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Hematopoietic stem cell transplantation in childhood: report from the bone marrow transplantation group of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP)

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ABSTRACT

Background and Objectives. **Transplantation of hematopoietic stem cells from different sources is being increasingly used to treat a variety of diseases in children. Transplant procedures and indications have changed considerably during recent years. Monitoring of information about these changes is useful for interpretation of nationwide collected data.**

Design and Methods. **Since 1985, Centers belonging to the AIEOP (*Associazione Italiana Ematologia Oncologia Pediatrica*), performing hematopoietic stem cell transplants (HSCT) in children, and members of the AIEOP-Bone Marrow Transplant (BMT) Group annually report data on their transplant activity to the AIEOP-BMT Registry employing specially prepared patient-oriented forms.**

Results. **From January 1985 to December 1998, a total of 2,474 bone marrow (BM), peripheral blood (PB) or umbilical cord blood (CB) transplants were reported: 1,296 (52%) were allogeneic (Allo) and 1,178 (48%) autologous (Auto) transplants. These transplants were performed in 19 Italian Centers on 2,249 patients aged less than 17 years. Among Allo-transplants, 1,198 (92%) were performed using BM progenitor cells, whereas 49 (4%) CB, 42 (3%) were PB, 4 BM plus PB, and 3 BM plus CB allografts; they were performed using HLA-identical sibling donors in 867 cases (67%) and alternative donors (i.e. partially-matched relatives or unrelated donors) in the remaining 429 (33%) cases. Allogeneic transplants were performed on 786 (67%) patients with malignancy and on 395 (33%) patients with non-malignant disorders. In the last 6 years, the number of Allo-transplants per year exceeded that of Auto-transplants. Of the Auto-transplants, 775 (66%) were performed using BM, and 403 (34%) using PB alone or combined with BM hematopoietic stem cells. Indications for Auto-BMT were myelo-lymphoproliferative disorders in 524 (49%) cases, solid tumor in 533 (50%) cases and non-malignant disease in 11 (1%) cases. In the last 5 years, the use of PB for autografts has increased from 7% to 70%.**

Interpretation and Conclusions. **These data reflect the development and present status of HSCT in Italy and provide a basis for patient counseling and health care planning.**
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Key words: hematopoietic stem cell transplantation, childhood cancer, leukemia, cord blood, leukemia, solid tumors, registry

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Hematopoietic stem cell transplantation (HSCT) has become an established therapy for a great number of congenital and acquired disorders of the lymphoid and hematopoietic system, as well as for solid tumors, in children.[1, 2]

Information organized in observational databases and derived from large series of consecutive patients treated in several centers provides a resource for evaluating results of HSCT and offers a complementary approach for addressing issues in this field. In fact, although randomized, controlled clinical trials are the best way to evaluate the efficacy of a given therapy, they are difficult to perform because of the high number of patients that must be accrued to achieve reliable and precise estimates of outcome and because of the cost and logistical difficulties in planning and conducting a prospective randomized study. These difficulties, combined with availability of new technologies for handling information, provided an impetus to explore alternative methods of investigation, such as retrospective analyses performed through information collected and stored in observational databases. Besides deriving data on the efficacy of HSCT in different disorders from these registries, it is also possible to retrieve relevant information for designing phase III trials and for calculating estimates of outcome necessary for definition of sample size.[3,4] Moreover, periodic and systematic assessments of overall results in specific disease are informative and useful for physicians, regional and/or central governmental agencies, and other individuals or organizations involved in health care.[5-8]

This report describes transplant activity for pediatric patients in Italy. Since transplantation of hematopoietic progenitors in our country is rapidly evolving, awareness of variations over time is essential for correct interpretation of current practice of HSCT in Italy. Knowledge of results of HSCT on a national scale also provides a basis for decision making in health care planning and management.

Design and Methods

Activity survey

Since 1985 the *Italian Association for Pediatric Hematology and Oncology* (AIEOP) has been collecting data concerning patients aged less than 18 years transplanted in 19 Centers nationwide. These Centers, all represented in AIEOP and forming the AIEOP-BMT (Bone Marrow Transplant) Group, are listed in the *Appendix*. Participating teams are required to register all consecutive transplants using patient-oriented forms. Many teams (47%) perform both allogeneic and autologous transplants. The percentage of Centres fulfilling the GITMO/EBMT criteria to be accredited for either autologous or allogeneic transplant is 68% and 63%, respectively.

