Original Article

Influence of rituximab and central nervous system directed prophylactic therapy on central nervous system relapse in high-risk diffuse large B-cell lymphoma

Mahender Yellu[1], Gunjan Guha[2], Chandana Kamireddy[3], Zartash Gul[1], Tahir Latif[1]

[1]Division of Hematology & Oncology, University of Cincinnati, Cincinnati, OH, USA; [2]School of Chemical and Bio Technology, SASTRA University, Thanjavur, Tamil Nadu, India; [3]Bone Marrow Transplantation, University of Cincinnati, Cincinnati, OH, USA

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Correspondence to: Tahir Latif, MD, MBA, FACP. Division of Hematology & Oncology, University of Cincinnati, 3125 Eden Avenue, ML 0562, Cincinnati, OH 45219, USA. Email: Tahir.Latif@uc.edu.

Background: Central nervous system (CNS) relapse in patients with diffuse large B-cell lymphoma (DLBCL) although rare, can be devastating. Conflicting reports have been published regarding the protective effect of systemic rituximab therapy and likely reduction in incidence of CNS relapse in post-rituximab era.

Methods: We retrospectively identified all the DLBCL patients at our institute between 2004 and 2014 who received systemic rituximab-based chemotherapy at initial presentation. Patients were categorized into two groups, "standard risk" with no risk factors and "high risk" with one or more of the following risk factors, elevated lactate dehydrogenase (LDH) (above the institute normal), international prognostic index (IPI) ≥3, involvement of testis, breast, bone, kidneys, adrenal gland, retroperitoneal lymph nodes, para-meninges, and bone marrow. Descriptive statistics were used to analyze incidence of CNS relapse, patient and disease characteristics. Historically reported incidence rates were used for comparison.

Results: A total of 122 patients received rituximab-based therapy at the initial diagnosis; 73 patients (60%) qualified for standard risk; 49 patients (40%) met the criteria for "high risk" based on the above definition. Standard risk group received no CNS directed prophylaxis and none of these patients had CNS relapse. Thirty-one of 49 (63%) "high risk" patients received CNS prophylaxis, mainly intrathecal (IT) methotrexate. Five patients (4.0%) developed CNS relapse in the entire study population. Percentage of patients developed CNS relapse in high-risk patients was 10.2% (5/49). Median time to relapse was 8.76 months and median survival after CNS relapse was 9.16 months. Four out of five patients who developed CNS relapse received prophylaxis with IT.

Conclusions: CNS relapse continued to be a rare but devastating complication in post rituximab era, however our study confirms that majority of the DLBCL patients do not need CNS directed therapy. Current CNS directed therapies are probably inadequate to prevent CNS relapse in high risk DLBCL patients, therefore further research to develop better agents is needed in this area.

Keywords: Lymphoma; rituximab; central nervous system (CNS) relapse; CNS prophylaxis

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Introduction

According to the cancer statistics, an estimated 72,240 new cases of non-Hodgkin's lymphoma (NHL) will be diagnosed and 20,140 deaths will occur in the year 2017 (1). Central nervous system (CNS) involvement by diffuse large B-cell lymphoma (DLBCL) is relatively an uncommon complication but carries very high morbidity and mortality (2). The median survival after CNS relapse of DLBCL is approximately 6 months with no uniformly effective treatment strategy available to date (3). Addition of CNS directed therapy at diagnosis is a common practice to prevent this complication. However, there is lack of consensus regarding proper selection of patients to offer prophylaxis and electing the most appropriate prophylactic regimen.

Addition of systemic rituximab to the standard chemotherapy regimen has significantly boosted the survival rate while adding only minimal toxicity (4,5). The reported incidence of CNS involvement by DLBCL varied across the studies in pre-and post-rituximab era. Although several studies found no significant reduction in CNS relapse with addition of systemic rituximab, some studies favored reduction in the incidence in post rituximab era (2,6,7). As such some authors argue against offering CNS prophylaxis even to the high risk DLBCL patients, especially those who received systemic rituximab based chemotherapy at diagnosis due to the low incidence of CNS relapse (8,9). In this report, we analyze the incidence of CNS involvement by DLBCL at our institution during the last decade and attempted to define the "high risk" group who were felt to benefit from CNS directed prophylactic therapy.

Methods

All DLBCL patients who received systemic rituximab based chemotherapy [rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) or rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide (R-CHEOP)] and treated between January 2004 and October 2014 at University of Cincinnati were included in this retrospective analysis. Patients were divided into "standard risk" group and "high risk" group based on high risk features identified in the published literature. High risk patients had one or more of the following risk factors: advanced Ann Arbor stage (III/IV) (2), lactate dehydrogenase (LDH) of greater than the institutional normal range (10), international prognostic index (IPI) of ≥3 (10), involvement of ≥1 extra nodal site such as testis (11), breast (12), bones (13), kidneys (14), adrenal glands (15), retroperitoneal lymph nodes (16), paranasal sinuses (17), and para-meninges (18), bone marrow (19), transformed lymphoma (20), double hit lymphoma (21) or c-myc rearrangement (22). Patients without any of the above risk factors were considered standard risk group. Incidence of CNS relapse among patients who received upfront systemic rituximab and the median survival after relapse was studied using descriptive statistics. The study was reviewed and approved by institutional review board (IRB).

