6% and according to CNS-IPI 1-3:0.8%, 4:3.6%, 5:3.8% and 6:21.8%. 2-year CNS relapse incidence for R/A was 10.0%. When excluding HDMTX (n=31) patients, there remained no change in unadjusted/adjusted CNS relapse for intrathecal prophylaxis effect according to CNS-IPI. CNS-IPI is valid in elderly R-CHOP-treated DLBCL patients with the highest risk in CNS-IPI 6

and R/A involvement. We observed no clear benefit for stand-alone intrathecal prophylaxis but observed an independent increased risk of infection-related admission during R-CHOP when intrathecal prophylaxis is administered.

Introduction

Diffuse large B cell lymphoma (DLBCL) is the commonest global lymphoid malignancy and is curable in 50-90% of patients with anthracycline-based immunochemotherapy depending on age, stage, patient fitness and disease biology (Davies, 2017). Systemic disease progression is the primary cause of treatment failure in DLBCL, however central nervous system (CNS) relapse occurs in approximately 2-5%, with very short median survivals (Schmitz *et al*, 20016; El-Galaly *et al*, 2017; Cabannes-Hamy *et al*, 2018; Tai *et al*, 2011; Boehme *et al*, 2009). Finding effective and non-toxic preventative strategies of CNS relapse is of critical importance across all age groups including the elderly. Several clinical and biological risk factors for CNS relapse have been described and include double hit (MYC plus BCL2 and/or BCL6 rearrangement) lymphoma (Oki *et al*, 2014), advanced stage III-IV disease, raised lactate dehydrogenase (LDH), >1 extranodal disease site and involvement of specific sites, for example, the testis, kidney or adrenal glands.

The CNS-IPI (international prognostic index) used the standard IPI with an additional point for renal/adrenal (R/A) involvement to define the risk of CNS relapse in a large cohort of patients with aggressive B cell lymphoma (n=2164; 18-80 years; 80% DLBCL) (Schmitz *et al*, 20016). This tool classifies patients according to their baseline CNS-IPI score into risk categories. Low-risk (CNS-IPI 0-1; 46%), intermediate-risk (CNS-IPI 2-3; 41%), and high-risk (CNS-IPI 4-6; 12%) patients demonstrated a cumulative 2-year risk of CNS relapse of 0.6% (95% confidence interval (CI) 0-1.2%), 3.4% (95% CI 2.2-4.4%), and 10.2% (95% CI 6.3-14.1%) respectively, with similar results seen within the British Columbia Cancer Agency validation data set. A separate validation study (El-Galaly *et al*, 2017) by El-Galaly and colleagues analysed 1532 patients with a median age of 65 years who were staged with PET-CT and treated with R-CHOP/R-CHOP-like regimens. Four percent of patients developed CNS relapse and the multivariable analysis found that baseline stage III/IV disease, raised LDH, kidney/adrenal and uterine/testicular DLBCL involvement were independent risk factors for CNS relapse. Patients with >2 extranodal sites had a 3-year cumulative CNS relapse incidence of 15.2% compared to 2.6% in patients with ≤2 extranodal sites ($p<0.001$). Predictive tools like these have enabled targeted CNS prophylaxis in higher risk patients.

Although the CNS-IPI is validated in younger (18-80 years) DLBCL patients (Schmitz *et al*, 20016) very few studies have assessed the incidence of CNS relapse, its associated risk factors, or the influence of CNS prophylaxis in elderly DLBCL patients treated with curative intent with R-CHOP (full or attenuated dose). A subgroup analysis from El-Galaly *et al* suggested that the CNS-IPI predicts CNS relapse in 494 patients ≥70 years (personal communication) (El-Galaly *et al*, 2017). There are few data pertaining directly to the elderly. However, a recent pooled analysis of two LYSA attenuated CHOP plus anti-CD20 phase II trials examined 270 trial-fit, selected patients ≥80 years (Cabannes-Hamy *et al*, 2018). In this analysis, no patients received CNS

prophylaxis, and the CNS relapse risk was 1.8% at 2 years and 3% overall. The CNS relapse risk did not differ according to CNS-IPI (low-intermediate 3% (versus (vs.) high 2.8%; p=1.00).

