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Invited Submission

The Survey on Cellular and Engineered Tissue Therapies in Europe in 2012*

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Following the coordinated efforts of five established scientific organizations, this report describes activity in Europe for the year 2012 in the area of *cellular and engineered tissue therapies*, excluding hematopoietic stem cell (HSC) treatments for the reconstitution of hematopoiesis. Three hundred thirteen teams from 33 countries responded to the cellular and engineered tissue therapy survey: 138 teams from 27 countries provided data on 2157 patients, while a further 175 teams reported no activity. Indications were musculoskeletal/rheumatological disorders (36%; 80% autologous), cardiovascular disorders (25%; 95% autologous), hematology/oncology, predominantly prevention or treatment of graft versus host disease and HSC graft enhancement (19%; 1% autologous), neurological disorders (3%; 99% autologous), gastrointestinal disorders (1%; 71% autologous), and other indications (16%; 79% autologous). Autologous cells were predominantly used for musculoskeletal/rheumatological (42%) and cardiovascular (34%) disorders, whereas allogeneic cells were mainly used for hematology/oncology (60%). The reported cell types were mesenchymal stem/stromal cells (49%), HSC (28%), chondrocytes (11%), dermal fibroblasts (4%), keratinocytes (1%), and others (7%). In 51% of the grafts, cells were delivered after *ex vivo* expansion, whereas cells were transduced or sorted in 10% and 16%, respectively, of the reported cases. Cells were delivered intra-organ (35%), intravenously (31%), on a membrane or gel (15%), or using 3D scaffolds (19%). The data are compared with those collected since 2008 to identify trends in the field and discussed in the light of recent publications and ongoing clinical studies.

Introduction

There is a large and relevant clinical demand for cell-based therapies to induce tissue or organ regeneration, as well as to modulate the immune system. Nonetheless, progression from first-in-human experiences in a few patients to full integration into routine clinical practice involves many steps and is often an uphill struggle.[1] To penetrate mainstream healthcare processes, critical scientific challenges must be addressed and acceptable standards of safety and potency must be achieved. This requires the development of new knowledge and the design of clinical studies that can teach on human cell biology. In addition, the translational pathway needs to overcome a series of non-scientific barriers, based on financing, regulatory, and public perception issues. Ultimately, healthcare systems are likely to struggle to meet the associated costs and it is unclear how priorities will be set with regard to reimbursement decisions.[2]

Against this background of innovations in science and the emerging regulatory environment, the European sections of the Tissue Engineering and Regenerative Medicine International Society-Europe (TERMIS-EU), of the International Society of Cellular Therapy (ISCT), and of the International Cartilage Repair Society (ICRS), in a joint initiative with the European Group for Blood and Marrow Transplantation (EBMT) and the European League Against Rheumatism (EULAR), established a survey on novel cellular therapies, now referred to as a survey of cellular and engineered tissue therapies. Since 2008, the number of patients treated in Europe with cells or engineered tissues has been collected and sorted by specific therapeutic indications, cell/tissue and donor types, along with the processing and delivery modes.[3–6]

Here, we report the results of the fifth survey for the activity in 2012, along with a comparison to previous years. The information presented is generally available ahead of

*For the Joint Survey Committee of the Tissue Engineering and Regenerative Medicine International Society (TERMIS)-Europe, the International Cartilage Repair Society (ICRS), the International Society for Cellular Therapy (ISCT)-Europe, the European Group for Blood and Marrow Transplantation (EBMT) and the European League Against Rheumatism (EULAR).

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published studies, because safety/efficacy data are not required for the report, and complementary to that available in public databases (e.g., www.clinicaltrials.gov) as the survey specifies the number of treatments effectively conducted as opposed to planned. Thanks to the continued efforts of the different working groups, the yearly availability of collected data represents a means of monitoring changes and capturing trends in a complex and still rather unpredictably developing field.

Patients and Methods

Definitions

For the purpose of this survey, *cellular and engineered tissue therapy* is any clinical treatment based on living cells excluding donor lymphocyte infusions and nonmanipulated hematopoietic cells for hematological reconstitution.

Data collection and validation

Participating teams were, as in previous years, requested to report their data for 2012 by indication, cell type and source, donor type, processing method, and delivery mode. The survey followed the traditional principles of the EBMT transplant activity survey, which concentrates on numbers of patients with a first cellular therapy. Six hundred eighty teams known to be actively transplanting in 48 countries (38 European and 10 affiliated countries) were contacted for the 2012 EBMT survey, to which were added members of the other four participating societies and teams who had contributed to any earlier survey. The non-European countries affiliated with the EBMT activity survey are Algeria, Iran, Israel, Jordan, Kazakistan, Lebanon, Nigeria, Saudi Arabia, South Africa, and Tunisia. Extended questionnaires, in the format displayed in Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/tea), were received in paper form and electronically.

Transplant rates

Transplant rates, defined as the reported numbers of patients receiving cellular or engineered tissue therapies and the number of teams reporting treatments per 10 million inhabitants, were computed for each country, without adjustments for patients who crossed borders or received treatment in a foreign country. Population numbers were obtained from the 2012 US census office database (www.census.gov).

Results

Participating teams

Three hundred thirteen teams from 33 countries (26 European, 7 EBMT affiliated countries) responded to the *cellular and engineered tissue therapy* survey. One hundred thirty-eight teams (27 countries: 23 European, 4 EBMT affiliated—Iran, Israel, Saudi Arabia, and South Africa) reported performing cellular or tissue-engineered therapies and provided detailed information on indication, cell source and type, donor type, cell/tissue processing, and delivery mode. A further 175 teams reported no activity. Teams that responded with activity are listed in the Appendix in alphabetical order of country, then city. In addition their EBMT CIC code (if applicable), the total number of reported cellular or tissue-engineered therapies and the split between allogeneic and autologous donor is included.

Number of cellular or tissue-engineered therapies and disease indications

According to the received reports, 2157 patients were treated with cellular or engineered tissue therapies, 672 (31%) with allogeneic and 1485 (69%) with autologous cells (Table 1). Indications were musculoskeletal/rheumatological disorders (36%; 80% autologous), cardiovascular disorders (25%; 95% autologous), hematology/oncology (predominantly prevention or treatment of graft versus host disease [GvHD], hematopoietic stem cell [HSC] graft enhancement) (19%; 1% autologous), neurological disorders (3%; 99% autologous), gastrointestinal disorders (1%; 71% autologous), and other indications (16%; 79% autologous).

