

# Letters

## RESEARCH LETTER

### Global Use of Peripheral Blood vs Bone Marrow as Source of Stem Cells for Allogeneic Transplantation in Patients With Bone Marrow Failure

Hematopoietic stem cell transplantation (HSCT) is a therapeutic option for many patients with bone marrow failure.<sup>1</sup> Bone marrow was initially the only stem cell source available until the 1990s when peripheral blood stem cells (PBSCs) and cord blood began to be used.

Currently, PBSCs are the major stem cell source,<sup>2</sup> owing to faster engraftment and ease of collection despite a higher rate of graft-vs-host disease and lower survival rates in patients with nonmalignant disorders.<sup>3</sup>

Therefore, bone marrow is currently recommended for HSCT in patients with bone marrow failure.<sup>4</sup> The objectives of this study were to investigate the use of PBSCs and bone marrow as stem cell sources for HSCT in patients with bone marrow failure worldwide and to identify potential factors associated with the use of each stem cell source.

**Methods** | Data from retrospective HSCT surveys by the Worldwide Network for Blood and Marrow Transplantation were used.<sup>5</sup> International and regional organizations collect the numbers of transplants annually by disease, donor type, and stem cell source from countries known to perform HSCT in World Health Organization (WHO) member states.<sup>5</sup>

Most data are from transplant registries; for countries without registries, transplant centers were contacted directly. We estimate that the data cover more than 90% of all transplants performed. No individual patient data were used and no ethics committee approval was mandated as per Swiss legal requirements.

We divided countries into 4 WHO regions and focused on allogeneic HSCTs for bone marrow failure performed in 2009 and 2010. Categorical variables (World Bank income categories, WHO regions, and stem cell sources) were compared using the  $\chi^2$  test.

The association between gross national income (GNI) per capita in \$US and stem cell sources was analyzed using linear regression. Goodness of fit was measured using the coefficient of determination ( $R^2$ ). All  $P$  values were 2-sided and those less than .05 were considered significant. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc).

**Results** | Among 194 WHO member states, 84 perform HSCT and 74 reported at least 1 HSCT during 2009 through 2010. Among 114 217 HSCTs reported by 1482 transplant teams, 3282 allogeneic HSCTs were performed for bone marrow failure (Table). Donor type and stem cell source differed between regions.

Table. Source of Stem Cells for Allogeneic Hematopoietic Stem Cell Transplantations for Bone Marrow Failure According to World Health Organization (WHO) Regions

	Americas (n = 843)		Asia-Pacific (n = 936) <sup>a,b</sup>		EM and Africa (n = 266)		Europe (n = 1057) <sup>c</sup>		
	Bone Marrow	Peripheral Blood Stem Cells	Bone Marrow	Peripheral Blood Stem Cells	Bone Marrow	Peripheral Blood Stem Cells	Bone Marrow	Peripheral Blood Stem Cells	
Family donor <sup>d</sup>	1154 (56.8)	878 (43.2)	445 (75.3)	146 (24.7)	221 (37.1)	375 (62.9)	123 (46.9)	139 (53.1)	218 (37.4)
Unrelated donor <sup>e</sup>	612 (57.2)	458 (42.8)	186 (73.8)	66 (26.2)	159 (46.8)	181 (53.2)	0	4 (100)	207 (43.7)

Abbreviation: EM, Eastern Mediterranean region.

<sup>a</sup> The percentages were calculated using the 2-column total (for bone marrow and peripheral blood stem cells) in each row as the denominator (eg, in row 1, there was a total of 2032 family donor HSCTs; 1154/2032 = 56.8% for bone marrow and 878/2032 = 43.2% for peripheral blood stem cells). Among the 194 WHO member states, 84 countries are known to be active for HSCT, of which 74 reported at least 1 HSCT between 2009 and 2010. In total, 3282 HSCTs for bone marrow failure were reported during this period. No information was available on the number of unreported patients or the number of patients with diseases requiring HSCT but who did not receive a transplant.

<sup>b</sup> Cord blood transplantations (n = 180) were excluded.

<sup>c</sup> Israel was included in Europe.

<sup>d</sup> Defined as being blood related to the recipient (eg, siblings, parents, cousins, etc). Includes twins, matched sibling donors, and mismatched family donors.

<sup>e</sup> Defined as being unrelated to the recipient.

Use of unrelated donors was highest in Europe (515/1107; 47%); use of matched sibling donors was highest in the Eastern Mediterranean region and Africa (249/274; 91%). Of the 3282 allogeneic HSCTs, the stem cell sources were bone marrow (1766; 54%), PBSC (1336; 41%), and cord blood (180; 5%).

Excluding cord blood, bone marrow was used in 1766 (57%) of the remaining 3102 HSCTs, with no difference between family and unrelated donors. Bone marrow was used most commonly in the Americas (631/843; 75%) and in Europe (632/1057; 60%), but not in the Eastern Mediterranean region and Africa (123/266; 46%) and in the Asia Pacific region (380/936; 41%; excluding Japan, 19%) ( $\chi^2 P < .001$  comparing the 4 regions).

The use of bone marrow increased from 20% in countries with low and low-middle incomes to 50% with high-middle incomes to 64% with high incomes ( $P < .001$ ). The GNI per capita and stem cell source had a weak but significant association ( $R^2 = 0.2, P = .002$ ; **Figure**).

**Discussion** | This study showed that the stem cell source used for HSCT for bone marrow failure varied worldwide, with PBSCs being used more frequently in regions with limited resources. Most likely PBSCs are still used, despite disadvantages in patients with bone marrow failure, because centers obtain PBSCs routinely for other indications and cell separators are available at any transplant center. These cells are associated with rapid engraftment, a cost-reducing benefit.