Data quality control

Data are stored in a central database (AIEOP-BMT Registry), organized at the AIEOP Operation Office, which is structurally integrated with other specific, disease-oriented national databases.[9,10] Second transplants for disease relapse and planned double procedures for the same patient are counted, whereas retransplants for graft failure are not. A printout report of collected patient's data is automatically prepared to capture missing information and to verify and validate data stored for each case in the BMT Registry, as well as in 6 otherdisease-specific databases.

Since 1997 the AIEOP-BMT Registry has also transferred data on the activity of each Center to the Registries for autologous and allogeneic transplants of the *Italian Group for Bone Marrow Transplantation* (GITMO). The procedure for transferring data to the GITMO Registries, and through them to the *European Blood and Marrow Transplantation* (EBMT) Registry, involves the extraction of data on newly-registered cases together with an update of previously registered patients. These data are retrieved and coded according to the minimal essential information form established by EBMT (i.e. Med.A form), separately for Allo- and Auto-transplants (Figure 1). The resulting files are transferred, once a year, by electronic network to the GITMO Registries, where they integrate information derived from patients given HSCT in Italian adult transplant Centers. In this process, information correctness and completeness are also controlled. The two GITMO Registries integrate file-hold information with the EBMT Unique Patient Number and send back to the AIEOP BMT Registry also the few pediatric cases transplanted in adult centers. From comparison of information amount in the AIEOP BMT Registry with that recorded by EBMT Med.A and Med.B forms, it can be calculated that over 90% of the information on childhood malignancies are included in this database. In the last two years, transfer of data from the AIEOP BMT Registry to the GITMO Auto- and Allo-Registries has also become crucial for the accreditation process according to EBMT and GITMO criteria necessary for pediatric Centers to perform different kinds of transplant, in particular those from unrelated donors.

A total number of 429 items are stored in the AIEOP BMT Registry, which is administered according to an

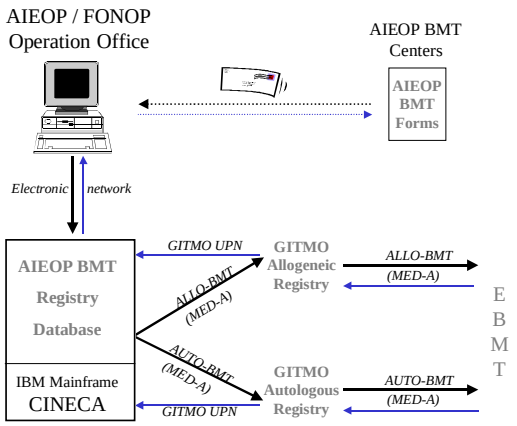

Figure 1. Schema of the data transfer process between AIEOP, GITMO and EBMT registries.

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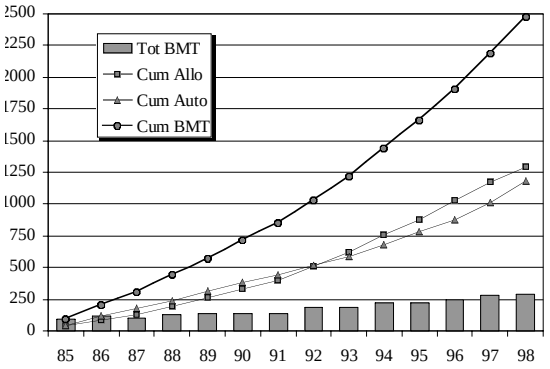

Figure 2. Annual number of transplants. Abbreviations: Tot BMT, total number of transplant per year; Cum Allo, cumulative number of allogeneic transplant; Cum Auto, cumulative number of autologous transplant; Cum BMT, cumulative number of transplant.