Among the *musculoskeletal/rheumatological disorders*, cartilage and bone repair were the most frequently reported indications, followed by reconstructive surgery/tissue enhancement. Treatments for decubitus and leg ulcers were the main reasons for a cellular or engineered tissue therapy among the *cardiovascular disorders*, followed by peripheral artery disease and then heart failure. The number of patients treated for *neurological and gastrointestinal indications* was rather limited (88) and mostly confined to multiple sclerosis, amyotrophic lateral sclerosis (*neurological*), and Crohn's disease (*gastrointestinal*). Among the remaining indications, most patients were treated for solid tumor or skin reconstruction (Table 1).

Cell type, source, and donor type

The reported cell types were mesenchymal stem/stromal cells (MSC) (49%), HSC (28%), chondrocytes (11%), dermal fibroblasts (4%), keratinocytes (1%), and others (7%). Of the 614 HSC treatments, 93% were autologous transplants (Table 1). From 1055 MSC-based therapies, 53% were autologous. Of the remaining cell sources, 70% of chondrocytes, 71% of keratinocytes, and all dermal fibroblast transplants were autologous.

Autologous cells were predominantly used for musculoskeletal/rheumatological (42%) or cardiovascular (34%) disorders and for solid tumors (10%), whereas the main uses of allogeneic cells were for hematology/oncology (60%) and, for the first time in any significant numbers, for musculoskeletal/rheumatological indications (24%). Of these, cartilage repair was the main indication (comprising 19% of the total and 81% within the musculoskeletal/rheumatological grouping) (Fig. 1).

The percentage of treatments using autologous versus allogeneic cells steadily increased from 36% in 2008 to 69% in 2012, with the actual number of patients treated with autologous cells more than doubling in this period (from 664 to 1485 patients). The number of patients treated with allogeneic cells also increased year on year (from 376 to 672), although the percentage of treatments in hematology/oncology was reasonably stable at around 60%, with a peak at more than 80% in 2011. The trends for the various therapy areas are reflected in Figure 2.

In 2012, MSC were mostly obtained from bone marrow (74%; of which 42% were autologous) or adipose tissue

Table 1. Number of Reported Cellular and Engineered Tissue Therapy Treatments in Europe in 2012 Sorted by Indication, Cell Source, and Donor Type

	Cell type and source														
	Autologous						*Allogeneic*								
Indication	*HSC*	*MSC*	*Chondrocyte*	*Keratinocyte*	*Dermal fibroblast*	*Other*	*HSC*	*MSC*	*Chondrocyte*	*Keratinocyte*	*Dermal fibroblast*	*Other*	*Autologous*	*Allogeneic*	*Total*
Cardiovascular															
Peripheral artery disease	103											7	103	7	110
Cardiomyopathy	55						2						55	2	57
Heart failure	73	19											92	0	92
Myocardial ischemia	46	10					19						56	19	75
Bypass graft	6												6	0	6
Decubitus and leg ulcers	150	45											195	0	195
Other/unspecified													0	0	0
Musculoskeletal/rheumatological															
Bone repair (maxillofacial)	19	5											24	0	24
Bone repair (orthopaedics)	3	11						7					14	7	21
Osteogenesis imperfect		12						1					12	1	13
Cartilage repair (orthopedics)		224	165					57	72				389	129	518
Muscle repair						8							8	0	8
Tendon/ligament													0	0	0
Reconstructive surgery/tissue enhancement		151	1					23					152	23	175
Sclerodoma	11	4											15	0	15
Arthritis	3	5											8	0	8
Other/unspecified		1											1	0	1
Neurological															
Multiple sclerosis	3	22											25	0	25
Amyotrophic lateral sclerosis	11	14											25	0	25
Parkinson's	1												1	0	1
Peripheral nerve regeneration (trauma)	3												3	0	3
Other/unspecified	5	7										1	12	1	13
Gastrointestinal															
Crohn's disease	4	7						6					11	6	17
Liver insufficiency	4												4	0	4
Hematology/oncology															
GvHD prevention or treatment							17	360					0	377	377
HSC graft enhancement		4					2	27					4	29	33
Miscellaneous															
Skin reconstruction				51	9			3		23			60	26	86
Cornea repair						1						3	1	3	4
Diabetes	15	3										3	18	3	21
Solid tumor	41	1				100							142	0	142
Other	14	11		4	3	17	4	15				20	49	39	88
Total	570	556	166	55	12	126	44	499	72	23	0	34	1485	672	2157

GvHD, graft versus host disease; HSC, hematopoietic stem cells; MSC, mesenchymal stromal/stem cells.

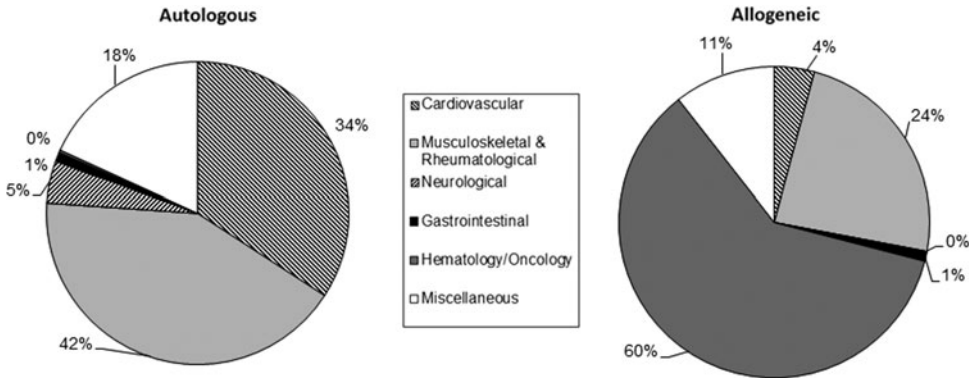

FIG. 1. Percentage of indications for cellular and engineered tissue therapies in Europe in 2012, sorted by donor type.

