incidence of GVHD and higher transplant-related mortality during follow-up. For patients with aplastic anemia and for patients with low-risk disease, such as chronic myeloid leukemia in first chronic phase, survival is significantly worse with PBSC than with BM transplants.[4] The higher T-cell count after AMD3100 collection might increase the risk of GVHD even further.

Lastly, little is known about the impact of AMD3100 on the donors at median or long-term follow-up. No information is yet available on toxicities with higher donor numbers. In a recent report, 1 donor death was reported to occur per roughly 10 000; severe adverse events, in 1 of about 1000 donors.[5] The potential risk of hematological malignancies after G-CSF mobilization still remains a matter of debate. Experience with AMD3100 is far too limited to exclude potential toxicity. The supplier of AMD3100 and the transplant community will both face challenges in collecting appropriate long-term data.

Despite these reservations, there is proof of principle now that stem-cell collection in sufficient numbers can become feasible within 1 day. A great relief for donors and harvest centers is in sight.

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CLINICAL OBSERVATIONS

Comment on Tam et al, page 975

Further progress in CLL therapy

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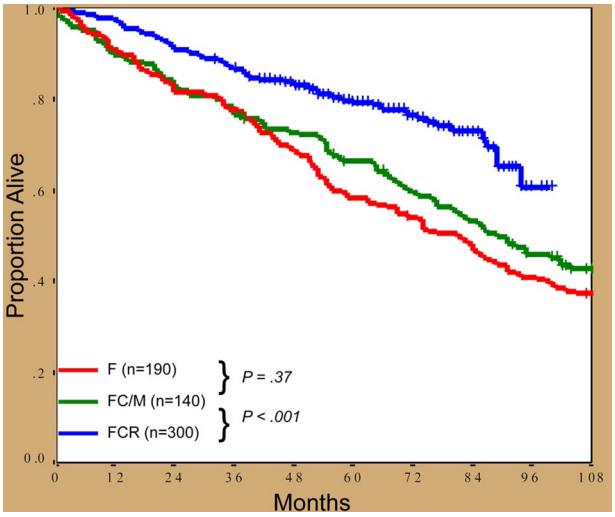
In this issue of *Blood*, Tam and coworkers, led by M. Keating, report mature results with FCR in previously untreated patients with CLL. The overall response rate was 95%, with an impressive CR rate of 72%. Six-year overall and failure-free survivals were 77% and 51%, respectively, and median time to progression was 80 months. Patients who achieved response had a much better outlook than those who did not respond.



CLL: Patient survival according to treatment modality.

What are the central messages from this study? In short, fludarabine, cyclophosphamide, and rituximab (FCR) combination therapy produces the largest proportion of complete responses (CRs) ever reported in CLL and, even more importantly, patients treated with this regimen have better outcomes, based on historical comparisons, than similar patients treated with fludarabine or fludarabine and cyclophosphamide or mitoxantrone (see figure). In addition, the relationship between the quality of the response and clinical outcome is confirmed. Furthermore, patients achieving CR with no detectable minimal residual disease (MRD)—albeit not studied by the technique currently considered preferable[1]—do much better than the rest, thus confirming that, whenever possible, obtaining MRD-negative status is a desirable treatment endpoint in CLL.[2] Notably, FCR abrogates the poor prognostic significance of classic variables, which indicates that it actually changes the natural history of CLL, the best that can be said for any new therapy for neoplastic disorders. On the downside, there are manageable toxicities, the poor response of patients with chromosome 17 abnormalities, the risk of secondary myelodysplasia, and the fact that all patients are eventually projected to relapse.

Based on this report, should FCR be considered *the* new gold standard for CLL therapy? It could be reasonably argued that the remarkable results of this study are not derived from a randomized phase 3 trial and that, consequently, the relative superiority of the FCR regimen needs validation in other series and, above all, in randomized studies. If this is the concern, we need only await the shortly due and eagerly expected results of the German CLL Group clinical trial comparing FCR to FC, recently closed because the main end-point of the study has been reached.

As happens with all good studies, the work of Tam et al not only offers important answers, but also raises important questions and inspires future research. Among these: Is FCR necessary for all patients? Should FCR be given as up-front therapy or could it be part of a more conservative, sequential therapy? Can FCR toxicity be reduced? What is a patient's fate once progression occurs? Is retreatment safe? Given that all patients eventually relapse, should some kind of maintenance therapy be considered? How should lessons from this study be applied to the predominantly elderly or physically unfit population of patients with CLL?

All in all, however, it is easy to predict that FCR will become *an* important new gold standard for CLL therapy. Treatment of patients with CLL is rapidly evolving, and we can surely expect dramatic improvements in the management of this common form of leukemia

founded on its biologic and clinical diversity, most likely not with a single, unique gold-standard therapy, but different and individualized treatment approaches.