Results

A total of 122 patients who received R-CHOP or R-CHOEP therapy during the study period were included; 73 patients (60%) were classified as "standard risk" while remaining 49 (40%) patients met criteria for "high risk". Summary of the number of patients who received CNS prophylaxis and the number who developed CNS relapse is provided in the table below (*Table 1*). Among the total study population, 4.09% (5/122) patients developed CNS relapse, all with at least one predefined high-risk features. All patients who experienced CNS relapse were confirmed by either identifying the malignant cells in significant cerebrospinal fluid (CSF) and or based on clinical and radiological diagnosis. Among the high-risk group, 10.2% (5/49) of patients developed CNS relapse. No patient in the standard risk group received CNS directed prophylaxis, whereas 63% (31/49) of high risk patients received CNS prophylaxis in the form of intrathecal (IT) methotrexate or cytarabine; 80% (4/5) of patients who developed CNS relapse has received CNS prophylaxis. Average number of doses of prophylaxis received by each patient was 3.2 (range, 1–7).

Male to female ratio among those who relapsed was 1:1.5. All patients who relapsed had advanced Ann Arbor stage (stage III or IV) at diagnosis. Median age at diagnosis in patients with CNS relapse was 53 years and median time to relapse was 8.76 months (range, 5.47–14.03 months). Median survival after the CNS relapse was 9.16 months (range, 1.6–20.47 months).

Discussion

Selecting appropriate patients for CNS prophylaxis and also selecting suitable prophylactic regimen continues to be a complex decision due to lack of consistent data. Physicians need to weigh the risks and benefits of offering prophylaxis

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Table 1 CNS relapse in in DLBCL patients treated with rituximab and chemotherapy

Patient characteristics	Standard risk	High risk	Total
Number of patients who were treated with rituximab	73	49	122
Patients received CNS prophylaxis, %	0	63 (31/49)	25.4 (31/122)
Patients with CNS relapse, %	0	10.2 (5/49)	4.09 (5/122)
Patients who developed CNS relapse despite receiving CNS directed therapy, %	0	12.9 (4/31)	4.09 (5/122)

CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma.

and appraise the intensity of specific risk factor in individual patients against the toxicity of CNS directed therapy. Methotrexate administered intrathecally is most commonly used method for prophylaxis, however methotrexate when given by this route can have uneven distribution within the neuroaxis (23,24). A recent study suggested that addition of systemic methotrexate and or cytarabine to IT methotrexate for CNS prophylaxis for high-risk DLBCL patients is associated with reduction in CNS relapse (3-year actuarial rates of 18.4%, 6.9% and 2.3% with IT methotrexate alone, IT methotrexate plus two cycles of intravenous methotrexate or hyperfractionated cyclophosphamide, vincristine, Adriamycin and dexamethasone (Hyper-CVAD) or cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate (CODOX-M)/ifosfamide, etoposide and high-dose cytarabine (IVAC) with IT or intravenous methotrexate respectively, P=0.009) (25). Abramson *et al.* also reported use of intravenous methotrexate concurrently with standard therapy for prevention of CNS relapse in DLBCL patients with CNS risk factors. The study found that using intravenous methotrexate is safe and reported reduced number of CNS relapses (2%) (26). To date no prospective randomized controlled studies are available to help determine best treatment option for patients with increased risk of CNS relapse. Systemic adverse effects of IT methotrexate are uncommon however neurological toxicity has been reported particularly in children. In one study "toxic syndrome" characterized by fever, headache and vomiting were observed in over 60% of young children receiving prophylactic IT methotrexate. This was attributed to cumulative effect from frequent dosing (27). Cytotoxic edema, Seizures and local toxicity from accumulation of methotrexate due to obstruction in CSF flow has also been reported (28,29).

CNS relapse in DLBCL patients carries an extremely poor prognosis. The reported incidence of CNS relapses in these patients' ranges between 2% to 25% (30). The SWOG 8516 study showed that CNS relapse occurs early with a median time to relapse of about 5.4 months from the time of diagnosis. This early occurrence of CNS disease likely reflects the presence of sub-clinical CNS involvement at the time of diagnosis (31). Identification of patients at substantial risk of CNS disease is of paramount importance for not only to develop effective preventative strategies but also to spare majority of patients from the toxicity related to CNS directed therapies. Majority of studies reporting the incidence of CNS relapse in DLBCL have not stratified patients based on risk factors and to the best of our knowledge our study is the first one describing the distinction of standard risk *vs.* high-risk group. Not only the validation of this distinction is needed, we feel that the definition of high risk is still very vague and further studies are needed to improve the patient selection for prophylactic CNS directed therapy. Recent publication of central nervous system-international prognostic index (CNS-IPI) is a significant step towards this direction however we believe further refinements may still be required. In this study the intermediate risk group had CNS relapse rate of 4% and considering the reported median overall survival after diagnosis of CNS relapse is 3.5 *vs.* 2.8 months in validation cohort, prevention of CNS relapses in this group is also important (19). In our data set CNS-IPI failed to identify these patients as two patients with CNS relapse belong to low risk group and three to intermediate risk group (*Table 2*). CNS-IPI risk model study also did not reliably exclude involvement of skin, testes, and bone marrow as independent risk factors for CNS relapse.