(25%; of which 87% were autologous), whereas in 2011 they were obtained from adipose tissue and bone marrow in almost equal amounts. MSC were mainly used for GvHD (34%) and for two musculoskeletal indications, namely cartilage repair (26%) and reconstructive surgery/tissue enhancement (16%). For the HSC treatments, cells were derived from peripheral blood (60%) or bone marrow (40%) and 71% of them were used to treat cardiovascular disorders. All chondrocyte preparations were for cartilage repair, while keratinocytes and dermal fibroblasts were almost exclusively used for skin reconstruction. The use of combinational treatments, for example, fat and peripheral blood cells in reconstructive surgery/tissue enhancement, was also reported but could not be consistently captured by the format of the questionnaire.

Cell processing and delivery mode

Of all the grafted products, just more than half underwent cell expansion (51%), 10% were transduced, and 16% were sorted (Table 2). Ninety-three percent of cardiovascular, 50% of musculoskeletal/rheumatological and 36% of neurological indications were treated with nonexpanded cells, while gastrointestinal indications were predominantly (62%) treated with expanded cells. Expanded cells were also used for 97% of hematology/oncology treatments and 80% of treatments for skin reconstruction.

Cell sorting was applied predominantly for musculoskeletal/rheumatological (51% of all sorted cells) and cardiovascular indications (18% of all sorted cells). One hundred seventy patients with musculoskeletal/rheumatological indications (22% of all patients in this group), of whom 161 were treated for cartilage repair, received treatment with sorted cells as did 59 patients with cardiovascular indications (11% of all patients in this group).

Transplanted cells were genetically transduced for 71% of diabetic cases, 27% of heart failure, 23% of cartilage repairs, 21% of solid tumors, and 3% of hematology/oncology cases. Fifty-six percent of all transduced cells were used for cartilage repair. This is the first year that transduced cells were used in any number for this indication (120 of 508 cartilage repair patients treated).

Of the 41% of cells reported to be processed using an automated device, most were used to treat cardiovascular (46%) and musculoskeletal/rheumatological (43%) indications. The previous year, we introduced the topic of whether cells were processed manually or by automated means (when at least one step of cell isolation or culture is performed with an automated device, i.e., a specifically designed instrument beyond a centrifuge or sorter). For patients treated in 2011, manual techniques were almost 4 times as likely to have been used (1377 manual vs. 382 automated) whereas for 2012 patients the ratio reduced significantly (1269 manual vs. 888 automated). The highest use of automated processing in both years was to treat patients for cardiovascular and musculoskeletal/rheumatological indications.

Thirty-five percent of the cell grafts were delivered intra-organ, 31% intravenously, 15% on a membrane or gel, and 19% using a 3D scaffold (Table 3). Cells were delivered intra-organ for 57% of cardiovascular, 48% of neurological, and 39% of musculoskeletal/rheumatological indications. Intravenous (i.v.) delivery was reported for all hematology/oncology treatments and for about half (48%) of gastrointestinal indications. The use

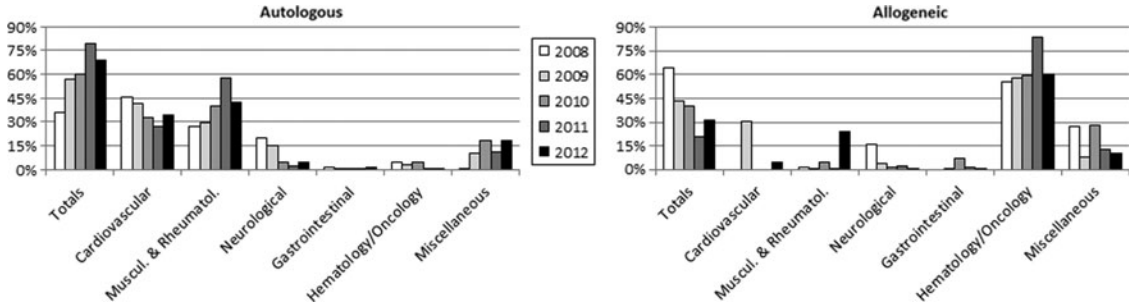

FIG. 2. Comparative analysis of indications for cellular and engineered tissue therapies in Europe from 2008 to 2012, sorted by donor type. Data used for this chart were derived from this study and the four previous reports.[3–6]

Table 2. Number of Reported Cellular and Engineered Tissue Therapy Treatments in Europe in 2012 Sorted by Processing Mode

	Cell processing							
Indications	*Nonexpanded*	*Expanded*	*Untransduced*	*Transduced*	*Unsorted*	*Sorted*	*Automated*	*Manual*
Cardiovascular								
Peripheral artery disease	103	7	109	1	100	10	77	33
Cardiomyopathy	57		57		32	25	52	5
Heart failure	74	18	67	25	88	4	48	44
Myocardial ischemia	65	10	75		61	14	29	46
Bypass graft	6		6			6	6	
Decubitus + leg ulcers	195		195		195		195	
Musculoskeletal/rheumatological								
Bone repair (maxillofacial)	24		24		24		22	2
Bone repair (orthopaedics)	11	10	21		17	4	9	12
Osteogenesis imperfecta	12	1	13		13		12	1
Cartilage repair (orthopaedics)	177	341	398	120	357	161	167	351
Muscle repair		8	8		8			8
Reconstructive surgery/tissue enhancement	162	13	175		175		162	13
Scleroderma	6	9	15		10	5	5	10
Arthritis	3	5	8		8		3	5
Other		1	1		1			1
Neurological								
Multiple sclerosis	3	22	25		23	2	1	24
Amyotrophic lateral sclerosis	11	14	25		25			25
Parkinson's	1		1			1		1
Peripheral nerve regeneration (trauma)	3		3		2	1	2	1
Other	6	7	13		8	5		13
Gastrointestinal								
Crohn's disease	4	13	17		17		1	16
Liver insufficiency	4		4		1	3		4
Hematology/oncology								
GvHD prevention or treatment	12	365	366	11	377		11	366
HSC graft enhancement	2	31	33		31	2	2	31
Miscellaneous								
Skin reconstruction	18	68	86		86			86
Cornea repair		4	4		4			4
Diabetes	3	18	6	15	18	3	15	6
Solid tumor	66	76	112	30	65	77	39	103
Other	37	51	76	12	76	12	30	58
Total	1065	1092	1943	214	1822	335	888	1269

of a membrane or a gel for cell delivery was mainly reported for skin reconstruction (76% of cases), for treatment of decubitus and leg ulcers (54% of cases), or for musculoskeletal/rheumatological (17% of cases) indications. A 3D scaffold was used for 42% of musculoskeletal/rheumatological treatments, in particular for cartilage or bone repair (37%). Other uses of a scaffold were for treating peripheral artery disease (42% of cases).