The majority of CNS relapse events in the rituximab era are intraparenchymal (Guirguis *et al*, 2012; Mitrovic *et al*, 2012), leading to an ongoing debate about the relative benefits of intrathecal (IT) prophylaxis and the more widespread adoption of high dose intravenous (IV) methotrexate (HDMTX) prophylaxis in younger (often <70 years) patients with adequate renal function and high risk clinical features (Savage, 2017). Although a small number of selected patients ≥70 years receive IV HDMTX and / or IT MTX, there is a relative lack of definitive evidence documenting the benefit of this approach and a lack of toxicity data utilising HDMTX in patients ≥70 years. Patients ≥70 years represent the minority of those studied in *post hoc* analyses from the RICOVER-60, R-CHOP 14 versus 21 trials (for example, 216/1080 (20%)) (Gleeson *et al*, 2017; Boehme *et al*, 2009), GOYA (Klanova *et al*, 2019) and retrospective series (Tomita *et al*, 2015; Kumar *et al*, 2012; El-Galaly *et al*, 2017). Collectively, these series failed to demonstrate any consistent benefit of IT prophylaxis across a broad range of ages. Furthermore, the relative benefit of CNS prophylaxis is uncertain in older patients who are more vulnerable to its potential toxicities (Savage, 2017) and this question has not been addressed.

We conducted a retrospective multicentre national analysis of the risk of CNS relapse in patients ≥70 years old with DLBCL treated with curative intent. We aimed to further validate the CNS-IPI in an elderly population, assess the influence of CNS prophylaxis on CNS relapse risk, and analyse its toxicity patterns in elderly patients.

Methodology

Data on 690 consecutively treated first line elderly DLBCL patients of ≥70 years were retrospectively collected across 8 UK centres from 2007-2018. All patients were untreated, *de novo* DLBCL or untreated transformed (to DLBCL) indolent B cell non-Hodgkin lymphoma (iNHL). Patients with leg-type DLBCL, post transplantation lymphoproliferative disease, concurrent CNS involvement, HIV-positivity and pre-treated transformed iNHL were excluded. All patients were treated with between 1-8 cycles of full or attenuated dose R-CHOP with curative intent. Baseline CNS evaluation was not mandated for inclusion in the study although this was performed routinely in patients with clinically concerning features of CNS involvement.

We collected baseline disease characteristics including the CNS-IPI and extranodal site involvement. Multiple lesions within one organ or tissue type (e.g. multiple skin or pulmonary lesions) were considered as a single extranodal site. Bone involvement was defined by focal lesions on PET-CT or standard CT, and/or by bone marrow involvement at biopsy. CNS prophylaxis was administered as per local protocol according to physician preference. Admission reason(s) and rate were collected following IV HDMTX. Patients were analysed according to whether they had received no prophylaxis, IT prophylaxis only, HDMTX only, or a combination of IT MTX and IV HDMTX. During the inclusion period, treating physicians typically administered IT MTX synchronously with R-CHOP and typically proceeded with up to 2 cycles of HDMTX following R-CHOP in selected patients. CNS relapse was defined by intraparenchymal, spinal cord, leptomeningeal or ocular recurrence which was documented either by histopathological, cytological or clinico-radiological features.