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

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CLINICAL OBSERVATIONS

Comment on Godeau et al, page 999

"Spare-spleen-uximab" for chronic ITP

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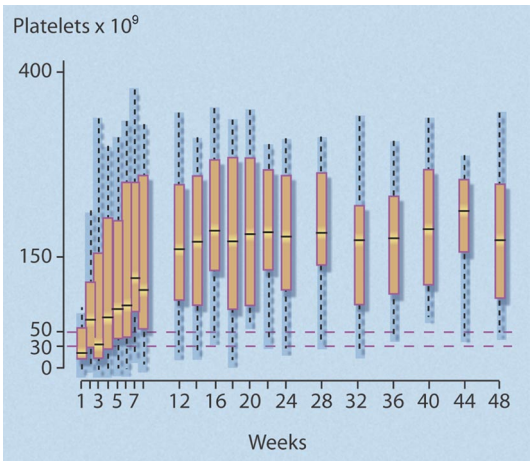
The potential for a splenectomy-sparing medical therapy to manage patients with severe chronic idiopathic (immune) thrombocytopenic purpura (ITP) prompted Godeau and colleagues to evaluate rituximab for this indication. Their prospective observational study provides evidence that rituximab may indeed be splenectomy-sparing for some patients.

Rituximab is a chimeric CD20-reactive monoclonal antibody with established efficacy in B-cell lymphomas and rheumatoid arthritis, and with increasing application in a variety of autoimmune disorders, including ITP. In a previous systematic review[1] that included 313 rituximab-treated chronic ITP patients—of whom half had not (yet) undergone splenectomy—platelet count response was achieved in 62.5%.

The French investigators have now evaluated this treatment option for adult patients with severe chronic ITP for whom splenectomy was being considered, by performing a multicenter prospective observational study of rituximab administered at 375 mg/m^2 weekly for 4 consecutive weeks. All of the patients had chronic ITP (> 6 months duration), with severe thrombocytopenia (platelet count < 30×10^9/L). Moreover, all treatments active against ITP had to have been stopped for at least 2 weeks before the first rituximab infusion, except for corticosteroids, which (if being given) had to be stopped within 21 days following the first rituximab infusion. The study enrolled 60 patients from 8 centers in France. All patients had previously received corticosteroids and/or intravenous gammaglobulin, with more than 80% showing transient response to these first-line therapies, and 21 patients (with a median platelet count of 15×10^9/L) were taking corticosteroids because of bleeding at the time of the first rituximab infusion.



Successive platelet counts for the 24 (40%) of 60 nonsplenectomized patients with chronic ITP who achieved a good response to rituximab that persisted to 48 weeks. Good response was defined as a platelet count greater than or equal to 50×10^9/L, with at least a doubling of the baseline platelet count, and no requirement for any agent to treat ITP. Median time to response was 4 weeks. Central bar indicates median; top and bottom box limits, 1st and 3rd quartile, respectively; and whisker limits, extreme data points. Professional illustration by Debra T. Dartez.

Response to rituximab treatment was defined as a platelet count increase to 50×10^9/L or higher, and with at least a doubling from pretreatment baseline. The primary end point was response that persisted at 1-year follow-up, without institution of any other therapy (including corticosteroids, or a repeat course of rituximab). Secondary end points were response at 2 years and the number of patients requiring splenectomy. The authors used an open-label, single-arm study design, and considered the effect of rituximab significant if it surpassed a preset minimum target of 25% response rate at 1 year (Fleming's single-stage design[2]).

The investigators found that 24 (40%) of 60 (95% confidence interval [CI], 28%-52%) study patients met the predefined criteria for response at 1year, which was significantly better than the 25% comparison rate ($P = .007$). Median time to response was rapid (4 weeks; interquartile range [IQR], 3-7 weeks), and most (18 of 24) responders maintained normal platelet counts ($> 150 \times 10^9$/L) after 1 year (see figure). Of the 36 (60%) patients who failed to respond, 25 eventually underwent splenectomy, the efficacy of which did not seem to be altered by prior rituximab treatment, as 15 (60%) of 25 responded.

Of the 24 responders, 20 maintained their response after 2 years, representing 33.3% of the initial cohort. In a regression analysis, younger age was associated with response to rituximab (odds ratio [OR]: 1.82 [1.26-2.63] per 10 years; $P = .001$). The data also suggested the magnitude of the initial response to rituximab predicted for response at 1 year, as follows: among 21 patients whose platelet count rose up to or above 150×10^9/L within the first 2 weeks following rituximab infusions, 18 (86%) had good responses at 1 year, while only 6 (40%) of the 15 patients with platelet counts between 50 and 150×10^9/L, and none of the 24 patients whose platelet counts did not rapidly reach 50×10^9/L, achieved a good response at 1 year.

In terms of safety, side effects occurred in 22 (36.7%) of 60 patients. Most were mild infusional reactions, although sigmoiditis and serum sickness were observed. Eight additional severe events that were judged unrelated to rituximab therapy occurred during the 2-year study, including atrial fibrillation, myocardial infarction, Guillain-Barré syndrome, and colon and pancreatic cancer.

Based on these results, it appears that the use of rituximab early in the course of chronic ITP may spare or delay splenectomy in some patients. This conclusion is congruent with other lines of evidence suggesting that rituximab may be most effective for patients with a short disease duration,[3] possibly as a result of the reversion of T-cell abnormalities following depletion of the CD20$^+$ B-cell pool.[4]

The observations by Godeau and coworkers will fuel the debate about timing of rituximab in chronic ITP,[5] but randomized controlled trials (RCTs) are needed to establish a