Over the 5 years of the survey, most cells were delivered intra-organ, followed by i.v. and membrane or 3D scaffold delivery (Fig. 3). There was some use of i.v. delivery in all indication groups over the 5 years, although to varying degrees: i.v. not only was the only delivery mode for GvHD treatments but also was used in treating musculoskeletal/rheumatological indications. While all gastrointestinal indications were treated via i.v. in 2008 and 2009, intra-organ delivery was introduced in 2010 (10% of patients), rising to about 50% in 2011 and 2012. The highest use of intra-organ delivery in 2012 was for cardiovascular indications (57%) and Crohn's disease (52% of gastrointestinal [GI] indications), followed by neurological (48%) and musculoskeletal/rheumatological indications (39%).

Transplant rates and active teams

Reported cellular and engineered tissue therapies were performed in a limited number of countries and with a different intensity. Figure 4 displays the reported transplants per 10 million inhabitants in the different European and EBMT-associated countries. High transplant rates (i.e., >100 per 10 million population) were reported in the Netherlands and Slovenia. The number of teams reporting cellular and tissue engineered therapies was also mapped in the different European and EBMT-associated countries after normalization to the inhabitant numbers (Fig. 5). The number of reporting teams per 10 million inhabitants was higher than four in Austria, Belgium, The Netherlands, Slovenia, and Switzerland. Interestingly, the top 10 countries (out of 27 total) accounted for 86% of all patients treated.

Discussion

The data collected in this fifth edition of the cellular and engineered tissue therapy survey indicate a further increase in the number of reporting teams (+27%) and of total

Table 3. Number of Reported Cellular and Engineered Tissue Therapy Treatments in Europe in 2012 Sorted by Delivery Mode

	Cell delivery mode			
Indications	*Intravenous*	*Intra-organ*	*Membrane/gel*	*3D scaffold*
Cardiovascular				
Peripheral artery disease	28	29	7	46
Cardiomyopathy	6	51		
Heart failure	5	87		
Myocardial ischemia	31	44		
Bypass graft		6		
Decubitus + leg ulcers		90	105	
Musculoskeletal/rheumatological				
Bone repair (maxillofacial)			17	7
Bone repair (orthopaedics)		2	3	16
Osteogenesis imperfecta	1			12
Cartilage repair (orthopaedics)		114	115	289
Muscle repair		8		
Reconstructive surgery/tissue enhancement		172		3
Scleroderma	11	4		
Arthritis		5		3
Other	1			
Neurological				
Multiple sclerosis	18	7		
Amyotrophic lateral sclerosis	9	16		
Parkinson's		1		
Peripheral nerve regeneration (trauma)		1	2	
Other	6	7		
Gastrointestinal				
Crohn's disease	6	11		
Liver insufficiency	4			
Hematology/oncology				
GvHD prevention or treatment	377			
HSC graft enhancement	33			
Miscellaneous				
Skin reconstruction	3		65	18
Cornea repair			4	
Diabetes	3	18		
Solid tumor	66	76		
Other	67	14		7
Total	675	763	318	401

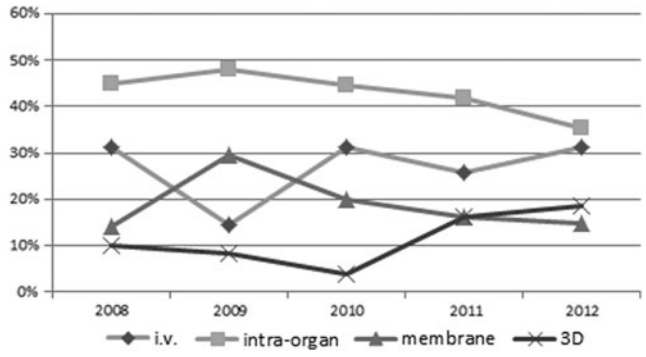

FIG. 3. Percentage comparison of cell delivery modes 2008 to 2012. Data used for this chart were derived from this study and the four previous reports.[3–6]

treatments reported (+23%) as compared with the previous year. Over the 5 years, the total number of reporting teams has more than doubled from 143 in 2008 to 313 in 2012, with the number reporting full data rising fourfold from 33 in 2008 to 138 in 2012 (Fig. 6). At the same time, the total number of patients treated has risen from 1040 in 2008 to 2159 in 2012.

These results indicate that, thanks to the networks of the involved societies, the follow up of teams who have previously reported, and the strategy of head-hunting for known active teams, the program is receiving a growing recognition as a reference platform for the collection and dissemination of information that is not available in public databases or scientific publications. Moreover, analysis of data generated in the five surveys[3–6] allows the identification of some established features.

We have compared the results obtained for patients treated in 2011 and 2012 for specific indications and have found that the largest differences can be attributed in most cases to additional reporting teams or to one or two teams