Statistical analysis

Baseline patient characteristics were summarised in a descriptive manner. Survival analyses were performed using Kaplan-Meier survival analysis (Kaplan & Meier, 1958) and Cox regression with comparisons between categories were made using the log-rank test. All time to event analyses were measured from the date of the initial DLBCL diagnosis until the event with patients censored at the date last seen if alive and event free. Time to CNS relapse and the cumulative incidence of CNS relapse at 2 and 3 years were analysed using competing risk survival analyses with death and systemic relapse counted as competing events. Survival following the time of relapse was measured as the time from relapse to either the date of death from any cause or censored at the last clinical contact. Patient follow-up was censored in February 2019. Univariable analyses of potential influencing factors for CNS relapse including the CNS-IPI, specific extranodal sites and use of CNS prophylaxis were performed. Multivariable analysis assessment the risk of infective re-admission was assessed by logistic regression analysis. For this analysis, the specific time point from which patients were considered at risk of infection was from the start of cycle 1 and during R-CHOP immunochemotherapy i.e. until 3 weeks following the final cycle. Infective admission for each patient was collected in a binary fashion. Analyses of admission data and the risk of CNS relapse according to CNS prophylaxis have been repeated for only patients who were alive and progression free at 6 months to attempt to resolve possible issues with immortality bias. Statistical analyses were performed in Stata 15.1 (StataCorp, College Station, TX, USA). 95% confidence intervals are presented for all estimates with $p<0.05$ taken as significant.

Results

Baseline characteristics of all 690 consecutive patients are displayed in Table I. 65.5% were aged 70-80 years and 34.5% were ≥80 years. There was an equal gender balance (50.7% male; 49.3% female) across all patients. The median age across all patients was 77.2 years and the median follow-up was 2.8 years (range 0.4-8.9). Higher CNS-IPI scores resulted in an inferior progression-free survival and overall survival in the expected manner (Fig S1).

CNS risk assessment

The CNS-IPI was 1 in 12.3%, 2 in 21.7%, 3 in 25.9%, 4 in 23.8%, 5 in 13.0% and 6 in 3.3%. 22 patients were unclassifiable due to a missing LDH (n=19) or ECOG performance status (n=3), though only ten could not be classified as low, intermediate or high risk (Table I). Two or more extranodal sites were noted in 30.9%. The median number of extranodal sites was 1 (range 0-5). The most common extranodal sites were bone (23.8%), liver (9.7%), small and/or large bowel (9.6%), and lung (8.3%) (Table SI). Renal and/or adrenal involvement was present in 8.8% of cases (42 renal only, 14 adrenal only, 5 both). Breast (1.4%; n=10), testicular (3.0%; n=21) or uterine involvement (0.6%; n=4) were uncommon at baseline imaging assessment.

CNS prophylaxis and readmissions

81.2% of patients received no CNS prophylaxis. 14.3% received IT MTX prophylaxis (typically between 2-4 IT doses), 2.0% received HDMTX only, and 2.5% received a combined of IV HDMTX and IT MTX (Table II). 63 total cycles of HDMTX were given over 30 patients (1 unknown cycle number). The median dose of HDMTX was 3000mg/m^2 (range 1000mg/m^2 to 3500mg/m^2). Patients with higher CNS-IPI were more likely to receive CNS prophylaxis (IT MTX and/or HDMTX). The rate of CNS prophylaxis according to CNS-IPI categories were; CNS-IPI 0-1; 14.6%, CNS-IPI 2-3; 10.7%, and CNS-IPI 4-6; 29.9% (p<0.001). 52.5% patients with renal/and or adrenal involvement who could be categorised by CNS-IPI received CNS prophylaxis compared to 15.6% without renal and / or adrenal involvement (p<0.001).

Of 31 (4.5%) patients receiving IV HDMTX, the median age was 72.4 years (range 69.5-84.5) with only 1 patient ≥80 years. The median CNS-IPI was 4 (range 1-6) and median estimated glomerular filtration rate of 83 ml/min/1.73m^2 (range 47 to >90). Sixteen percent (5/31) of patients were readmitted with complications directly following the administration of HDMTX (neutropenic fever (NF) (n=1), non-neutropenic fever (n=1), mucositis (n=1), pericarditis (n=1), and pneumonia/SIADH (n=1)). The readmission rate per cycle was therefore approximately 8% (5/63). A single CNS relapse occurred in a patient who received HDMTX (3.2%).

