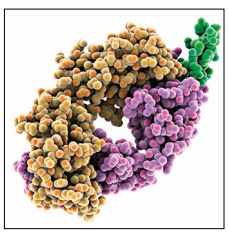
CNS border posts against rituximab?



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Rituximab, an antibody that targets CD20, is a standard treatment for non-Hodgkin B-cell lymphomas, including systemic diffuse large B-cell lymphoma. Treatment of non-Hodgkin B-cell lymphoma with rituximab leads, almost without exception, to improvements in disease response and survival.[1] Primary CNS lymphoma is a diffuse large B-cell lymphoma that is confined to the CNS compartment, without any systemic manifestation.[2] In contrast to the established R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) protocol used to treat systemic diffuse large B-cell lymphoma, treatment protocols for primary CNS lymphoma vary, although intravenous high-dose methotrexate is widely accepted as a fundamental component. There has been substantial debate as to whether intravenous rituximab sufficiently accumulates in the CNS to exert its full potential in primary CNS lymphoma.

In *The Lancet Oncology*, Jacoline Bromberg and colleagues[3] report results from the HOVON 105/ALLG NHL 24 intergroup randomised phase 3 trial in an attempt to answer this question. We praise the investigators for completing this study; projects in orphan diseases[4] require international collaboration and sustained commitment, and well-conducted randomised trials are urgently needed to improve outcomes for patients with primary CNS lymphoma.

200 patients from centres in the Netherlands, Australia, and New Zealand with newly diagnosed primary CNS lymphoma were randomly assigned to receive rituximab in addition to high-dose methotrexate-based induction chemotherapy (99 patients analysed), or the induction chemotherapy alone (100 patients analysed). After induction, all responding patients received consolidation chemotherapy with cytarabine, and those aged 60 years or younger received additional whole-brain radiotherapy; patients older than 60 years did not receive radiotherapy. Besides treatment being stratified solely by an arbitrary age cutoff, another issue is whether whole-brain radiotherapy should be chosen for consolidation in young patients treated with curative intent. Results from the second randomisation of the IELSG32 trial[5] showed that consolidation with high-dose chemotherapy and autologous stem cell transplantation is an intensive, but safe and effective, alternative to whole-brain radiotherapy, which mitigates against the risk of long-term neurotoxicity.[6,7]

The primary endpoint of the HOVON 105/ALLG NHL 24 trial[3] was event-free survival, defined as not achieving a complete response after end of treatment, lymphoma relapse, or death. In the primary analysis, after 32·9 months (IQR 23·9–51·5) of follow-up, there was no difference between the two treatment groups in event-free survival (hazard ratio [HR] 1·00, 95% CI 0·70–1·43). The HR for progression-free survival was 0·77 (95% CI 0·52–1·13) and for overall survival was 0·93 (0·59–1·44); both sets of results were not significantly in favour of rituximab. In post-hoc subgroup analyses by age, there was an unexplained but persistent subgroup effect suggesting that patients younger than 60 years might benefit from addition of rituximab in terms of progression-free survival (HR 0·48, 95% CI 0·26–0·88), event-free survival (0·56, 0·31–1·01), and overall survival (0·59, 0·28–1·24).

How should we interpret these results? This question is important for the patients enrolled in this trial but equally relevant for the broader population of patients with primary CNS lymphoma, particularly in view of the evidence from the randomised IELSG32 trial,[8] in which a benefit of rituximab was shown. First, event-free survival is a problematic endpoint, because appraising complete remission on brain MRI can be difficult in primary CNS lymphoma, particularly in the absence of central imaging review (not done in this trial). Second, Bromberg and colleagues[3] have commented that, since the IELSG32 trial[8] was a phase 2 study, it did not have the confirmatory design to show a benefit of adding rituximab to the control treatment of high-dose methotrexate plus high-dose cytarabine and they argue that findings of the IELSG32 trial[8] might have been due to chance. However, such an argument could also be made against the findings of this present trial,[3] especially the unexplained subgroup effect by age, which creates uncertainty regarding the overall results. Do we really believe that an arbitrary age cut-off at 60 years drives this difference? Or is it rather an interaction with the treatment protocol (whole-brain radiotherapy *vs* observation) of the trial? This ultimately remains unclear. To address these uncertainties and inform clinical decision making, all available evidence from randomised trials must be considered. Bromberg

and colleagues[3] identified the IELSG32 study[8] as the only other randomised trial investigating rituximab in primary CNS lymphoma. In IELSG32,[8] the HR for progression-free survival was 0·52 (95% CI 0·32–0·86) and for overall survival was 0·63 (0·42–1·02), both strongly in favour of rituximab.

Although the HOVON 105/ALLG NHL 24 trial did not meet its primary endpoint, to conclude from this single study that rituximab is not active in primary CNS lymphoma neglects the total body of clinical evidence. Considering the established benefit for rituximab in systemic diffuse large B-cell lymphoma[1] and results from both randomised trials[3,8] in primary CNS lymphoma, we believe rituximab should remain an indispensable component in the treatment of patients with primary CNS lymphoma, irrespective of age.

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Self-collected versus clinician-collected samples for HPV testing


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In *The Lancet Oncology*, Nicole Polman and colleagues[1] report the results of a randomised trial, nested in the Dutch cervical screening programme, in which clinical performance of human papillomavirus (HPV) testing was compared between self-collected and clinician-collected samples. Encouragingly, testing done on self-samples was non-inferior to that done on clinician-collected samples in terms of detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+; relative sensitivity 0·96 [95% CI 0·90–1·03]; relative specificity 1·00 [0·99–1·01]) and cervical intraepithelial neoplasia grade 3 or worse (CIN3+; relative sensitivity 0·99 [0·91–1·08]; relative specificity 1·00 [0·99–1·01]).

For the past 50 years, screening for and treatment of precancerous lesions have helped to decrease the incidence of cervical cancer.[2] However, cervical screening has some challenges.

First, cytological assessment of clinician-collected samples has been the backbone of cervical screening, originally in the form of manual assessment of conventional smears and, during the past decade, as liquid-based cytology with computer-assisted reading. The sensitivity of cytology, however, is low, and repeated testing every 3–5 years is needed for effective disease control.[3] In Europe, a woman is typically invited for cervical screening 13–15 times between the ages of 25 years and 64 years,[4] and screening can be a burden, both on women and on health-care resources. HPV testing is now an attractive alternative to cytology because HPV testing of clinician-collected samples has been proven to provide better protection against cervical cancer than does cytological assessment of these samples,[5] and primary HPV screening thus allows for a longer screening interval than does cytological screening.

Second, despite efforts in many countries to organise screening in population-based programmes, attendance rates are rarely more than 75%, and about half of cervical