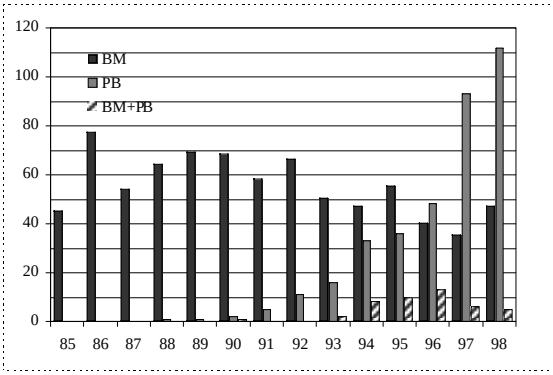

Figure 3. Autologous hematopoietic transplants by stem cell sources. Abbreviations: BM, bone marrow; PB, peripheral blood.

information management system described previously.[4,9,10] Detailed information on peripheral blood (PB) and cord blood (CB) stem cell transplants has been collected since 1990 and 1995, respectively.

Statistical analysis

The average number of transplants performed in each center was calculated excluding years during which activity was suspended for any reason.

Differences in frequency of main indications were calculated for procedure types by the Chi-square test for comparison of proportion.[11]

The relative transplant activity per million inhabitants and thousand children aged 0-17 years was calculated by comparing the number of teams and transplants performed with the number of inhabitants in Italy derived from Italy's National Statistical Institute (ISTAT) data.[12]

Life-table analysis was conducted according to the method of Kaplan and Meier.[13] Survival (SUR), Event-free survival (EFS) and 100-day transplant-related mortality (TRM) for disease, disease status and transplant type were assessed.

For evaluation of EFS, recurrence and death due to any cause, whichever came first, were counted as failure. Death from any cause was considered an event in the calculation of the overall probability of SUR. For calculating TRM, death due to any transplant-related cause occurring in the first 100 days after HSCT was considered as failure. For these analyses, patients were censored at the date of last follow-up if no failure was reported.

Results

Transplant figures

The AIEOP BMT Registry database includes information on 2,584 transplants updated to December 1998. Out of these, 2,474 were performed on 2,249 patients aged less than 18 years at the time of HSCT. A total number of 207 and 18 cases were registered as 2nd and 3rd transplants, respectively. The number of procedures per year has been increasing up to a maximum of 288 in 1998. This represents a two-fold increase over the 135 transplants registered in 1991, and a three-fold increase over the 90 transplants performed in 1985. This increase results from both an increase in the number of new institutions (9 in 1985, 19 in 1998) and a higher number of HSCT performed by established teams (Figure 2). A median number of only 5 (range 1-12) children per year were transplanted in adult Centers.

Children were given either allogeneic (1,296, 52% of the total number of cases) or autologous HSCT (1,178, 48% of the whole population). While in the period between 1986 and 1992 Auto-transplants were the most frequently performed graft, in the most recent years we noted a progressive increase in the number of allografts which, in 1997, represented 52% of the total.

Stem cell source

Among 1,178 autografts, 775 (66%) were performed using bone marrow (BM) progenitors, 358 (30%) PB and 45 (40%) combining BM and PB hematopoietic stem cells. PB stem cell transplants were performed mainly in the last few years; this rapid shift in the source of stem-cells employed is illustrated in Figure 3.

Figure 4 represents the different stem-cell sources employed for allografts. Until 1994, only BM transplants (BMT) were reported. In 1998, 98 (79%) of the allografts were BMT, 13 (10%) were PB and 11 (9%) were CB transplants. In 2 cases, BM plus PB or BM plus CB progenitors were utilized.

A total of 49 allogeneic CB transplants from either related or unrelated donor were reported by 9 centers. These transplants represent 4% of all allografts.

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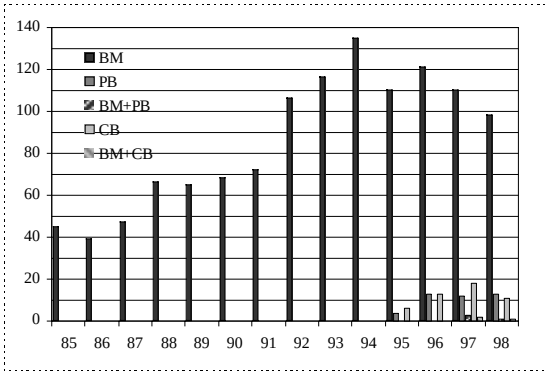

Figure 4. Allogeneic hematopoietic transplants by stem cell sources. Abbreviations: BM, bone marrow; PB, peripheral blood; CB, umbilical cord blood.

