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No potential conflict of interest relevant to this letter was reported.


THE AUTHORS REPLY: The use of extracorporeal means of removing toxic immunoglobulin free light chains responsible for cast nephropathy in patients with myeloma is controversial. The largest of the three randomized trials to test plasma exchange did not show a statistically significant difference in the composite outcomes defined by the study.1 Unfortunately, this study had many limitations, including a lack of a clear clinical or histologic definition of myeloma cast nephropathy, the type of renal injury amenable to extracorporeal removal of free light chains.2 Two other smaller, randomized trials of plasma exchange suggested meaningful clinical benefit.3,4 All three trials were done before the introduction of new agents in myeloma. In this context, given the recognized adverse impact of renal failure on survival, its potential reversibility, and the safety of the treatment procedure, we recommend additional trials.

The issue of whether an extended duration of dialysis with high-cutoff dialyzers is more effective than plasma exchange at removing free light chains or reversing renal failure is not settled. No comparative trials have been conducted to date. So far, high-cutoff dialyzers have been tested only in in vitro studies and in small uncontrolled clinical trials. Their purported effectiveness in reversing renal failure is primarily in patients treated with concurrent chemotherapy and having a response to such treatment. Further, other researchers report similar rates of reduction in levels of free light chains between plasma exchange and high-cutoff dialyzers when a standard duration of dialysis is used.5 Thus, the data are insufficient to suggest that one method is superior to the other.

In terms of the type of chemotherapy, we currently use bortezomib and dexamethasone in combination with either cyclophosphamide or thalidomide in these patients. In our letter, it was not our intention to separate the contribution of plasmapheresis from bortezomib-based therapy. We wholeheartedly agree that a formal clinical trial is needed. As Hutchison and colleagues mention, recent evidence suggests that the speed at which a reduction in levels of free light chains occurs may be as important as the amount of reduction. We hope that the high rate of renal response that we reported will inspire further studies of plasma exchange and other methods of extracorporeal removal of free light chains as adjuvant strategies in modern myeloma therapy.

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The trial was not designed to measure vaccine efficacy. However, to monitor safety, passive surveillance of all episodes of illness, including clinical malaria, was maintained during the ensuing malaria-transmission season in a blinded fashion. Since numerous episodes of malaria were recorded, we considered examining the possibility of a protective effect induced by the MSP3 vaccine. A plan to compare the incidence of clinical malaria among the three groups was agreed on before the analysis began. Given the agreement of this manuscript.

The incidence rates of clinical malaria were substantially lower in each of the two groups that received the MSP3 vaccine (1.2 and 1.9 cases per 100 days, respectively), than in the group that received the hepatitis B vaccine (5.3 cases per 100 days) (P = 0.01) (Fig. 1). Thus, despite the small sample size and the high cumulative incidence in all groups, there was some indication that MSP3 vaccine protected against clinical malaria, at least in the short term. A sensitivity analysis with the use of a threshold density of 10,000 parasites per microliter showed broadly similar results (P = 0.03). The similar incidence rates in the two MSP3 vaccine groups are consistent with their similar immune responses. These results are in keeping with the reduction in episodes of malaria associated with naturally occurring MSP3 antibodies.

Figure 1. Kaplan–Meier Plot of the Time to the First Episode of Clinical Malaria.

There were 660, 519, and 244 days at risk (until the first episode of malaria or the end of the risk period) for the 15 patients who received MSP3 at a dose of 15 μg, the 15 patients who received MSP3 at a dose of 30 μg, and the 15 patients who received hepatitis B vaccine, respectively, yielding an incidence rate of 1.2, 1.9, and 5.3 cases per 100 days, respectively. A total of 8, 10, and 13 children in these groups had an episode of clinical malaria. A log-rank test indicated evidence of a difference in the incidence rate among the three groups (P = 0.01). When a threshold density of 10,000 parasites per microliter was used, similar results were obtained with periods at risk of 715, 563, and 296 days, respectively, and incidence rates of 1.0, 1.6, and 4.1 cases per 100 days (P = 0.03). The period of analysis shown here starts after full immunization (i.e., 4 weeks after the third immunization, when antibody titers peak), and increases to the end of transmission.
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