By contrast, bone marrow harvest requires trained physicians, specific equipment, and hospitalization of the donor. The correlations with GNI per capita support the hypothesis that short-term financial considerations are important.

This study has limitations. Participation was voluntary. Some countries had no formal data quality control. There were a limited number of HSCT cases in low-income countries, leading to weak correlations between stem cell source and GNI per capita.

National and international transplant organizations and authorities should foster regional-accredited bone marrow harvest centers for patients with nonmalignant disorders and provide resources to establish such infrastructures. Unrelated donor registries should provide information on the necessity of bone marrow donation for patients with bone marrow failure.

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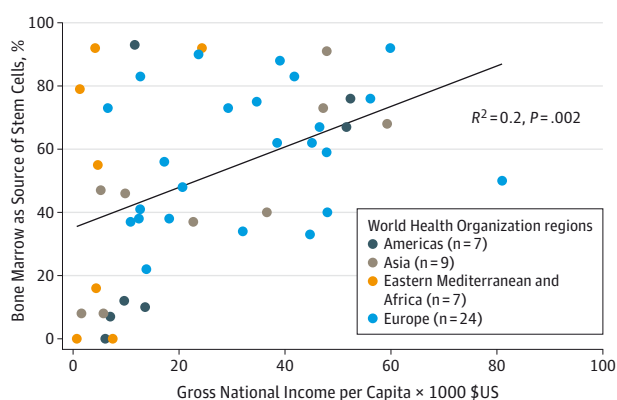
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**Figure. Correlation Between Stem Cell Source and National Income**



There were 49 countries with more than 5 hematopoietic stem cell transplantations for bone marrow failure between 2009 and 2010 according to World Health Organization regions. Each data marker represents the proportion of bone marrow as stem cell source and gross national income per capita in each country. Association of these variables was estimated by linear regression analysis using the least-squares method. Taiwan and Argentina were excluded from the analysis because of the lack of data about gross national income per capita.

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**Author Contributions:** Dr Yoshimi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Gratwohl and Kodera contributed equally.

**Study concept and design:** Yoshimi, Horowitz, Niederwieser, Gratwohl, Kodera.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Yoshimi, Baldomero, Gratwohl.

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## COMMENT & RESPONSE

### Tinzaparin vs Warfarin for Acute Venous Thromboembolism

**To the Editor** Primary results from the Comparison of Acute Treatments in Cancer Hemostasis (CATCH) trial<sup>1</sup> were reported as negative, but the authors found an association between tinzaparin use compared with warfarin and reduction in the secondary outcome of clinically relevant nonmajor bleeding. Analysis of serious adverse events and mortality from this trial leads us to question the authors' overall conclusions.

Mortality and serious adverse events are 2 of the most important outcomes in randomized clinical trials. The authors appropriately defined serious adverse events in their protocol consistent with the standard definition, which includes death. The trial demonstrated a 6% increase in serious adverse events in the tinzaparin group (49.2%) compared with the warfarin group (43.2%; *P* not reported).

Although the authors reported no difference in mortality, deaths in the tinzaparin group exceeded the warfarin group (150 [33.4%] for tinzaparin vs 138 [30.6%] for warfarin).<sup>1</sup> The 6% increase in serious adverse events for tinzaparin cannot be offset by a 4.4% decrease in nonmajor bleeding compared with warfarin.

Comparisons between the tinzaparin and the warfarin groups may have introduced a bias in favor of tinzaparin. For example, the median treatment duration for the tinzaparin group was longer than for the warfarin group (168 days vs 127 days).

Furthermore, the tinzaparin group received an injection for at least 75% of the treatment days, whereas the warfarin

group achieved a therapeutic international normalized ratio only 47% of the time (mean time: 26.1% below the therapeutic range; 26.9% above the therapeutic range).

We think tinzaparin should not be considered over warfarin for the treatment of acute venous thromboembolism in patients with active cancer because the potential harms outweigh the benefits.

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**In Reply** Ms Maruyama and colleagues question the conclusions of the CATCH trial of tinzaparin vs warfarin for the treatment of cancer-associated venous thromboembolism and raise concerns with the reporting of serious adverse events and mortality. We note that the CATCH trial was the largest study of treatment of acute venous thromboembolism in patients with active malignancy ever conducted and included a diverse study population, thereby increasing its generalizability and validity in the real-world setting. All safety and efficacy analyses were conducted with intention to treat, capturing all 900 randomized patients.

The randomized clinical trial design ensures patients enrolled to each group are balanced in terms of baseline characteristics that can influence outcomes; however, once enrolled, patients' outcomes and exposure to the study interventions may differ based on differences in efficacy and safety.

Thus, the longer median treatment duration for patients randomized to tinzaparin is accounted for by the fact that these patients experienced fewer recurrences and bleeding episodes, and therefore remained on the study drug longer. Accordingly, it would be more informative to report the incidence of serious adverse events and adverse events adjusted for study drug exposure duration.

For serious adverse events, the rates per 1 patient-year of exposure were 2.78 for tinzaparin vs 2.34 for warfarin; for adverse events the rates were 15.44 for tinzaparin vs 17.40 for warfarin. Similarly, for serious adverse events deemed related to study drug by local investigators, the rates were 0.05 for tinzaparin vs 0.27 for warfarin; for related adverse events, the rates were 1.20 for tinzaparin vs 4.42 for warfarin.