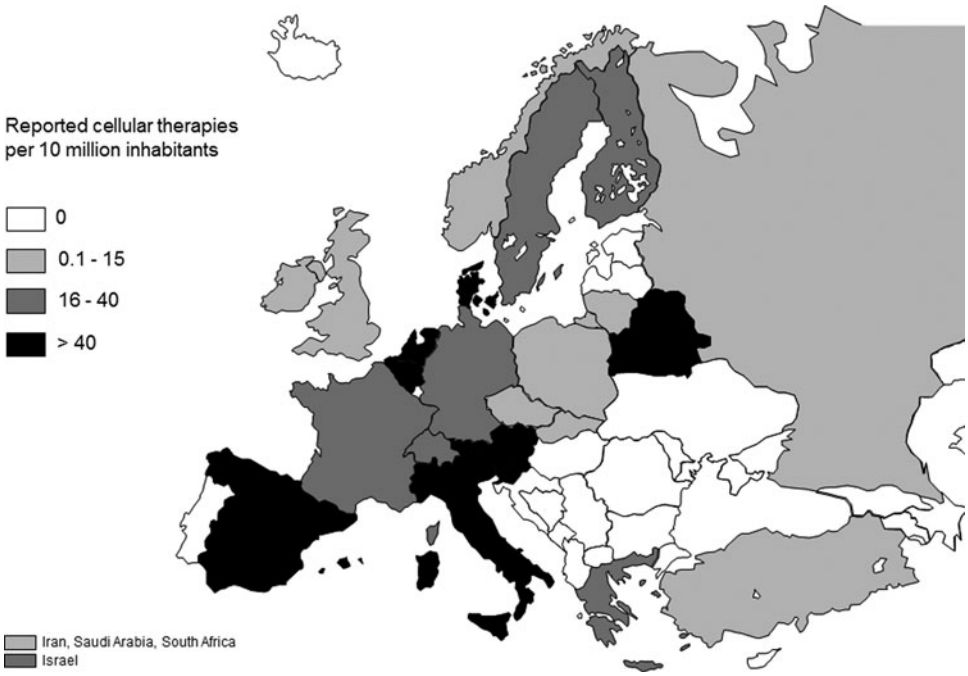

FIG. 4. Number of cellular and engineered tissue therapies per 10 million inhabitants reported in Europe in 2012.

reporting the treatment of a higher number of patients. For example, for solid tumors, there were two newly reporting teams who between them accounted for 89 patients and therefore for most of the increase (38 in 2011, 142 in 2012). Conversely, the increase in the number of patients treated for decubitus and leg ulcers (58 in 2011, 195 in 2012) as well as for heart failure (51 in 2011, 92 in 2012) was predominantly due to the increased activity of one or two teams. This consideration prompts for a degree of caution in the interpretation of developing trends, as the data are possibly affected by fluctuations and ''noise'' driven by a restricted number of teams.

The most used cell source in 2012 was MSC (1055 treatments), and the most represented indication for their use was GvHD prevention or treatment (360 patients). In the 4 years 2008–2011, the average number of patients treated for GvHD (268, range 240–298) was consistently one of the largest. Enthusiasm for the use of MSC for treating GvHD has been built on the evidence from phase II clinical trial data published by European collaborative groups in recent years.[7] This is despite the failure of a large, predominantly US-based multicenter phase III trial, examining the use of an industrial MSC product to treat acute GvHD, to meet the primary endpoint.[8–10] The product, Prochymal®, initially

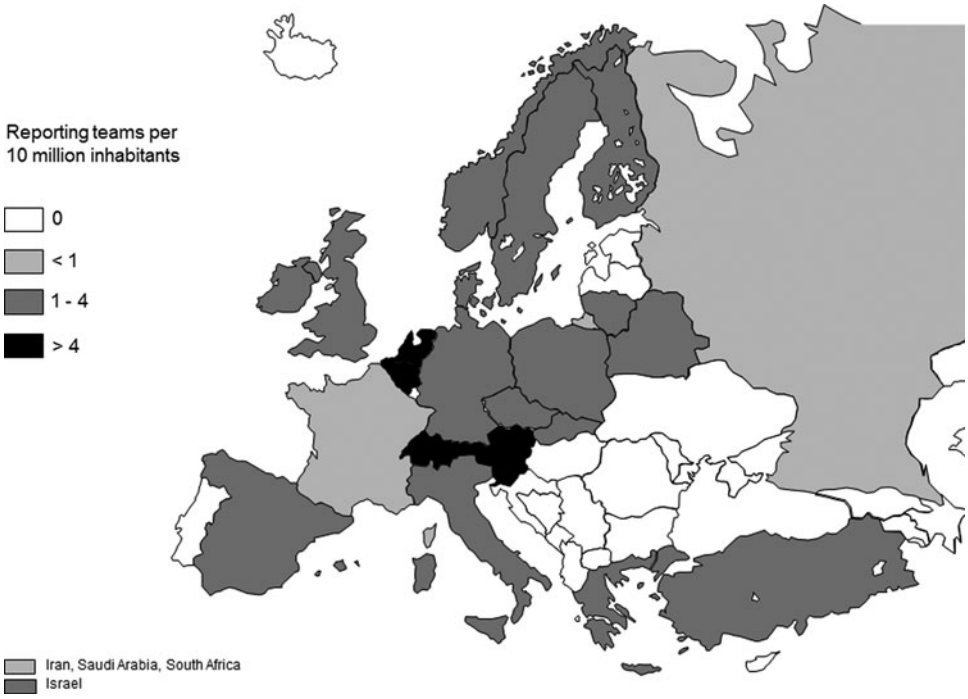

FIG. 5. Number of teams per 10 million inhabitants reporting cellular and engineered tissue therapies in Europe in 2012.

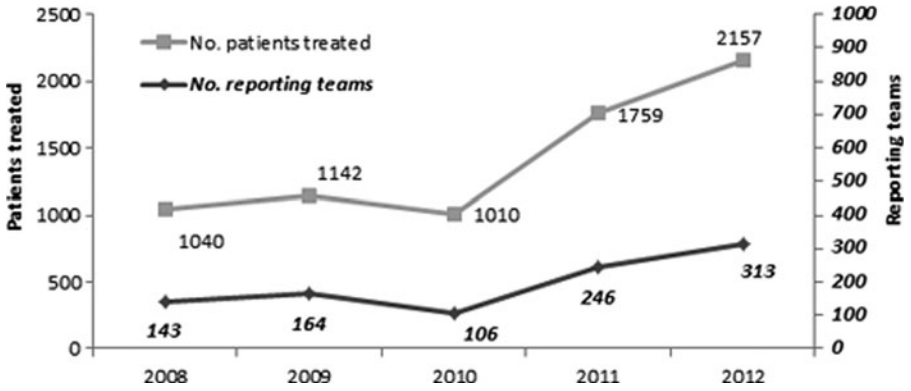

FIG. 6. Number of reporting teams and number of patients treated using cellular and engineered tissue therapies from 2008 to 2012. Data used for this chart were derived from this study and the four previous reports.[3–6]

owned by Osiris Therapeutics Inc. and acquired by the Mesoblast Group in October 2013,[11] is the world's first approved allogeneic stem cell therapeutic for the treatment of acute GvHD in children. According to a recent expert opinion article,[12] the negative trial results and availability of alternative therapies means that the product in its current form is unlikely to find widespread use in the treatment of acute GvHD. However, publication of the results of the Phase III study is needed to provide clarity on the clinical activity and to derive any conclusion.

