Response: Re: High-Dose Chemotherapy with Autotransplantation in AL Amyloidosis: A Flawed Meta-analysis

The primary claim put forward by Dr. Mehta et al. is that there is “reliable” evidence that autologous stem cell transplantation is superior to conventional chemotherapy. Any reasonable observer would conclude with the main findings of our systematic review that there is a paucity of reliable data on the efficacy of autologous stem cell transplantation in AL amyloidosis, and this is precisely the conclusion of our manuscript [1].

Dr. Mehta’s main critique relate to omission of an article by Dispenzieri et al. [2] from the systematic review, and inclusion of this article would have somehow changed the findings. Unfortunately, Mehta and colleagues did not read the inclusion criteria of the systematic review attentively. The study by Dispenzieri et al. [2] is a retrospective study as stated in the first sentence of the Methods section. The inclusion criteria of this systematic review [1] clearly mentions inclusion of prospective studies only. Nevertheless, for the sake of academic discussion, even if we included retrospective case-controlled studies, we would not know which of the studies published by Dispenzieri et al. are to be included. In 2001, Dispenzieri et al. [3] published a study concluding that there is no difference in outcomes between conventional chemotherapy and autologous stem-cell transplantation. Using essentially the same population of amyloid patients but different selection criteria for controls, in 2004, the authors reported that autologous stem cell transplant might be superior [2]. Additionally, in both the articles Dispenzieri et al. [2,3] called for randomized-controlled trials to definitively address the role of transplant in AL amyloidosis as the correct methodologic approach to settle differences highlighted in variety of nonrandomized controlled trials. Consequently, we are puzzled by this apparent reversal of this stand, as expressed in the letter by Dr. Mehta and colleagues.

Mehta et al. further state that, centers in France [4] have limited experience in treating primary AL amyloidosis, and in his opinion that is the main reason for high treatment-related mortality [4] while claiming the superiority of the specialized centers in treating primary systemic AL amyloidosis. The proclaimed superiority of the specialized centers can be equally explained by selection bias, as these centers may treat selective group of patients (ie, good-risk patients) as originally pointed out by Dispenizeri et al. [3]. Therefore, if indeed, the specialized centers have better outcomes with autologous transplantation in comparison with other centers, the onus of proving such claim rests with physicians practicing in such centers (eg, by undertaking an RCT to test this hypothesis).

In another incidence of misstatement of facts, Dr. Mehta and colleagues refer to a meta-analysis published in the Journal of the National Cancer Institute as “erroneous” without referring to the author’s reply, which highlights the lack of basic understanding of the meta-analytic techniques [5]. Of note, the editorial board of Journal of the National Cancer Institute extensively reviewed the manuscript and reached a decision that the meta-analysis was properly performed, and thus we strongly believe represents important addition to the existing knowledge on treatment of patients with multiple myeloma [5,6].

In summary, critique of our article by Dr. Mehta et al. [1] is compromised by poor understanding of the hierarchy of evidence and how reliable data are generated in clinical research. The key message our systematic review highlights is the absence of good methodological quality data on the efficacy of autologous transplantation in AL amyloidosis, and the urgent need for adequately powered and good methodological quality RCTs to conclusively address the issue related to the efficacy of autologous transplantation for AL amyloidosis. We cannot understand how any researcher with even a minimum understanding of the principles of evidence-based medicine would conclude otherwise. We understand that Mehta and colleagues do not agree with the results of our meta-analyses [1,6]. However, we hope that in the future critiques will be based on true scientific merit rather than distorted attacks using unreasonable language.

REFERENCES

Critical Situation of Bone Marrow Transplantation: Information Distribution Regarding the Problem of a Shortage of Bone Marrow Filters

Many drugs and devices are essential to conduct hematopoietic stem cell transplantation (HSCT). The hematopoietic transplant community has been influenced by numerous drug and device shortages over the past several years in both Japan and other countries. This problem has included critical drugs for hematopoietic transplantsations such as gancyclovir, dexamethasone, lenograstim, imipenam, and cephepine. Recently, the discontinuation in the supply of the anticancer drug thio-tepa was announced by a pharmaceutical company in Japan; however, this process and decision were not sufficiently disclosed by the Ministry of Health, Labor, and Welfare (MHLW). As a result, the hematopoietic transplant communities are thus considered to urgently require the establishment of effective management in the event of such future crises. Although information disclosure is a key to crisis management, how to disclose bad news to patients remains a difficult issue [1-3] because proactive information disclosure may unnecessarily stir up the anxiety of the patients. The number of studies focusing on this topic in the medical field is limited [4].

In December 2008, a termination of the supply of the Bone Marrow Collection Kit (BMCK) made by Baxter Limited (Tokyo, Japan) was identified in Japan. This kit is used for filtering bone marrow(BM) aspirate during BM transplantations (BMT) [5], and it is essential for the prevention of thrombosis associated with the infusion of BM aspirate. As an alternative, the Bone Marrow Correction System made by the venture company BioAccess Inc. (Baltimore, MD) is available, but this product had not been approved in Japan, although it has been approved by the U.S. Food and Drug Administration (FDA). In Japan, peripheral blood stem cell transplantations (PBSCs) from unrelated donors are not approved, thus resulting in a reliance on BM only, so there was a possibility that the disruption in the supply of the BM filters would result in a complete suspension of HSCT from unrelated donors. Considering the stock quantity within Japan (approximately 500 units) held by Baxter at the end of December, it was predicted that BMT would not be available until mid-March 2009.

This problem was eventually resolved by the prompt approval of the kit from BioAccess by MHLW on February 26, 2009. However, during this period, the problem of the disruption in the supply of the BM filters was widely reported throughout the media in Japan, thereby generating great public interest. This case shows the unfavorable impact on medical practice if the government does not proactively disclose information to society. The responses of MHLW were slow, and no information was disclosed

Figure 1. Bone marrow transplantation from unrelated donors on a year-to-year basis. The number of bone marrow transplantations from unrelated donors per month from November 2008 and May 2009 is represented on a year-to-year basis (percent increase in 2009 by same month in 2008). There were 78 cases in February 2009, which was 78% compared with the same month in the previous year. The number of bone marrow transplantations from unrelated donors was obtained from the JMDP Website.