The median CNS-IPI for those who received IT MTX was 4 (range 1-6) compared with 3 (range 1-6) for those not receiving IT MTX prophylaxis. When patients who received IT MTX were compared to those receiving no IT MTX, the readmission rate during R-CHOP with all-cause infection was 44.4% (44/99) vs. 25.2% (140/556; 3 unknown) respectively (p<0.001). There were no CNS infections noted in either group. When CNS-IPI factors, baseline haemoglobin, baseline albumin, CIRS-G (Cumulative Illness Rating Scale for Geriatrics) scores and number of cycles were included within a multivariable logistic regression model, intrathecal prophylaxis retained its independent increased risk of readmission for all-cause infection during R-CHOP therapy (odds ratio (vs no prophylaxis) 2.20 (95% CI 1.31-3.67; p=0.01) (Table III). These findings also remained very similar when only patients who were alive and progression free at 6 months were included (odds ratio 2.24 (95% CI 1.26-4.00; p=0.021)).

Cumulative CNS relapse risk: by age and CNS-IPI

The overall estimated 2-year and 3-year incidence of CNS relapse was 2.6% (95% CI 1.6-4.2) and 3.1% (95% CI 2.0-5.0) respectively (Fig 1A). According to CNS-IPI 2 and 3-year cumulative incidences were: CNS-IPI 1-3**:** 0.8% (95% CI 0.3-2.5) and 1.7% (0.7 – 4.1), CNS-IPI 4: 3.6% (95% CI 1.5-8.4), CNS-IPI 5: 3.8% (95% CI 1.2-11.3) and CNS-IPI 6: 21.8% (95% CI 8.6-49.3). The cumulative 2-year and 3-year incidence of CNS relapse in patients with renal and/or adrenal involvement was 10.0% (95% CI 4.2-22.7) compared to 1.9% (95% CI 1.1-3.5) and 2.5% (95% CI 1.4-4.3) respectively without renal and/or adrenal involvement (Fig 1B-C).

Univariable predictors of CNS relapse

Univariable factors significantly associated with an increased risk of CNS relapse include ECOG performance status >1 (hazard ratio (HR) 3.03 (95% CI 1.14 – 8.06); p=0.02) and renal and/or adrenal involvement (HR 4.08

(95% CI 1.47 - 11.34); p=0.004) (Table IV) with borderline significance seen for raised LDH (HR 3.10 (95% CI 0.90 - 10.65); p=0.058). The hazard ratios (reference CNS-IPI 0-3) for CNS relapse in patients with a CNS-IPI 4 was 2.26 (95% CI 0.69 - 7.41), CNS-IPI 5 was 2.69 (95% CI 0.67 - 10.77) and CNS-IPI 6 was 15.45 (95% CI 4.35 - 54.85) respectively (p<0.001) (Table IV/V). There was no difference in the risk of CNS relapse according to age, sex or by extranodal sites (0-1 vs. >1 or by continuous form: HR 1.29 (0.93 - 1.80), p=0.132).

Influence of CNS prophylaxis on the risk CNS relapse per CNS-IPI

The unadjusted hazard ratio for CNS relapse of patients who received CNS prophylaxis when compared to those who did not receive prophylaxis was 2.11 (95% CI 0.83 - 5.56; p=0.12). When adjusted for the CNS-IPI the HR was 1.34 (95% CI 0.46 - 3.86; p=0.59) (Table V). Although this analysis does not exclude the effect of other potential confounding factors and may not overcome selection bias, there was no evidence of a reduction in risk for patients given CNS prophylaxis. When the 31 patients, including a single CNS relapse, who received IV HDMTX were excluded from the analysis, there remained no discernible change in the risk of CNS relapse according to CNS-IPI with and without adjustment for CNS prophylaxis (IT MTX) (Table SII).