The apparent discrepancy between the European experience (MSC mainly manufactured by academic centers)[7] and that of the industry-sponsored study (industrial MSC) is discussed by Galipeau[13] and could be explained by variance in donor characteristics, responsiveness to interferon-γ activation, the scale of cellular product expansion, inducible immunogenicity of the cells, and/or changes after cryopreservation. Indeed, interest in the area remains high and several clinical trials in Europe are ongoing.[12] A search on clinicaltrials.gov for open studies on GvHD and MSC in European Centers yielded three phase I trials, five phase II trials, and a double-blind placebo-controlled randomized phase III trial comparing steroids and MSC as first-line therapy against steroids alone.[14] The results of the current survey reflect the continuing clinical activity of participating centers, distributed throughout Europe.

In 2008 and 2009, all skin reconstruction treatments were performed using keratinocytes (36 patients in 2008, 51 in 2009). Dermal fibroblasts were introduced in 2010 as an alternative cell source for this indication (50 out of 104 patients), followed in 2011 by MSC (29 out of 96 patients although only 3 out of 86 patients in 2012). The identified trends are consistent with the developing scientific literature. In fact, it is increasingly recognized that both fibroblasts and keratinocytes have a role in healing chronic wounds,[15,16] and that tissue-engineered skin with superficial fibroblasts and keratinocytes holds promise for the treatment of patients with basement membrane disorders and other skin blistering diseases.[17] A review focusing on the benefits of MSC in skin wound healing and tissue regeneration indicated a possible contribution of MSC to reconstituting skin in cutaneous wounds.[18] Although the mechanism of action is far from being understood, the reported clinical activity reflects the possible trophic role by MSC in skin wound closure by affecting both dermal fibroblast and keratinocyte migration, along with a contribution to the deposition of extracellular matrix.[19]

The number of patients treated for solid tumor rose from 38 in 2011 to 142 in 2012. The primary source of cells in both years was ''other'' (28 in 2011 and 100 in 2012). A review of the results of a search on clinicaltrials.gov for nondrug treatments for solid tumors shows a current interest in the use of dendritic cells.[20,21] These two trials, taking place in Belgium and Spain, correspond to the locations of the most active reporting groups for this indication. We would, therefore, assume that the ''other'' is likely to be dendritic cells and that the increase in patient numbers relates to current trials. We expect to confirm this assumption in the next survey edition, as the form for patients treated in 2013 was revised to include dendritic cells as a specific cell source.

Throughout the 5-year period of the survey, the use of cells for cartilage repair has displayed a number of developing trends. Despite some yearly fluctuations, the introduction of MSC along with chondrocytes is being consolidated, as 54% of the total treatments in 2012 used MSC. The data are consistent with ongoing clinical studies, including the injection of autologous adipose-derived MSC in patients with moderate or severe osteoarthritis of the knee.[22] It is also worth highlighting that in 2012 we received the first reports of transduced cells being used for cartilage repair (23%). Based on the available literature,[23,24] these treatments are likely to be targeting degenerative as opposed to traumatic cartilage pathologies. Finally, while all reported cartilage repair treatments in 2011 used autologous cells, in 2012, 20% of MSC (57 of 281 patients) and 30% of chondrocytes (72 of 237 patients) were from allogeneic sources. The trend may be a direct consequence of previous studies indicating safety and feasibility of allogeneic cells for cartilage lesions[25] and reflect ongoing clinical trials.[26,27]

The earlier assessments for a few representative indications confirm that cellular and engineered tissue therapies, outside the field of hematological malignancies, are still in their infancy and predominantly embedded in the context of clinical trials. Challenges for the routine clinical translation of laboratory investigations, beyond the initial assessment of safety, are of a different nature. From a scientific standpoint, in most cases there is still a limited understanding of the biological processes initiated by implanted cells or engineered tissues and of their mechanisms of therapeutic function. This knowledge is critical to derive predictive

assays of potency, which is, in turn, necessary to define relevant in-process controls and release criteria to guarantee repeatable quality of the graft.[28,29] From an engineering and economic perspective, an increased robustness in manufacturing, cost-effectiveness for the service provider and sustainability for the healthcare system will likely require an introduction of technological innovations to automate and streamline production processes.[30] From a clinical and regulatory standpoint, the organization of multicenter trials will be important to increase the level of evidence for clinical effectiveness. To this end, the fact that within Europe different national organs are in charge to implement Good Manufacturing Practice (GMP) guidelines or to approve clinical trials adds to the intrinsic complexity of the strict framework in the field of Advanced Therapy Medicinal Products (ATMP).[29] In all these regards, analyses of trends in cellular and engineered tissue therapies, based on an early and open communication of patient treatments, will be critical to guide future initiatives and coordinate efforts of the different working parties.

Acknowledgments

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Appendix: List of Reporting Cellular Therapy/Tissue Engineering Centers in Europe in 2012

Format: City, Hospital, Department, CIC (EBMT teams), Physicians (Total treatments: allogeneic/autologous)

CIC = Center Identification Code (as used in the standard EBMT survey)

Austria

Krems, University Krems, Regenerative Medicine and Orthopedics, S. Nehrer (9: 9/0)

Linz, AO Krankenhaus, 3. Medizinische Abteilung, M.A. Fridrik, S. Hennerbichler (20: 4/16)

Vienna, Medical University Hospital, Traumatology, S. Marlovits, Ch. Albrecht (2: 0/2)

Vienna, Universitätsklinik für Innere Medizin-AKH, CIC 227, H. Greinix, P. Kalhs (1: 1/0)

Belarus

Minsk, Belorussian Center, CIC 591, O. Aleinikova (29: 24/5)

Minsk, Hospital No. 9, Belorussian Transplant Center, N. Milanovich (17: 2/15)

Belgium

Antwerp, Orthopaedic Center, Knee Surgery and Sports Traumatology, P. Verdonk (10: 10/0)

Antwerp, Stuivenberg ZH, CIC 339, P. Zachee (2: 2/0)

Antwerp, University Antwerpen, Hematology, CIC 996, W. Schroyens, Z. Berneman (42: 3/39)

