To the Editor:

In a recent Blood report, authors Reiner, Gernsheimer, and Slichter have concluded that pulse intravenous cyclophosphamide therapy should be strongly considered in idiopathic thrombocytopenic purpura (ITP) patients deemed "refractory to standard therapy." In view of deficiencies in several aspects of this study, namely, patient selection, treatment goals, and data interpretation, we believe that criteria for treating ITP patients with cyclophosphamide have not been defined by the investigators.

Patient selection. The reported patients were treated by community physicians who sought consultation when their patients appeared to have refractory disease. On the basis of the investigators' success with an initial patient, who responded to a single dose of cyclophosphamide, the physicians were "routinely advised" to treat their refractory patients with monthly high-dose intravenous cyclophosphamide. Refractoriness was judged by inability to increase platelets to a "safe level" or manage the patient with "acceptable doses" of corticosteroids or other agents. Definitions of these guidelines were not given, nor was it mentioned whether definitions were the same for all patients or depended on impressions of individual physicians who may not have been experienced in caring for ITP patients.

Half of the patients were deemed refractory unusually soon after the onset of ITP—4 within 1 month, 2 in 2 months, 2 in 4 months, 3 in 6 months, and 2 in 8 months. These periods of observation are too short to distinguish acute from chronic ITP with their known differences in prognosis and response to therapy. Also, platelet counts and responses to therapies tend to be most variable, and spontaneous remissions more frequent, early after onset of ITP. Perhaps this is why short duration of disease correlates with better results of all forms of therapy, including cyclophosphamide.

Various treatments increased the patients' platelet counts from a mean value of $7 \times 10^9/L$ at presentation to a mean of $68 \times 10^9/L$ (spread of 1 to $534 \times 10^9/L$) before cyclophosphamide was initiated, suggesting that the precyclophosphamide counts of most patients were consistent with adequate hemostasis. This is corroborated by symptoms listed in Table 1 showing that 12 of the 20 patients had no skin hemorrhage, which is a sensitive indicator of symptomatic thrombocytopenia. Figure 1 and Table 2 are inaccurate because they mistakenly contain the lowest platelet count recorded, not the count just before cyclophosphamide therapy, and give the false impression that all prior therapies were completely ineffective.

Treatment goals. Definitions of treatment responses were based solely on platelet counts: $<50 \times 10^9/L$ was considered "no response"; $>150 \times 10^9/L$ was a "complete response"; and in-between levels, "partial response." Physicians who routinely treat ITP patients are well aware that symptomatic improvement is as important a criterion as the platelet count in assessing response to therapy. Many ITP patients have no spontaneous hemorrhage at $10 \times 10^9$ (or even fewer) platelets/L, and must have essentially normal hemostasis above $50 \times 10^9/L$. Such symptomatic improvement would be classified as "no response" by the investigators. If the goal of treatment is maintaining an arbitrary platelet level rather than preventing symptoms, refractoriness to therapy will be overdiagnosed and patients will receive excessive intervention. Treatment may have been overzealous in a number of patients in this series, particularly those splenectomized and given cyclophosphamide in the first 2 months of illness and possibly in the 13 of 20 patients who had had ITP less than 1 year.

Data interpretation. Results in the current report are interpreted as indicating that cyclophosphamide was the most important component of the combination chemotherapy used in a previous report to treat refractory immune thrombocytopenic purpura. This conclusion assumes that cases in the two studies are comparable. They are not. In all patients studied in ref 2, except one with lymphoma, refractoriness had persisted for over a year and hemorrhagic symptoms were more serious than those of patients in the current report. Treatment in the previous study involved a number of cycles of intensive combination chemotherapy, but no further therapy was required after complete remissions were induced. By contrast, six of the seven present patients appeared to have "complete responses" to a single dose or two of cyclophosphamide, but all patients received corticosteroids and sometimes other treatments during and after cyclophosphamide therapy. Under these circumstances it is difficult to evaluate the role of cyclophosphamide. Results of treating thrombocytopenic systemic lupus erythematosus (SLE) patients with pulse cyclophosphamide were invoked to support the contention that this therapy is beneficial in ITP. However, patients in the SLE study were treated primarily for renal disease and platelet levels increased as the underlying disease improved, which is characteristic of SLE regardless of therapy. Furthermore, the lupus patients did not have serious or refractory thrombocytopenia in that precyclophosphamide counts ranged from 42 to $132 \times 10^9/L$.

The conclusion that "there is a relatively low incidence of side effects" from cyclophosphamide therapy is not supported by the several serious complications cited in this study. The known potential immediate and delayed toxicities of cyclophosphamide should preclude its use in all but the most severe cases of ITP. One possible complication, not often referred to, is suppression of thrombopoiesis, which, even if mild, could place an ITP patient at great risk.

There may be a place for pulse cyclophosphamide in treatment of refractory ITP, but this report does not clarify the issue.

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The following are our responses to the comments made by Drs Reid and Shulman regarding our manuscript on the use of pulse cyclophosphamide to treat autoimmune thrombocytopenic purpura.

