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Research Article

Economics and Outcome After Hematopoietic Stem Cell Transplantation: A Retrospective Cohort Study

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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is a lifesaving expensive medical procedure. Hence, more transplants are performed in more affluent countries. The impact of economic factors on patient outcome is less defined. We analyzed retrospectively a defined cohort of 102,549 patients treated with an allogeneic (N = 37,542; 37%) or autologous (N = 65,007; 63%) HSCT. They were transplanted by one of 404 HSCT centers in 25 European countries between 1999 and 2006. We searched for associations between center-specific microeconomic or country-specific macroeconomic factors and outcome. Center patient-volume and center program-duration were significantly and systematically associated with improved survival after allogeneic HSCT (HR 0·87; 0·84–0·91 per 10 patients; $p < 0·0001$; HR 0·90;0·85–0·90 per 10 years; $p < 0·001$) *and* autologous HSCT (HR 0·91;0·87–0·96 per 10 patients; $p < 0·001$; HR 0·93;0·87–0·99 per 10 years; $p = 0·02$). The product of Health Care Expenditures by Gross National Income/capita was significantly associated in multivariate analysis with all endpoints ($R^2 = 18\%$; for relapse free survival) after allogeneic HSCT. Data indicate that country- and center-specific economic factors are associated with distinct, significant, systematic, and clinically relevant effects on survival after HSCT. They impact on center expertise in long-term disease and complication management. It is likely that these findings apply to other forms of complex treatments.

1. Introduction

The close relationship between the economy of individual countries and the extent of their medical activities has long been accepted as reality but has become a topic of research only in the last decade (Waitzkin

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2003). The relevance of macroeconomics in health provision has recently been highlighted by the World Health Organization (WHO), with more solid organ and hematopoietic stem cell transplants (HSCT) performed in more affluent countries (White et al. 2014; Gratwohl et al. 2015). Allogeneic HSCT represents one role model of a low volume, high cost, but lifesaving medical procedure (Copelan 2006; Majhail et al. 2013; Khera et al. 2012). There is a strong association of country-specific economic factors with its use. Extensive studies have indicated significant correlations between transplant rates, e.g. the number of transplants compared to the number of inhabitants, and macroeconomic indices such as Gross National Income/capita (GNI/cap) or the availability of an unrelated donor registry. For a functioning national transplant network, a country must have a minimum size and a minimum of resources, teams require a minimum of support, donors must be available and patients have to have access to the transplant (Gratwohl et al. 2015; Gratwohl et al. 2010a; Gratwohl et al. 2010b).

It is intuitive that country-specific macroeconomic factors could have an impact on outcome as well. The vast numbers of well recognized patient-, disease-, donor- and transplant technique associated risk factors hamper simple comparisons (Copelan 2006; Giebel et al. 2010; Gratwohl et al. 2009). There is as well a potential independent role of center-specific microeconomic factors at the level of the individual team. Complex medical procedures require the close cooperation of multiple persons and institutions, training, competency and experience; in short, team expertise. The role of "minimal center size" or "patient/hospital volume" has been discussed for many years, with conflicting data (Loberiza et al. 2005; Gratwohl et al. 1989; Frassoni et al. 2000; Matsuo et al. 2000; Giebel et al. 2013; Klingebiel et al. 2010; Horowitz et al. 1992; Taylor et al. 2013).The topic of "center experience" is not restricted to HSCT but a matter of debate in many fields of medicine. Data suggest that minimum numbers of specific practice are required to perform complex medical procedures safely; again, results have been conflicting (Hunsicker et al. 1993; Ozhathil et al. 2011; Guba 2014; Birkmeyer et al. 2003; Lüchtenborg et al. 2013). Hence, relatively arbitrary thresholds have been set in accreditation standards (Jones et al. 2006; http://www.jacie.org/standards/6th-edition-2015 n.d.). However, patient interest groups, health policy makers, competent authorities and other stakeholders are increasingly asking for objective measures of patient safety and outcome. They expect transparency and fair systems of comparisons between centers (Horowitz et al. 1992; Logan et al. 2008).

We previously identified JACIE accreditation as a center-specific factor after allogeneic HSCT and found indications for an effect of patient volume (Gratwohl et al. 2014). We used this well-defined large cohort of patients to investigate the multifaceted relationship between potential center- and country-specific economic factors and long-term outcome after the less complex autologous or the more complex allogeneic HSCT.