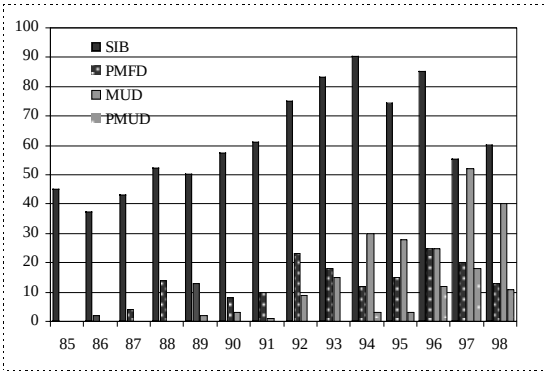

Figure 5. Allogeneic hematopoietic stem cell transplants by donor type. Abbreviations: SIB, sibling donor; PMFD, partially matched family donor; MUD, matched unrelated donor; PMUD, partially matched unrelated donor.

Table 1. Number of procedures by diagnosis according to transplant type.

	Allogeneic		Autologous		Total	
Diagnosis	*# cases*	*%*	*# cases*	*%*	*# cases*	*%*
ALL	485	69.9	208	30.1	693	28
AML	212	47.2	237	52.8	449	18.1
CML	60	95.2	3	4.8	63	2.5
MDS	58	96.7	2	3.3	60	2.4
HD	2	5.9	32	94.1	34	1.4
NHL	39	41.9	54	58.1	93	3.8
Lympho-myelo proliferative disorders						
Total	856	61.5	536	38.5	1392	56.2
CNS	0	0	92	100	92	3.7
NB	8	2.5	318	97.5	326	13.2
ES	2	3	64	97	66	2.7
WT	0	0	35	100	35	1.4
RMS	1	2.2	45	97.8	46	1.9
Other ST	3	3.8	77	96.2	80	3.2
Solid Tumors						
Total	14	2.2	631	97	645	26.1
SAA	68	100	0	0	68	2.7
FA	37	100	0	0	37	1.5
ID	153	96.8	5	3.2	158	6.4
THAL	167	99.4	1	0.6	168	6.8
Other NMD	1	16.7	5	83.3	6	0.3
Non Malignant Disorders						
426	97.5	11	2.5	437	17.7	
Global	1296	52.4	1178	47.6	2474	100

Abbreviations: ALL. Acute Lymphoblastic Leukemia; AML. Acute Myeloblastic Leukemia; CML. Chronic Myelogenous Leukemia; MDS. Myelodysplastic Syndrome; HD. Hodgkin Disease; NHL. Non-Hodgkin Lymphoma; CNS. Central Nervous System Tumors; NB. Neuroblastoma; ES. Ewing Sarcoma; WT. Wilms Tumor; RMS. Rabdomyosarcoma; ST. Solid Tumors; SAA. Severe Aplastic Anemia; FA. Fanconi Anemia; ID. Immunodeficiencies; THAL. Thalassemia; NMD. Non-malignant Diseases.

Donor type

The majority of allografts (67%) were performed from an HLA-identical sibling. However, the growing availability of HLA-typed volunteers in the different Bone Marrow Donor Registries has led to increasing use of matched unrelated donors (MUD), these donors having been employed in 3% of allogeneic BMT in 1989 and in 32% in 1998. Moreover, in the last five years, partially-matched unrelated donors (PMUD) were considered as valid alternatives to partially matched family donors (PMFD) (see also Figure 5). CB transplants from PMUD have also been increasingly used in the last few years.

Main indications for HSCT

Main indications for HSCT, listed in Table 1, were lympho-myeloproliferative disorders (56.2%), followed by solid tumors (26.1%) and non-malignant disorders (17.7%). In particular, leukemia was the main indication for allogeneic transplants, whereas most children receiving an autograft had solid tumors.

Outcome

During the study period, the overall TRM was 12% and showed a trend to decrease. As compared to Auto-transplants, allografts were associated with a relatively higher TRM, mainly due to graft versus-host disease (GVHD), infections, pulmonary and liver toxicity (data not shown). Malignancy, together with advanced disease, was the single most important factor influencing TRM.

Subdivision of results according to the type of donor employed shows that the probability of TRM was 11%, 29%, 38%, and 37% for matched family donor, MUD, non-identical family donor, and PMUD transplant recipients, respectively.

In patients given a transplant of placental blood progenitors, TRM was 11, 16, and 46% for recipients of matched family donor, MUD, and non-identical MUD transplants, respectively.

