Sir,

I read with great interest the research article “survival and failure outcomes in primary central nervous system lymphoma (PCNSL) with whole brain radiation therapy (WBRT) followed by cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) chemotherapy: An alternative treatment approach in community settings in low resource countries” published in the July-August issue of your esteemed journal. The authors have concluded that though the standard of care in the management of PCNSL is high-dose methotrexate (HD-MTX) based chemotherapy; considering poor compliance and tolerability to treatment in low resource countries in routine clinical setting, WBRT, followed by systemic chemotherapy with standard CHOP regimen for treatment of PCNSL demonstrates reasonably good outcome. This study opens up the opportunities to conduct further larger randomized controlled studies in the poor resource settings to compare the standard treatment versus CHOP after WBRT.

However, there are some important issues which could have been addressed in this study. There was listing of various prognostic factors such as age, performance status (PS), location of the tumor and extent of the surgery, but there was no use of risk stratification strategy. international extranodal lymphoma study group has recommended the use of a combination of five independent predictors of response and survival, that is, age, PS, serum lactate dehydrogenase level, cerebro-spinal fluid protein concentration, and the involvement of deep structures, to distinguish three risk groups based on the presence of 0-1, 2-3, or 4-5 unfavorable features. The table of patient characteristics shows that a patient of age as young as 30 years and five patients of Kernofsky performance score as good as 80 were included in the study. These patients, in the absence of other unfavorable features, could have been benefitted more with the use of standard of care HD-MTX based regimens. Even, Ferreri et al. have recommended the use of combination of HD-MTX and HD-cytarabine in patients of age <75 years with acceptable toxicity. They obtained a complete remission rate of 18% (95% confidence interval [CI]: 6-30) in HD-MTX alone versus 46% (95% CI: 31-61) in the combination arm, \( P = 0.006 \).

CHOP regimen exhibits negligible activity in PCNSL; this has been confirmed in a randomized trial with incomplete accrual. In a retrospective series, the addition of CHOP to HD-MTX resulted in higher toxicity without improving outcome compared with HD-MTX alone. Most patients treated with CHOP have an immediate radiographic response, followed by early progression, probably because of the normalization of the disrupted blood brain barrier (BBB). This suggests that the bulky tumor not protected by the BBB responds while the microscopic tumor is not adequately treated and progresses. In line with this evidence, CHOP chemotherapy has been abandoned in classic PCNSL. However, CHOP-rituximab combination may be prescribed with good CNS bioavailability agents to patients with neurolymphomatosis or intravascular large B-cell lymphoma with CNS involvement as tumor cells of these lymphomas mostly grow in structures (nerves and blood vessels, respectively) variably, or not, protected by physiologic barriers.

To conclude, the possible use of standard CHOP regimen in the patients of PCNSL can be decided on the basis of prognostic scoring and the site of the disease. However, this needs to be confirmed by well-designed randomized prospective studies. The patients with good prognostic factors should be offered the standard of care HD-MTX based chemotherapy, unless otherwise indicated.

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Blinatumomab: A ray of hope for relapsed/refractory adult B-cell acute lymphoblastic leukemia

Sir,

Acute lymphoblastic leukemia (ALL) of B-cell lineage is a relatively infrequent disease in adults that is usually treated with intensive chemotherapy. However, the prognosis for the patients, who are refractory to initial treatment, or relapse (r/r B-ALL), is very poor. A bispecific antibody blinatumomab as a single agent therapy has demonstrated anti-leukemic activity in adult patients with r/r B-ALL, including those who responded poorly to prior therapy. Blinatumomab is the result of translational research project leading to the formation of Bispecific T-cell Engager (BiTE) antibodies. A BiTE monoclonal antibody has two variable regions, one specific to CD3 for T-cell recruitment and activation and the other targeting a different leukemic or neoplastic membrane antigen. With blinatumomab, CD19+ blast cells of B-precursor ALL are linked to CD3+ T-cells and subject to perforin-mediated cytotoxicity [Figure 1].

The drug is active at very low concentration, and once cell lysis is completed, the effector-blinatumomab complex is released to start over again. Conceptually, this is immunotherapy at its best because autologous effector cells are brought into direct contact with the target and nothing else. This is a key distinction with the immune effects provided by an allogeneic stem cell transplant, where unrestricted T-cell activation can lead to the serious clinical consequences of graft-versus-host disease.

With single-agent blinatumomab, a complete and durable molecular remission was observed in approximately 70% of adult patients with minimal residual disease (MRD+) ALL, and similar activity is also being reported in relapsed ALL. [2]

The goal of the treatment of relapsed patients is to achieve complete remission (CR) and subsequently offer hematopoietic stem cell transplantation (HSCT). MRD can now be detected in over 90% of B-ALL patients with a detection limit of 0.01% compared to 5% using microscopy, allowing a more refined measurement of response. In the first-line treatment of B-ALL, achieving an MRD response in addition to hematologic CR is associated with a better outcome. The results of the largest study so far (n = 189) were presented by Nicola Gökbuget during the 19th European Hematology Association congress in Milan. [3]

The clinical study recruited 189 patients ≥18 years old who had Ph-negative r/r B-ALL, and poor prognosis. A central reference lab evaluated both the cytologic and MRD response. The primary endpoint was CR or CR with partial hematologic recovery (CRh*) within the first two cycles of treatment. In addition, MRD response within the first two cycles was an exploratory endpoint. The median age of the patients was 39 years (range: 18-79). The CR/CRh* rate within two cycles was 43% (95% confidence interval [CI]: 36–51%) in all patients and 45% in those who underwent prior HSCT. Among patients who did not receive prior HSCT the rates of CR/CRh* varied, with lower rates observed in patients receiving ≥2 prior salvage treatments.

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