Patient selection. The refractory AITP patients reported in our study were treated by local hematologists/oncologists who are very experienced in the management of both routine and refractory AITP. In our medical community we are generally consulted only about the treatment of AITP patients who are particularly difficult or refractory to therapy. Therefore, 19 of the 20 patients included in this study had failed both corticosteroids and splenectomy, and many had failed several second- and third-line AITP agents as well.

It is true that about half of our patients (11 of 20) received pulse cyclophosphamide therapy within 6 months of diagnosis of AITP, and thus may not strictly fit the definition of "chronic" AITP. However, these patients had severe AITP characterized by platelet counts of less than 10 x 10^9/L despite treatment with multiple agents. Ten of the 11 patients had significant bleeding manifestations. Furthermore, 5 of these 11 patients with AITP of relatively short duration were older than 60 years and were at greater risk for more severe bleeding episodes. Thus, despite the relatively short disease duration in some study patients, we believe that treatment with pulse cyclophosphamide was warranted because of the relative disease severity, as well as their lack of response to several different agents.

As mentioned in the Results section, the reason that the mean platelet count of our study patients was elevated at the time of initiation of pulse cyclophosphamide therapy compared with baseline (68 x 10^9/L vs 7 x 10^9/L, respectively) was due to the fact that 6 of the 20 patients had received either high-dose corticosteroids or IV IgG immediately before pulse cyclophosphamide treatment. These responses to corticosteroids or IV IgG were either documented or assumed to be transient, because in each case these agents had previously failed to produce a lasting response. The baseline nadir platelet count, platelet count at the time of initiation of cyclophosphamide, and the specific therapy that resulted in the transient elevation from baseline for each of these six patients are listed in Table 1. For the remaining study patients, the platelet count at baseline and at the time of initiation of pulse cyclophosphamide were essentially the same (ie, >10 to 15 x 10^9/L).

Treatment goals. In response to the comment that our patients were treated overzealously, again, our patients had clinically severe AITP, regardless of duration, that was characterized by baseline platelet counts of less than 10 x 10^9/L and the majority had skin and/or active mucosal bleeding. We agree that the goal of treatment in AITP is to maintain a platelet count of ~30 x 10^9/L or at least a count high enough to prevent bleeding. However, before cyclophosphamide, none of our patients was able to achieve or to be maintained at a platelet count of 30 x 10^9/L without continuing treatment with IV IgG or unacceptable long-term doses of corticosteroids (>5 mg prednisone per day).

Data interpretation. To clarify again the evaluation of response to pulse cyclophosphamide therapy, although all patients were receiving some form of therapy (usually corticosteroids and/or IV IgG) at the time of initiation of pulse cyclophosphamide, patients who achieved either a complete or partial response to cyclophosphamide were able to maintain an adequate platelet count off all therapy. It may not be clear from the last column in Table 1 of our report that the agents listed under the heading "Current Therapy" represent agents that were being administered at the time of initiation of pulse cyclophosphamide (ie, "concurrent" therapy) rather than at the time of last follow-up when responses to therapy were evaluated.

As far as the general role of pulse cyclophosphamide therapy in the treatment of refractory AITP, we clearly discuss the acute side effects of cyclophosphamide in our study (the frequency of which is comparable with many other agents used in the treatment of refractory AITP), as well as the potential long-term side effects of secondary malignancies and infertility. Thus, as we have stated, the use of pulse cyclophosphamide requires careful consideration of the relative risks and benefits for each patient. For the patient with clearly refractory and/or severe thrombocytopenia, treatment options are limited, and pulse cyclophosphamide should be considered. As with all retrospective studies, the precise role of pulse cyclophosphamide, as well as the optimum dosage and treatment schedule of this agent in the management of patients with refractory AITP, can only be clarified by prospective studies.

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REFERENCES


Table 1. Patients With Discrepant Values for Baseline Platelet Count and Platelet Count Immediately Pre-cyclophosphamide Therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Baseline Platelet Count (10^9/L)</th>
<th>Immediate Pre-cyclophosphamide Platelet Count (10^9/L)</th>
<th>Immediate Pre-cyclophosphamide Therapy</th>
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<tbody>
<tr>
<td>8</td>
<td>5</td>
<td>534</td>
<td>Dexamethasone 16 mg OD</td>
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<tr>
<td>9</td>
<td>6</td>
<td>299</td>
<td>Prednisone 30 mg OD</td>
</tr>
<tr>
<td>11</td>
<td>9</td>
<td>68</td>
<td>Prednisone 100 mg OD</td>
</tr>
<tr>
<td>18b</td>
<td>9</td>
<td>160</td>
<td>Danazol 200 mg BD</td>
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<tr>
<td>17a</td>
<td>10</td>
<td>43</td>
<td>IVIG 40 g x 2 d</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>204</td>
<td>Prednisone 100 mg OD</td>
</tr>
</tbody>
</table>

Abbreviations: OD, once per day; BID, twice per day.

Patient numbers and baseline counts are taken from Table 1.