Brussels, Clinique Universitaire St. Luc, CIC 234, X. Poiré, C. Vermylen (2: 2/0)

Brussels, Institut Jules Bordet, Children's Hospital, CIC 215, D. Bron, C. Devalck, A. Ferster (2: 0/2)

Brussels, Military Hospital Queen Astrid, Burn Wound Center, G. Verbeken (24: 23/1)

Brussels, U.L.B. Hôpital Erasme, Hematology, CIC 596, B. Bailly, A. Kentos, M. Lambermont (1: 0/1)

Leuven, University Hospital Gasthuisberg, CIC 209, J. Maertens, G. Verhoef, M. Renard (1: 1/0)

Liège, CHU Liège, Gastrology, E. Louis (1: 1/0)

Liège, CHU Liège, Surgery and Transplantation, M. Meurice (6: 6/0)

Liège, University Hospital Sart-Tilman, CIC 726, Y. Béguin, B. de Prijck (8: 8/0)

Czech Republic

Prague, Academy of Sciences, Institue of Experimental Medicine, Z. Kollarova (9: 0/9)

Denmark

Copenhagen, The Heart Center Rigshospitalet, Cardiac Catherization Lab., J. Kastrup (33: 0/33)

Finland

Helsinki, HUCH Jorvi Hospital, Orthopedics, Traumatology, T. Paatela (10: 0/10)

Kuopio, University Hospital, Orthopedics, Traumatology and Hand Surgery, A. Joukainen (1: 0/1)

France

Grenoble, CHU de Grenoble, Pathology, Neurovascular, O. Detante, A. Moisan (2: 0/2)

Grenoble, CHU Grenoble, Hôpital A. Michallon, Hematology, Oncology, CIC 270, J.Y. Cahn, P. Drillat, C.E. Bulabois (9: 3/6)

Marseille, Arthosport Center, Knee Institute, M. Assor (120: 0/120)

Paris, Hôpital St. Antoine, CIC 775, N.C. Gorin, L. Fouillard (1: 1/0)

Paris, Hôpital St. Louis, Cell Therapy Unit, J. Larghero (40: 7/33)

Germany

Chemnitz, Klinikum Chemnitz GmbH, Innere Medizin Lll, CIC 104, M. Hänel, A. Morgner (2: 2/0)

Dinslaken, St. Vinzenz Hospital, Unfall und Orthopädie, W. Zinser (61: 0/61)

Dresden, Universitätsklinikum Carl Gustav Carus, CIC 808, G. Ehninger, M. Bornhäuser, M. Gahr (31: 31/0)

Essen, Universitätsklinikum, KMT Klinik, CIC 2591, D.W. Beelen (2: 2/0)

Frankfurt, J. W. Goethe Universität, Kinderheilkunde lll, CIC 138, T. Klingebiel, P. Bader (5: 5/0)

Frankfurt, Klinikum Frankfurt Oder, Innere Medizin, CIC 190, M. Kiehl (12: 11/1)

Halle, Clinic Bergmannstrost, Neurosurgery, H.J. Meisel (8: 0/8)

Hannover, Medizinische Hochschule, Hematology, Oncology, CIC 295, A. Ganser, J. Krauter (3: 0/3)

Hannover, Medizinische Hochschule, Pediatric Hematology and Oncology, CIC 295, C. Kratz, K.W. Sykora (2: 2/0)

Munich, Klinikum Rechts der Isar, lll. Med Klinik, CIC 558, C. Peschel, M. Verbeek (1: 1/0)

Regensburg, Universitätsklinikum, Hematology, Oncology, CIC 787, R. Andreesen, S. Corbacioglu (1: 1/0)

Tübingen, Universitätsklinikum, Pediatrics, CIC 535, R. Handgretinger, P. Lang (9: 8/1)

Würzburg, Universitätsklinikum, Pediatric Hematology and Oncology, CIC 196, P. Schlegel (3: 3/0)

Greece

Athens, Academy of Athens, Hellenic Cord Blood Bank, A. Papassavas, C. Stavropoulos-Giokas (18: 0/18)

Athens, Aghia Sophia Children's Hospital, Pediatrics, CIC 752, S. Graphakos (2: 2/0)

Thessaloniki, Sports Clinic, E.T. Papacostas (2: 0/2)

Iran, Islamic Rep.

Shiraz, Nemazee Hospital, CIC 188, M. Ramzi (9: 0/9)

Teheran, Shariati Hospital, Hematology, Oncology, CIC 633, A. Ghavamzadeh, M. Jahani (3: 3/0)

Ireland

Galway, University College Hospital, Hematology, CIC 408, A. Hayat (2: 0/2)

Israel

Jerusalem, Hadassah University Hospital, CIC 258, R. Or, S. Slavin (18: 18/0)

Petach-Tikva, Beilinson Hospital, Adult Hematology, CIC 409, M. Yeshurun (1: 1/0)

Petach-Tikva, Children's Medical Center, Pediatrics, CIC 755, J. Stein (1: 1/0)

Italy

Bergamo, Ospedale Riuniti, CIC 658, A. Rambaldi (6: 6/0)

Bologna, Hospital St. Orsola, Inst. Hematology, CIC 240, G. Bandini, M. Baccarani, F. Bonifazi (3: 0/3)

Bologna, 6th div, Istituto Ortopedico Rizzoli (IOR), RIT-Cell Factory, L. Roseti (17: 0/17)

Bologna, Istituto Ortopedico Rizzoli (IOR), Orthopedic Pathology, Osteoarticular TR, D. Donati (14: 0/14)

Bolzano, Ospedale S. Maurizio, CIC 299, S. Cortelazzo, M. Casini, I. Cavattoni (2: 2/0)

Florence, Policlinico di Careggi, CIC 304, A. Bosi, S. Guidi (4: 1/3)

Genoa, Istituto Giannina Gaslini, Hematology, Oncology, CIC 274, G. Dini, E. Lanino (1: 1/0)

Milan, OASI Bio-research Foundation, Orthopedic Arthroscopic Surgery International, A. Gobbi, D. Lad (6: 0/6)

Milan, University of Milan IRCCS, CIC 265, A. Cortelezzi, E. Tagliaferri (1: 1/0)