In patients with acute lymphoblastic leukemia

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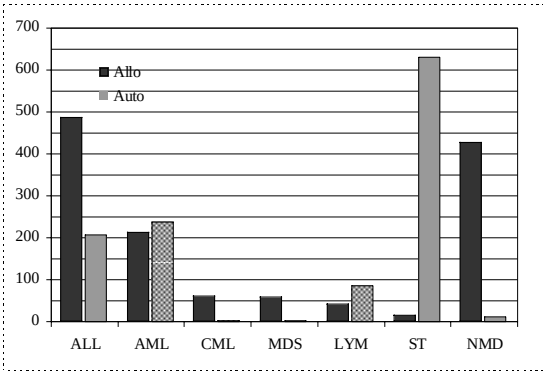

Figure 6. Number of transplants by disease. Abbreviations: Allo, allogeneic; Auto, autologous; ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloblastic Leukemia; CML, Chronic Myelogenous Leukemia; MDS, Myelodisplastic Syndrome; LYM, Lymphomas; ST, Solid Tumors; NMD, Non Malignant Diseases.

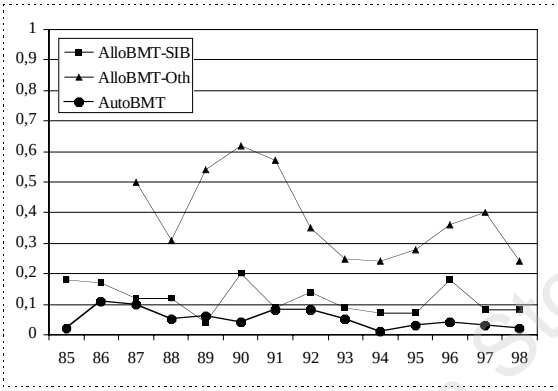

Figure 7. 100-day mortality probability. Abbreviations: AutoBMT, autologous; AlloBMT-SIB, allogeneic-sibling family donor, AlloBMT-Oth, allogeneic-other donors.

(ALL) transplanted using a compatible sibling, TRM probability increased from 9%, when HSCT was performed in 1st–2nd remission, to 18%, when the allograft was given to children with more advanced disease. The same tendency was observed in children with acute myeloid leukemia (AML). AML patients given HSCT from an HLA-identical sibling donor had a TRM of 6%, 9% and 26% when the transplant was performed in 1st or 2nd complete remission or in more advanced disease, respectively.

For autologous transplants, TRM decreased (p<.05) from 11% in 1986 to less then 5% in 1998 (Figure 7) and was not apparently influenced by status of disease at transplantation.

The TRM observed in centers with the greatest activity and which had been performing transplants for a longer tim was not different if compared to that that of centers with less transplant activity.

The AIEOP BMT Registry database also allowed several analyses on survival for different subgroups of patients. Five-year EFS overall by disease, and by disease status and across transplant type are reported for malignancies in Table 2. The same table reports five-year SUR by disease across transplant type for non malignant diseases.

Geographical variations

As shown in Table 3, in Italy, there are relevant differences between regions in terms of facilities and activities. According to WHO indications, the optimal ratio between BMT Centers and inhabitants is considered to be 0.20, (i.e. 1 Center every 5 milion inhabitants).

In 7 regions (Valle d'Aosta, Trentino-Alto Adige, Marche, Molise, Basilicata, Calabria and Sicilia) there is no BMT team, 5 regions (Piemonte, Veneto, Emilia-Romagna, Campania, Puglia) have a ratio between 0.15 and 0.25, whereas 8 (Lombardia, Friuli Venezia Giulia, Liguria, Toscana, Umbria, Lazio, Abruzzi, Sardegna) have a ratio greater than 0.25. A clear discrepancy between the North-Center and South of Italy is seen, with a maximum concentration of BMT teams (74%) in the North-Center. This discrepancy may be explained by several cultural, social and economic factors.

Registry activity

During these 14 years of activity, 3 to 5 people held different roles (Clinical, Statistical, Data Management, and Administrative). The AIEOP BMT Registry has facilitated 29 studies. A total of 86 publications focusing on preparative regimens,[14-19] GVHD prophylaxis and treatment,[20,21] technical aspects,[22-29] complementary approaches,[30,31] and acute[32] or late[33] complications have been prepared by different authors on behalf of the AIEOP BMT Group. Over this same period, the average Impact Factor (IF) of published papers increased gradually from 2,259 in 1989-90 to 4,942 in 1997-98.