2. Methods

2.1. Study design

This retrospective observational analysis was based on a previously published cohort. It consists of patients transplanted between January 1st 1999 and December 31st 2006 and reported by 404 teams (see appendix) to the European Society for Blood and Marrow Transplantation (EBMT) database (www.ebmt.org) (Gratwohl et al. 2014). The analysis was initiated on January 1st 2013; when all analyses were completed, patient's survival data were updated as of January 1st, 2015. Last follow-up time was used as endpoint. Endpoints in all analyses were overall survival, relapse, non-relapse mortality and relapse free survival. They served as indicators for team expertise in complication management (non-relapse mortality), and as indicators for team expertise in disease management (relapse incidence). Relapse incidence and non-relapse mortality were taken as competing risks. All data were censored at 8 years post HSCT to provide for a homogeneous observation period.

All EBMT teams are required to obtain patients' consent and to have internal review board approval for their transplant programs and for data transfer to EBMT. The present study was released by the Ethics Committee Nordwest- and Zentralschweiz (www.eknz.ch).

2.2. Patient population

The cohort was restricted to 102,549 patients, 59% males, with a first allogeneic (N = 37,542; 37%) or autologous HSCT (N = 65,007; 63%) for an acquired hematological malignancy from 1999 to 2006 (Table 1). This corresponds to 93% of all patients transplanted during this time frame by the participating teams with these indications (see appendix). The cohort was heterogeneous; there was an increase in acute and a decrease in chronic myeloid leukemia and an increase in EBMT risk score over time (Gratwohl et al. 2009). Allogeneic HSCT was preferentially used for acute leukemias (N = 21,991; 78% allogeneic), chronic leukemias (N = 7486; 83% allogeneic) and myelodysplastic/myeloproliferative disorders (N = 3864; 94% allogeneic); autologous HSCT was preferentially used for lymphoma (N = 32,358; 91% autologous) and plasma cell disorders (N = 24,500; 95% autologous) (Table 1; Fig. 1). There were significant differences between centers regarding program duration (Fig. 1a, b; supplementary Fig. 1a), and patient volume (Fig. 1c; supplementary Fig. 1b), and between accredited and non accredited centers (Gratwohl et al. 2014).

2.3. Definitions of selected economic factors

Economic factors were defined at the center (microeconomic) and country (macroeconomic) level as follows. *Center program duration was* defined by the numbers of years since the first transplant. Years were counted separately for the combination of each main indication and transplant type (allogeneic versus autologous HSCT) from the first transplant in the center up to the transplant of the individual patients included in the study (Fig. 1b; supplementary Fig. 1a). C*enter patient volume* was defined by the number of HSCT by transplant type for each main indication in the respective year of each of the transplants

Table 1
Patient characteristics
Demographics of 102,549 HSCT (allogeneic 37,542; 37% and autologous 65,007; 63%) between 1999 and 2006 in Europe.

	Allogeneic HSCT	Autologous HSCT	Total
N centers	299	401	404
JACIE* accredited	119	133	135
JACIE* not accredited	180	268	269
N Patients	37,542	65,007	102,549
Male %	21,797 (58.2%)	38,089 (58.7%)	59,886 (58.5%)
Age			
Median (years)	39·2	53·4	49·1
<20 years	7326 (20%)	2240 (3%)	9566 (9%)
20–40 years	12,055 (32%)	11,800 (18%)	23,855 (23%)
40–60 years	15,563 (41%)	33,973 (52%)	49,536 (48%)
>60 years	2598 (7%)	16,994 (26%)	19,592 (19%)
Disease			
Acute leukemia	21,991 (59%)	6361 (10%)	28,352 (27%)
Chronic leukemia	7486 (20%)	1556 (2%)	9042 (9%)
MDS/MPS	3864 (10%)	232 (<1%)	4096 (4%)
Lymphoma	3307 (9%)	32,358 (50%)	35,665(35%)
PCD	894 (2%)	24,500 (38%)	25,394 (25%)
Year Transplant			
1999–2002	17,589 (47%)	29,368 (45%)	46,957 (46%)
2003–2006	19,953 (53%)	35,639 (55%)	55,592 (54%)
0–I	5444(15%)	3755 (6%)	9199 (9%)
II–III	16,680 (44%)	35,623 (55%)	52,303 (51%)
IV–V	13,352 (36%)	25,629 (39%)	38,981 (38%)
VI–VII	2066 (5%)	0	2066(2%)

* JACIE = Joint Accreditation Committee of the International Society for Cellular Therapy and the European Society for Blood and Marrow Transplantation (www.jacie.org).