Monza, L'Università di Milano-Bicocca, Ospedale San Gerardo del Tintori, CIC 544, E. Pogliani, P. Pioltelli, M. Parma (3: 2/1)

Monza, Ospedale San Gerardo, CTMO-Clinica Pediatrica, CIC 279, A. Rovelli (7: 7/0)

Padua, Centro Leucemie Infantili, CIC 285, C. Messina, M. Pillon, E. Calore (2: 2/0)

Pavia, Policlinico IRCCS St. Matteo, Pediatrics, CIC 557, M. Zecca (4: 4/0)

Piemonte, Ospedale degli infermi di Biella, Orthopedics, A. Siclari (52: 52/0)

Rome, Università ''La Sapienza,'' Plastic Surgery, A. Conversi, N. Scuderi (27: 0/27)

Rome, Università degli Studi di Roma ''Tor Vergata,'' Reconstructive Surgery, V. Cervelli, D.J. Bottini, B. De Angelis (425: 0/425)

Lithuania

Vilnius, University Children's Hospital, Hematology, Oncology, CIC 508, J. Rascon (3: 2/1)

Netherlands

Amsterdam, University Medical Center VUMC, Orthopedic Surgery, M. Helder (5: 0/5)

Amsterdam, VU Medical Center, Dermatology, S. Gibbs (13: 0/13)

Amsterdam, VU University Medical Center, Pediatric Hematology and Oncology, CIC 588, E. Meijer, G.J. Ossenkoppele (3: 3/0)

Groningen, University Hospital, Hematology, CIC 546, G. van Imhoff (8: 8/0)

Leiden, University Hospital, CIC 203, J.H. Veelken, M. Egeler (63: 13/50)

Utrecht, UMC, Orthopedic Surgery, D. Saris (58: 58/0)

Utrecht, UMCU/WKZ, Pediatrics, CIC 2392, M. Bierings, N.M. Wullffraat (6: 6/0)

Utrecht, University Hospital UMCU, CIC 239, E. Petersen (47: 47/0)

Norway

Oslo, Rikshospitalet-Radiumhospitalet, G. Lauritzen, S. Kvaloy (1: 0/1)

Poland

Bydgoszcz, Nicolaus Copernicus University, Pediatrics, CIC 764, M. Wysocki, J. Styczynski, R. Debski (10: 0/10)

Cracow, University Children's Hospital JUMC, CIC 507, J. Gozdzik (1: 1/0)

Katowice, Regional Blood Center, Tissue Bank Department, A. Wysocka-Wycisk (21: 0/21)

Warsaw, Carolina Medical Center, R. Smigielski, Z. Pojda (2: 0/2)*

Warsaw, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, S. Mazur, Z. Pojda (28: 0/28)*

Wroclaw, University of Medicine, Pediatrics, CIC 817, A. Chybicka, J. Owoc-Lempach (3: 3/0)

Russian Federation

Moscow, Federal Research Center, Pediatric Hematology, CIC 694, A. Maschan, D. Balachov (7: 7/0)

Moscow, Research Hematology Center of RAS, CIC 930, V.G. Savtchenko (21: 21/0)

Moscow, The Russian Children's Research Hospital, CIC 411, E. Skorobogatova (3: 3/0)

Novosibirsk, Research Institute for Clinical Immunology, CIC 376, V. Sergeevuicheva (5: 2/3)

St. Petersburg, Pavlov Medical University, Hematology, CIC 725, B.V. Afanasyev, L. Zubarovskaya (32: 5/27)

St. Petersburg, Research Institute of Hematology, Hematology, K.M. Abdulkadirov (9: 0/9)

Saudi Arabia

Riyadh, King Faisal Specialist Hospital, Hematology, Oncology, CIC 397, M. Al Jurf (1: 0/1)

Slovak Republic

Bratislava, 2nd. Children's Clinic, University Hospital, CIC 684, J. Horàkovà, S. Sufliarska, I. Bodova (1: 1/0)

Slovenia

Ljublijana, Educell d.o.o, N. Kregar-Velikonja (9: 0/9)

Ljublijana, UMC Ljubljana, Cardiology, B. Vrtovec (78: 0/78)

Ljublijana, University Medical Center, Hematology, CIC 640, S. Zver, J. Pretnar (39: 0/39)

South Africa

Cape Town, Constantiaberg Medical Clinic, Hematology, CIC 772, A. Abayomi, M. Du Toit (13: 13/0)

Spain

Barcelona, Institut de Teàpia Regenerativa Tissular, F. Soler, C.M. Teknon (92: 0/92)

Barcelona, University Hospital Dexeus, J. Monllau (7: 7/0)

Cordoba, Hospital Reina Sofia, Hematology, CIC 238, A. Torres-Gomez (30: 0/30)

Granada, Hospital Virgen de la Nieves, Hematology, CIC 559, J.M. De Pablos Gallego, M. Jurado Chacon (2: 2/0)

Madrid, Hospital de la Princesa, Hematology, CIC 236, A. Figuera, A. Alegre (2: 1/1)

Madrid, Hospital General La Paz, CIC 734, R. Arrieta (1: 0/1)

Madrid, Hospital General Universitario Gregorio Marañón, Materno Infantil, Oncology, CIC 410, C. Belendez (1: 0/1)

Madrid, Hospital Universitario Puerta de Hierro, CIC 728, J.R. Cabrera Martin (8: 8/0)

Madrid, Hospital Universitario San Carlos, Hematology, J. Diaz-Mediavilla, L. Llorente, R. Martinez (3: 0/3)

Malaga, Carlos Haya Hospital, Hematology, CIC 576, M. Gonzalez, M. Pascual (13: 13/0)

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Pamplona, Hospital de Navarra, Hematology, CIC 577, E. Olavarria (4: 4/0)

Salamanca, Complejo Hospital, Hematology, CIC 727, D. Caballero (25: 18/7)

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Sweden

Stockholm, Karolinska University Hospital, Huddinge, CIC 212, P. Ljungman, O. Ringden (29: 24/5)

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* = Late report, not included in the analysis and tables

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London, St. Bartholomew's and the Royal London Hospital, CIC 768, J. Gribben, J. Cavenagh, S. Agrawal, T. Lister (19: 19/0)

Manchester, School of Cancer and Enabling Sciences, CT Unit, R. Guest (2: 0/2)

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