Discussion

The present report, the first from the AIEOP-BMT Registry, provides information on transplant number, donor source, donor type, disease type, outcome and geographical variation for childhood HSCT in Italy.

The two particular features of the AIEOP BMT Registry are its being an exclusively pediatric database and the adoption of shared technologies for information handling.[9] Its structure, designed to organize information in a dedicated observational database, specific for pediatric HSCT, provides an important complementary approach to addressing issues in several fields of pediatric hematology and oncology.

One of the aims of this report is to describe the quantitative and qualitative evolution of HSCT in children in our country, where this type of procedure accounts for 12% of all transplants.

The number of transplants performed per year is constantly increasing, due to both the increasing indications for autografts and the growing availability of alternative sources of hematopoietic stem cells (i.e. unrelated donors of BM or CB progenitor cells). As mentioned above, the quality of results shows a positive trend in terms of reduction of TRM, too.

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Table 2. Event-free survival or Survival by diagnosis (a) and by disease status at transplant (b) according to transplant type.

(a)

Dx.	ALLOGENEIC - SIBLING # cases	# events	% 5-yrs EFS	SE	ALLOGENEIC - OTHER DONOR # cases	# events	% 5-yrs EFS	SE	AUTOLOGOUS # cases	# events	% 5-yrs EFS	SE
ALL	310	155	47.0	3.0	145	104	21.1	4.1	207	131	34.7	3.4
AML	145	63	52.3	4.6	27	21	19.0 *	8.4	231	122	43.5	3.5
CML	27	10	60.7	9.9	30	18	24.8	12.1	2	2	-	-
MDS	26	12	51.1	10.4	23	14	33.1 *	10.2	0	-	-	-
HD	2	1	-	-	0	-	-	-	31	14	53.1	9.7
NHL	29	21	31.0	8.6	10	7	-	-	53	26	48.4	8.1
CNS	0	-	-	-	0	-	-	-	76	37	33.8	8.4
NB	7	4	-	-	0	-	-	-	273	167	30.4	3.2
ES	2	2	-	-	0	-	-	-	57	27	44.5	7.5
WT	0	-	-	-	0	-	-	-	34	17	43.5	9.2
RMS	0	-	-	-	0	-	-	-	38	27	23.7	7.5
Other ST	2	0	-	-	1	1	-	-	55	26	40.6	8.0
Diagnosis	# cases	# events	% 5-yrs	SUR SE	# cases	# events	% 5-yrs	SUR SE	# cases	# events	% 5-yrs	SUR SE
SAA	49	13	74.3	6.5	12	9	22.2	12.8	0	-	-	-
FA	20	3	85.0	8.0	13	11	23.1 **	11.7	0	-	-	-
ID	48	6	85.9	5.5	93	43	50.8	5.7	5	0	-	-
THAL	146	32	77.3	3.5	13	1	92.3	7.4	1	1	-	-
Other NMD	0	-	-	-	1	0	-	-	5	1	-	-

(b)

Dx.	Disease status	ALLOGENEIC - SIBLING # cases	# events	% 5-yrs EFS	SE	ALLOGENEIC - OTHER DONOR # cases	# events	% 5-yrs EFS	SE	AUTOLOGOUS # cases	# events	% 5-yrs EFS	SE
ALL	1ST CR	71	24	64.8	5.8	11	10	-	-	20	9	52.6	11.6
	2ND CR	143	61	53.6	4.5	67	41	27.6	7.1	129	74	39.4	4.5
	Other	96	70	24.7	4.6	67	53	16.9	5.3	58	48	20.0	5.3
AML	1ST CR	103	34	63.1	5.3	12	6	48.6 *	14.8	163	78	46.6	4.4
	2ND CR	11	6	41.6	15.6	5	5	-	-	53	32	40.4	6.9
	Other	31	23	16.6	8.8	10	10	-	-	15	12	20.0	10.3
CML	1ST CP	20	7	62.9 *	11.2	14	7	49.6 *	14.8	2	2	-	-
	Other	7	3	57.1 *	18.7	16	11	29.2 *	11.8	0	-	-	-
NB	1ST CR+VGPR	3	0	-	-	0	-	-	-	121	65	37.8	5.1
	Other	4	4	-	-	0	-	-	-	152	102	24.7	3.9