CNS relapse cases

Nineteen patients experienced CNS relapse. Table IIIS summarises the characteristics of these 19 patients. All cases were diagnosed radiologically and all were intraparenchymal in nature with only 1 case having concurrent leptomeningeal involvement. The single patient with leptomeningeal involvement had previously received IT prophylaxis. The 19 cases included isolated CNS relapse (n=13) and concurrent CNS and systemic relapse (n=6). The median time to CNS relapse was 9.4 months (range 1.8-70.8 months) from initial diagnosis. 12/19 CNS relapse events occurred within 1 year follow-up and 16/19 CNS relapse events within 2-years post DLBCL diagnosis. Sixty-eight percent (13/19) of CNS relapses had a CNS-IPI 4-6.

Survival post CNS relapse

142/159 patients who relapsed with either systemic and/or CNS DLBCL have died. The median overall survival (OS) following relapse of any cause was 3.3 months (range 0.5 days - 57 months). 12 of 13 patients with isolated CNS relapse have died, with a median overall survival of 2.1 months (range 1 day - 3.8 months)). The median overall survival for patients with concurrent CNS and systemic relapse was 1.7 months (6 days - 3.3 months). Overall, this is similar to the median OS of patients who progressed with systemic disease only (median 3.7 months) (Fig S2).

Discussion

To the authors' knowledge, this is the largest published series to systematically analyse the risk of CNS relapse in a representative, unselected R-CHOP-treated cohort of elderly (≥70 years) DLBCL patients in the first line setting. It is the first study systematically to assess the risk of infection due to standalone IT prophylaxis in the rituximab era. Across the whole cohort, the rate of CNS relapse is low and consistent with recent pooled trial data (Cabannes-Hamy *et al*, 2018). As previously described (El-Galaly *et al*, 2017; Schmitz *et al*, 2016), an

increased risk was seen in patients with a CNS-IPI 4-6 with a particularly increased risk in the minority (n=22) with a CNS-IPI 6 and with renal and/or adrenal involvement (n=61). There were no differences in CNS relapse incidence according to age (70-80 versus ≥80 years), gender or number of extranodal sites (≤2 vs. 2+ or continuous). We were able to validate further the role of the CNS-IPI and renal and/or adrenal involvement in the risk stratification in elderly patients.

Notably, the rate of CNS relapse, adjusted for CNS-IPI, was similar regardless of whether or not CNS prophylaxis was administered. Outcomes were unchanged when patients receiving HDMTX were excluded. This finding is consistent with *post hoc* analyses from recent trials (Klanova *et al*, 2019) and retrospective analyses which have examined this question, typically across all age groups (El-Galaly *et al*, 2017). Our data therefore add to the accumulating evidence suggesting that IT prophylaxis has little role in the rituximab era (Boehme *et al*, 2009; Gleeson *et al*, 2017; Kumar *et al*, 2012; Tomita *et al*, 2015; Guirguis *et al*, 2012; Villa *et al*, 2009; Wudhikarn *et al*, 2017; Kanemasa *et al*, 2016; Tai *et al*, 2011; Shimazu *et al*, 2009). An increased risk of readmission with infection was independently associated with intrathecal prophylaxis when CNS-IPI, baseline albumin, baseline haemoglobin and CIRS-G scores were taken into account. Since most CNS relapses were documented intraparenchymal, IT CNS prophylaxis is of limited theoretic utility, and indeed our data have failed to demonstrate its efficacy in preventing CNS relapse in most patients. The increased rate of infection in patients receiving IT prophylaxis shifts the risk/benefit balance away from prophylaxis in those patients with a lower CNS IPI and without renal/adrenal involvement.

