less than that associated with oral melphalan and lenalidomide, which is reassuring because autologous stem-cell transplantation with intravenous melphalan conditioning is a standard therapy. The risk of second primary malignancy after tandem transplantation might possibly be greater than after a single autologous stem-cell transplant, as suggested by results of the Intergroupe Francophone du Myélome (IFM) study. The actions of lenalidomide are complex and the mechanism of how it might cause second primary malignancies is not understood. Perhaps, in the case of treatment-related myelodysplasia and acute myeloid leukaemia, it might be related to a stem-cell effect, in view of lenalidomide’s ability to impair haemopoietic stem-cell mobilisation after prolonged use.

Palumbo and colleagues’ meta-analysis does have limitations, including a failure to include several studies, either because they were ongoing and unpublished (eg, the Myeloma XI trial [ISRCTN49407852]), or because the data were unavailable. Disappointingly, this included the large study by the IFM that was one of the first to show an increased risk of second primary malignancies in patients with myeloma who received lenalidomide maintenance after autologous stem-cell transplantation. In Palumbo and colleagues’ meta-analysis, 502 patients received lenalidomide for more than 2 years and no obvious effect was noted with respect to duration (and, presumably, cumulative dose) and risk of second primary malignancies. Long-term follow-up of a greater number of patients receiving lenalidomide for longer than 2 years might be needed for reassurance regarding this point, particularly since lenalidomide is still given until disease progression. Recording of the development of second primary malignancies was not a prospectively designed endpoint of the studies included in this meta-analysis, and so some might not have been recorded. Finally, although second primary malignancies started to increase after 18 months, none of these studies can address whether a very long latency period takes place between exposure to lenalidomide and the peak in development of second primary malignancies, which would be useful to know as outcomes continue to improve for myeloma patients.

The overwhelming message from this meta-analysis is that the risk of developing second primary malignancies after treatment with lenalidomide is low, and far outweighed by the risk of death from myeloma. Nevertheless, the combination of oral melphalan and lenalidomide might be best avoided, and alternatives used. Whether second primary malignancies will become clinically relevant as survival for patients with myeloma starts to improve beyond 7–10 years is uncertain. In future studies, second primary malignancies should be carefully recorded and assessed for any possible links with lenalidomide dose and duration, particular combination regimens, and possible host biological factors.

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I have received travel grants and speaking honoraria from Celgene (makers of lenalidomide).

Subcutaneous rituximab: a practical approach?

Rituximab, a chimeric anti-CD20 monoclonal antibody, has improved the therapeutic outcomes of patients with B-cell non-Hodgkin lymphoma of various histopathological subtypes and B-cell chronic lymphocytic leukaemia; however, its conventional administration method of intravenous infusion for up to 6 h is inconvenient and burdensome on health-care resources. An alternative strategy would be rapid rituximab infusion for 60 min or 90 min. Subcutaneous administration could be

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another solution, if feasible; however, the relatively large volume of the intravenous rituximab dose has hindered its subcutaneous administration. This hurdle might be overcome by concentration of the intravenous rituximab formulation and addition of recombinant human hyaluronidase (rHuPH20) as a permeation enhancer. In addition, subcutaneous delivery of rituximab could also reduce the incidence of severe reactions related to infusion and costs related to administration.

To compare subcutaneous with intravenous forms, an international pharmacokinetic and clinical study (SABRINA) is underway as a two-stage, phase 3 randomised study for patients with untreated follicular lymphoma. Patients in the study underwent induction chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or cyclophosphamide, vincristine, and prednisone [CVP]) plus rituximab, followed by maintenance rituximab for 2 years. The study was designed to show pharmacokinetic non-inferiority of fixed-dose subcutaneous rituximab (1400 mg) versus the standard intravenous formulation in a 3 weekly dosing interval. In The Lancet Oncology, Andrew Davies and colleagues report results of stage 1 of the SABRINA study for 127 patients. The median injection time of subcutaneous rituximab was 6·1 min (IQR 6·0–7·0). The primary endpoint was novel and carefully chosen as the ratio of observed rituximab serum trough concentrations between groups (subcutaneous to intravenous) at cycle 7 (before dose 8) of induction treatment in patients in a per-protocol population. The ratio was 1·62 (90% CI 1·36–1·94), which met the primary endpoint of exceeding the non-inferiority margin of 0·8. In addition, area under the concentration time curve at cycle 7 was higher in the subcutaneous group than the intravenous group, and median rituximab serum trough concentrations were higher in the subcutaneous group during each cycle of induction treatment.

Between treatment groups, the investigators noted no significant differences in overall response and adverse events, apart from more frequent injection-site erythema in the subcutaneous cohort, which was clinically manageable. Davies and colleagues concluded that switching from intravenous to subcutaneous administration does not seem to impair the anti-lymphoma activity of rituximab, and that subcutaneous fixed-dose rituximab administration is feasible in this population. This study was very carefully designed and well conducted, and the interpretations of the results are reasonable. Although few novel findings are reported, the report will provide practically useful information for oncologists.

However, further study is needed to accurately assess the usefulness of subcutaneous rituximab in the treatment of B-cell non-Hodgkin lymphoma. In addition to data from the stage 2 of the SABRINA study, with 280 patients, final results are awaited of the two-stage SparkThera study of maintenance rituximab for untreated and relapsed follicular lymphoma and of a randomised phase 3 study (PrefMab; NCT01724021) investigating patient preference for subcutaneous or intravenous rituximab plus chemotherapy for the first-line treatment of diffuse large B-cell lymphoma or follicular lymphoma. Moreover, previous reports have suggested presence of a sex difference in rituximab pharmacokinetics, and more female than male patients were enrolled in the subcutaneous rituximab group of SABRINA. Thus, careful analysis of a larger number of patients is needed.

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