did not show significant differences in early infection risk compared with those recorded in the preceding (non-rituximab-containing) regimens. Similarly, in randomized prospective comparisons of fludarabine versus F-R,6 fludarabine, cyclophosphamide, and mitoxantrone (FCM) versus FCM-rituximab,7 and fludarabine, mitoxantrone, dexamethasone (FND) versus FND-rituximab,8 no excess in early infections was recorded in the rituximab-containing arms. We and others9 have previously examined the risk of early or late infections among 160 patients receiving FC or FC-R, and have found no significant differences in infections either during chemotherapy or in the first year of remission, even among patients at high predicted risk of infectious complications. In contradistinction to the results reported by the AIDS Malignancy Consortium, we did not observe significant increases in Herpes simplex, Varicella zoster, Pneumocytis jiroveci, or fungal infections among patients receiving FC-R, despite the lack of antimicrobial prophylaxis or growth-factor support in more than 70% of our patients.

In conclusion, despite theoretical concerns about combined immunosuppression leading to increased infections in patients receiving combination fludarabine and rituximab therapy, there is little evidence at present to support this concern. One explanation for this apparent discrepancy may be related to the observation that prolonged CD4 lymphopenia following purine analog therapy is associated with lower infection risk than when similar levels are observed among patients with HIV infection.10 Fludarabine and rituximab combinations are among the most potent regimens in the treatment of patients with indolent lymphoproliferative malignancies, and current safety data support the ongoing exploration of these promising regimens.

Constantine S. Tam and John F. Seymour

Correspondence: Dr. John F. Seymour, Leukaemia/Lymphoma Service, Haematology Service, Peter MacCallum Cancer Centre, Locked Bag 1, A’Beckett Street, Melbourne, VIC 8006, Australia; e-mail: john.seymour@petermac.org.

References


To the editor:

The case for rituximab in AIDS-related lymphoma

We read with interest the recent Blood paper by Kaplan et al,1 in which they conclude that adding rituximab (R) to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy for AIDS-related lymphoma (ARL) does not improve clinical outcome due to increased infectious deaths.1 While these results suggest a risk benefit against the use of rituximab in ARL, omitting rituximab should not be taken lightly. A review of this study raises several issues. Although the median study follow-up was 137 weeks, the Kaplan-Meier plots provide no follow-up beyond 150 weeks, thereby obscuring any potential late differences between the treatment arms. Furthermore, while the authors noted that most treatment-related infectious deaths occurred in patients with CD4 counts less than 50/mm3, survival plots are only shown for CD4 counts less than or equal to and greater than 100/mm3, thereby not examining the effect of rituximab in patients at lowest risk of infectious death.

The R-CHOP-associated infectious deaths demonstrated a variable time course, suggesting different etiologies. Approximately 62% occurred during cycle 1 or 2, and were associated with chemotherapy-related neutropenia, whereas 38% occurred during or within 6 months of maintenance rituximab. It is known that rituximab with chemotherapy increases grade 4 neutropenia and infections during treatment, as well as late-onset neutropenia (LON) after treatment.2-4 Hence, we routinely increase medical surveillance during rituximab-based chemotherapy in patients with low CD4 cell counts, and inform all patients of the risk of neutropenia and fever following treatment. Maintenance rituximab, which does not improve the outcome of R-CHOP in HIV-negative patients, may also unnecessarily increase the risk of neutropenia.5 In this regard, we have shown that LON is associated with clinical outcome due to increased infectious deaths.1 While these results from Cancer and Leukemia Group B (CALGB) study 9712, a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma, suggest that rituximab increases LON in patients with HIV infection, the risk of infectious deaths was not evaluated in this study.6 Hence, we routinely increase medical surveillance during rituximab-based chemotherapy in patients with low CD4 cell counts, and inform all patients of the risk of neutropenia and fever following treatment. Maintenance rituximab, which does not improve the outcome of R-CHOP in HIV-negative patients, may also unnecessarily increase the risk of neutropenia.5

The benefit of rituximab on tumor control should not be underestimated. It is well established that rituximab is an important treatment adjunct in HIV-negative DLBCL, particularly in bcl-2 positive tumors, which are mostly of the activated B-cell (ABC) type.5,7 In the Kaplan et al study, both progression on treatment ($P_2 = 0.02$; χ-squared test) and death due to lymphoma ($P_2 = 0.02$;
χ-squared test) were significantly lower in patients receiving R-CHOP treatment. That the progression-free survival (PFS) plot does not reveal this finding is somewhat confusing, until one notes that this is actually an event-free survival (EFS) plot, as death without progression is not censored. It should also not escape attention that while most treatment-related infectious deaths occurred in patients with low CD4 cell counts, this group is probably enriched with ABC-tumor types and most likely to benefit from rituximab. The limited number of cases with bcl-2 immunohistochemistry precludes a rigorous analysis of this effect.

We are investigating etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) treatment with dose-dense rituximab (375 mg/m² on days 1 and 5) in untreated ARL. Results in 21 patients suggest a benefit of rituximab in patients with CD4 counts less than 100/mm³, demonstrating 57% survival as compared with 16% using EPOCH alone, at 19 and 53 months.

Notably, EPOCH-R results were achieved with 50% fewer cycles compared with EPOCH. Increased neutropenia and LON were observed with EPOCH-R, but these were managed without patient deaths.

Hence, we believe it unwise to omit rituximab from the treatment of ARL and hasten to add that while treatment-related infectious deaths can be ameliorated with careful medical attention, disease progression cannot.

Kieron Dunleavy and Wyndham H. Wilson

Correspondence: Wyndham H. Wilson, National Cancer Institute, Building 10, Room 4N115, 10 Center Dr, Bethesda, MD 20892-1374; e-mail: wilsone@nih.gov.

Response:

Rituximab, chemotherapy, and HIV-associated lymphoma

We appreciate the comments of Drs Dunleavy and Wilson. It is worthwhile to use this response to emphasize points made in both our article 1 and in their letters. It is important to recognize that our article does not conclude that rituximab should be omitted in the setting of HIV infection, nor does it conclude that rituximab is of no benefit in this population. It does, however, point out a potential risk to the administration of rituximab in certain HIV-seropositive individuals, specifically those with very poor immune function. A recent series of studies of HIV–non-Hodgkin lymphoma (NHL) patients reported from Italy 2 also suggests an increased risk of life-threatening infection when rituximab is combined with the cyclophosphamide, doxorubicin, and etoposide (CDE) chemotherapy regimen. Our report suggests better disease control with the addition of rituximab, although improvement in time to progression did not reach statistical significance as the study was not powered to detect such differences. The AIDS Malignancies Consortium (AMC) is committed to exploiting the beneficial effects of rituximab while minimizing its potential risks in this patient population. One way to accomplish this is through the use of antibiotic prophylaxis for enteric organisms. Recently published data suggest a clinical benefit from the use of this approach in non-immunocompromised patients with solid tumors and lymphomas. 3,4 Our current AMC trial is evaluating the use of sequential or concurrent rituximab with the same dose-escalated etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) regimen used by the National Cancer Institute (NCI). Unlike the previous AMC trial, patients in the current study receive enteric prophylaxis. We look forward to the final results of both the AMC and NCI EPOCH-rituximab trials with the hope that these will better define the most beneficial use of this agent.

Lawrence D. Kaplan

Correspondence: Lawrence D. Kaplan, University of California at San Francisco, Box 0324, San Francisco, CA 94143-0324; e-mail: lkaplan@medicine.ucsf.edu.

References

The case for rituximab in AIDS-related lymphoma

Kieron Dunleavy and Wyndham H. Wilson