There are conflicting data in the literature on the benefits of high dose IV CNS prophylaxis in reducing the risk of CNS relapse, with some studies suggesting a lack of benefit (Dann *et al*, 2015; Cortelazzo *et al*, 2016) and others showing possible benefit (Holte *et al*, 2013; Cheah *et al*, 2014; Abramson *et al*, 2010; Ferreri *et al*, 2015). Most studies examining high dose IV anti-metabolites are characterised by the relatively small number of patients studied (n=65 to n=246); a focus on younger patients (median age 51-65 years); and a risk assessment in the era prior to the CNS-IPI score. IV HDMTX given in the small number of selected, fit patients ≥70 years with adequate renal function in our series was associated with a tolerable 8% (5/63) readmission rate per cycle and no non-relapse deaths. As such, our data suggest that HDMTX is infrequently used in patients ≥70 years, although it can be relatively well tolerated in selected fit patients. The small numbers receiving HDMTX limit the conclusions on the efficacy in reducing CNS relapse in this population and it is possible that the outcomes of patients treated with HDMTX suffer from the risk of immortality bias. A clear consensus in these elderly patients has historically not been based on robust prospective evidence. However on the basis of our data, consideration of prophylaxis could justifiably be confined to patients who are fit for HDMTX with a baseline CNS-IPI 6 and/or renal/adrenal involvement but in the knowledge that we found no clear evidence of benefit of prophylaxis in any risk groups.

Weaknesses of our study include its retrospective, non-randomised nature, together with the inherent potential risk of variation in medical chart interpretation. There are imbalances across the ages and baseline

characteristics across subgroups studied and a lack of consistent use of baseline PET-CT across all patients studied to document extranodal sites. It is possible that some of the genuine associations described in the literature to date, such as the association with CNS relapse and increasing extranodal sites, were not possible to ascertain or reproduce in this elderly population due to the absolute patient numbers studied or the lack of 100% PET-CT scanning at initial staging. Although our study is the largest to report in this age group, the absolute number of CNS relapse events was low. Therefore, the confidence intervals for hazard ratios within a number of subgroups reported in the univariable and adjusted analysis are wide and the power to detect differences within some groups may be lacking. We were also unable to provide a full multivariable analysis due to the low number of events so it is possible that other confounders and unavoidable selection bias may have theoretically prevented us from showing a benefit from CNS prophylaxis. We also lack data on MYC, BCL2 and BCL6 translocations by fluorescence *in situ* hybridisation as these were not routinely performed on the majority of the cohort. Although we report data on re-admissions with HDMTX, we acknowledge that these results represent a small cohort (4.5%, n=31/690) of the overall population within the study and it is different to draw firm conclusions regarding the toxicity and benefit of this approach in this age group. Finally, we did not collect specific data on the exact timepoint during the treatment cycles when patients were admitted with infection. Although it is common practice for IT MTX to administered early in treatment cycles, this was not specifically collected. As such, it is possible that the results associating infection and IT MTX could be confounded, and this need assessing within prospective clinical trial analysis.

In conclusion, we report the largest independent study to validate the CNS-IPI in elderly people treated with full or reduced dose R-CHOP. We demonstrate that CNS relapse typically occurs early (median 9.1 months) after diagnosis and is commoner in patients with a high CNS-IPI, particularly CNS-IPI 6, and in those with renal and/or adrenal involvement. We show there is toxicity associated with IT prophylaxis, with an increased risk of readmission for infection during R-CHOP therapy. We were unable to demonstrable any reduction in risk of CNS relapse following adjustment for CNS-IPI. In light of the potential morbidity associated with CNS prophylaxis, it should be used judiciously in the elderly, with a focus on those with an especially high risk of CNS relapse.

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Author contributions

TE designed the study; TE, NMC, CH, HP, MK, JB, CM, FD, SB, JG, JW, AM, CF, MB, RO, PF, + 1 collected the majority of the data. AAK performed the statistical analysis. TE wrote the manuscript, which all authors critically reviewed. TE, AM, CF, MB, SB, PF, GC and CH managed many patients in the study.

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