FCA: Forget Chemoimmunotherapy with Alemtuzumab?

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A randomized phase 3 trial conducted in France and Belgium shows that a chemoimmunotherapy consisting of fludarabine, cyclophosphamide, and alemtuzumab (FCA) causes an excess mortality and is less efficient compared with fludarabine, cyclophosphamide, and rituximab (FCR), the current standard therapy for physically fit patients with chronic lymphocytic leukemia (CLL).1,2

The monoclonal antibody targeting CD52, alemtuzumab, has a more potent anti-leukemic activity compared with the antibody targeting CD20, rituximab. CLL cells express more CD52 than CD20.3 Finally, the combination of fludarabine with alemtuzumab (FA) was shown to be effective and safe.4,5 Hence, it seemed a logical step to combine alemtuzumab with FC chemotherapy, the most efficient backbone of current chemoimmunotherapies for CLL.6 Therefore, the French cooperative group on CLL and Waldenstrom Macroglobulinemia (FCGCLL/MW) and Groupe Ouest Est des Leucémies et Autres Maladies (GOELAMS) conducted a joint multicenter, phase 3 trial comparing FCA with FCR. In January 2009, the Data and Safety Monitoring Board (DSMB) decided that the recruitment had to be stopped because of an excess mortality observed in the FA arm. Overall 8 patients died in the FCA arm due to infectious complications and secondary lymphoma. No toxic death was observed in the FCR arm. Moreover, FCA induced a significantly lower rate of complete responses than FCR. The importance of a careful, systematic, sequential, clinical development for new drug combinations cannot be over-stressed. The current trial would have benefitted from a carefully conducted phase 2 trial performed in pretreated patients prior to embarking on a phase 3 trial in untreated patients. As a matter of fact, recent data from a phase 2 trial suggested that FCA had more toxicity with inferior therapeutic efficacy (response rate and time to progression) compared with FCR or FA.7

The subcutaneous route of application seems to achieve therapeutic plasma levels only when using higher cumulative doses and only after more than 3 weeks of thrice-weekly administrations of alemtuzumab.10 Therefore, it is possible that the intermittent, subcutaneous dosing regimen of alemtuzumab as applied in the French trial, every 4 weeks for 3 days, produced alemtuzumab plasma concentrations that were sufficient to deplete T cells but not high enough to exert sufficient tumor killing. Unfortunately, alemtuzumab plasma levels were not determined in the trial.

The trial confirms the current treatment algorithm that recommends FCR as standard first-line therapy for CLL patients with a good performance status (see figure). As in previous publications, FCR showed a higher rate of complete responses and remissions that were minimal residual disease (MRD) negative.2,11

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Current recommendations on first line therapy of CLL. FCR indicates fludarabine, cyclophosphamide, rituximab; AlloSCT, allogeneic stem cell transplantation; CLB, chlorambucil; Al, alemtuzumab; HD, high dose; R, rituximab; O, ofatumumab; P53mut, mutation of the p53 gene; and del(17p), deletion of the short arm of chromosome 17.
REFERENCES


In light of the results of the French study, one can only agree with the recommendation of Lepretre et al that FCA should not be used for the treatment of CLL outside of clinical trials. The question of whether alemtuzumab should no longer be used in any chemoimmunotherapy is an entirely different issue. It should be emphasized that a recent randomized trial showed that the second-line use of fludarabine plus intravenous alemtuzumab, FA, led to a significant improvement of the overall survival rate without excess toxicity, in particular in CLL patients with advanced Rai stages. Therefore, it is likely that alemtuzumab will have a defined, valuable role in the management of CLL, for example, for high-risk patients or at relapse.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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**REFERENCES**


**CLINICAL TRIALS**

Comment on Inbal et al, page 5111

**Novel treatment for congenital FXIII deficiency**

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Congenital Factor XIII (FXIII) deficiency is a rare autosomal recessive inherited disease leading to severe bleeding diathesis. In this issue of Blood, Inbal and colleagues report on a safe and novel treatment of this rare disorder with recombinant FXIII (rFXIII).

**Healthy individual**

- FXIII subunit assembly in vivo

**Patient with congenital FXIII deficiency**

- FXIII subunit assembly in vivo after administration of rFXIII

FXIII B-subunit, the carrier protein, is synthesized and secreted by the liver, whereas FXIII A-subunit is synthesized and released by cells of bone marrow origin. Both subunits are assembled in plasma to tetrameric FXIII in the same way as in healthy subjects.

**Plasmatic subunit assembly**

- FXIII tetramer

In 1960, Duckert et al described the first clinical case of congenital FXIII deficiency. They investigated a young Swiss boy presenting with severe bleeding diathesis associated with slow and poor wound healing but normal routine coagulation tests. They observed an increased lability of the clot and although no proof was available, they postulated the deficiency of a plasma protein that makes the fibrin clot insoluble in urea and suggested a deficiency of fibrin stabilizing factor described by Laki and Lorand in 1948. After transfusing the patient with fresh frozen plasma, his bleeding symptoms improved. It is interesting to note that this very patient took part in a genetic study 45 years later and congenital FXIII A-subunit deficiency could be confirmed by sequencing, structural analysis, and cell expression.

What do we learn from this case report published 52 years ago? Quite a lot. First of all, congenital FXIII deficiency needs prophylactic replacement therapy to avoid fatal or severely disabling bleeding complications after...
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