Several studies in post rituximab era have shown conflicting results regarding the influence of rituximab in reducing the incidence of CNS relapse. Some studies have shown decreased incidence in contrast to other studies showing no reduction in the CNS relapse rates despite using rituximab (*Table 3*). Villa *et al.* showed a trend towards decreased incidence of CNS relapse at 3 years in patients

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Table 2 CNS-IPI in the study population

CNS-IPI risk	Score	Total patients (n=120)
Low	0–1	61
Intermediate	2–3	50
High	4–6	9

CNS-IPI, central nervous system-international prognostic index.

Table 3 CNS relapse in DLBCL patients treated with rituximab based therapy

Study	No. of patients	CNS relapses (%)	Survival after CNS relapse (months)
Current study	122	4.0	9.16*
Feugier *et al.* (2)	202	5.34	<4
Villa *et al.* (32)	309	6.4	3.6*
Kanemasa *et al.* (14)	413	6.5	7*

*, median survival. CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma.

treated with R-CHOP (9.7% *vs.* 6.4%, P=0.085) in a cohort of 435 patients with DLBCL (32). In this study, for patients who achieved complete response, the incidence of CNS relapse was significantly better in R-CHOP arm (5.8% *vs.* 2.2%, P=0.009).

Similarly, Shimazu *et al.* also reported rituximab may have protective effect on CNS relapse in patients with DLBCL (HR =0.48, P=0.027) (19). Feugier *et al.* evaluated the impact of rituximab on CNS relapse from the patients included in Groupe d'Etude des Lymphomes de l'Adulte (GELA) study (2). A total 399 patients with DLBCL were studied and found that 11 of 202 patients who received 8 cycles of R-CHOP developed CNS relapse as opposed to 9 of 197 patients who were treated with CHOP only (P=0.688). This study also showed that advanced age, elevated LDH, poor performance status (PS) and high age adjusted IPI was associated with high relapse rate (2). Similarly, in another study by Yamamoto *et al.* (7), rituximab did not impact CNS recurrence (3.9% in R-CHOP arm *vs.* 2.9% in CHOP arm; P=0.71). In our study population, 4% of all patients and 10% of high-risk patients developed CNS relapse, showing that CNS relapse is still a devastating problem. Systemic rituximab may be ineffective in preventing CNS relapse due to its inability to cross blood brain barrier and achieve CSF concentrations. This was demonstrated in a study where the rituximab concentration in CSF after intravenous infusion was found to be almost negligible (0.1%) compared to peak serum levels (16). In another study Harjunpaa (33) showed that although CSF concentration of rituximab can increase after multiple systemic infusions, it remains significantly lower than the serum level (below 0.55 µg/mL compared to a 400 µg/mL in peripheral blood). One of the potential strategies to overcome this limitation can be intrathecal administration of rituximab. Intrathecal administration has been studied in multiple phase I studies to treat known CNS involvement by lymphoma. For example, in one phase I study with 10 recurrent CNS NHL patients, use of IT rituximab at varied doses (10, 25 or 50 mg) demonstrated a maximum tolerated dose of 25 mg, with six patients exhibiting cytological response and four patients complete response. Additionally, the levels achieved in CNS were similar to the peak levels achieved with high dose systemic therapy (34). Another phase I study included 14 refractory CNS NHL patients, IT rituximab was given at a dose of 10 or 25 mg twice weekly along with IT methotrexate. No serious toxicities were reported. In this study 75 % of patients achieved cytological response while 43% achieved CR (35). To the best of our knowledge this strategy has not been applied in the prophylactic setting.

Conclusions

CNS relapse continued to be a rare but devastating complication in post rituximab era, however our study confirms that majority of the DLBCL patients does not need CNS directed therapy. Patients with standard risk should not receive prophylaxis due to very low risk of CNS relapse whereas high-risk patients may benefit from CNS prophylaxis. In the rituximab era we need to better define high-risk patients in prospective studies to limit toxicity. Secondly, development of better prophylactic agents including combination therapies, and appropriate route of administration is needed to prevent CNS relapse, as survival after relapse is dismal in spite of aggressive treatment strategies.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest

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to declare.

Ethical Statement: The study was approved by the Institutional Review Board (ID: CR1_2014-3392).

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