*Abbreviations: EFS, Event-free Survival; SUR, Survival; SE, Standard Error, CR, Complete Remission; VGPR, Very Good Partial Remission; ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloblastic Leukemia; CML, Chronic Myelogenous Leukemia; MDS, Myelodysplastic Syndrome; HD, Hodgkin Disease; NHL, Non-Hodgkin Lymphoma; CNS, Central Nervous System Tumors; NB, Neuroblastoma; ES, Ewing Sarcoma; WT, Wilms Tumor; RMS, Rabdomyosarcoma; ST, Solid Tumors; SAA, Severe Aplastic Anemia; FA, Fanconi Anemia; ID, Immunodeficiencies; THAL, Thalassemia; NMD, Non Malignant Diseases; * = 3-yrs EFS; ** = 3-yrs SUR.*

Table 3. AIEOP-BMT Group data.

	Region	Pop Mil	Pop 0-17Mil	TEAMs NUMBER Tot	Auto	Allo	Auto + Allo	Per Mil	Per Mil 0-17	BMTs NUMBER Total Mean x yr	Total Per Mil 0-17	Allo Mean x yr	Allo Per Mil 0-17	Auto Mean x yr	Auto Per Mil 0-17
NORTH	Piemonte	4.29	0.62	1			1	0.23	1.61	16	25.8	7	11.3	9	14.5
	Lombardia	8.99	1.41	4	1		3	0.44	2.84	64	45.4	40	28.4	24	17.0
	Veneto	4.47	0.72	1			1	0.22	1.39	13	18.1	6	8.3	7	9.8
	Liguria	1.64	0.20	1			1	0.61	5.00	33	165.0	11	55.0	22	110.0
	Friuli V. Giulia	1.18	0.16	1			1	0.85	6.25	10	62.5	6	37.5	4	25.0
	Emilia-Romagna	3.95	0.52	1			1	0.25	1.92	14	26.9	4	7.7	10	19.2
CENTER	Toscana	3.53	0.50	2	1		1	0.57	4.00	17	34.0	3	6.0	14	28.0
	Umbria	0.83	0.13	1			1	1.20	7.69	5	38.5	2	15.4	3	23.1
	Abruzzi	1.28	0.24	1			1	0.78	4.17	12	50.0	11	45.8	1	4.2
	Lazio	5.24	0.91	2	1		1	0.38	2.20	22	24.2	6	6.6	16	17.6
SOUTH	Campania	5.80	1.41	1			1	0.17	0.71	4	2.8	2	1.4	2	1.4
	Puglia	4.09	0.90	1			1	0.24	1.11	3	3.3	0	-	3	3.3
	Sardegna	1.66	0.32	2		2		1.20	6.25	10	31.2	7	21.9	3	9.3
ITALIA		57.56	10.27	19	3	2	14	0.33	1.85	223	21.7	105	10.2	118	11.5

Abbreviations: Auto, autologous; Allo, allogeneic; Pop, population inhabitants; Mil, million; 0-17, age 0-17.

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Recent studies have documented the effectiveness of high-dose therapy followed by autologous stem-cell transplantation,[24,27,34,35] this procedure being increasingly utilized for solid tumors or in children with ALL experiencing an isolated central nervous system relapse. The relative safety of autologous HSCT (especially when performed using PB progenitor cells), with a transplant-related mortality steadily under 5% in the last five years, has led to new indications, such as severe autoimmune disorders.[36,37]

Since 1992, a shift in stem-cell source from BM to PB-derived progenitor cells is evident in autologous and, less markedly, also in allogeneic transplants. The demonstration of an earlier recovery of hematopoiesis is the principal explanation for this phenomenon. More rapid engraftment may result in a reduction of days of antibiotic therapy, total parenteral nutrition, fever, with earlier discharge from the hospital and an associated reduction of costs.[38] Moreover, with the use of PB progenitors as stem cell source not only is the general anesthesia necessary for BM harvest avoided but also the product infused is possibly less contaminated by tumor cells.

BM still remains the main source of stem cells utilized in allogeneic transplants. However, in the last few years, CB and PB progenitor cells, either from a sibling or an unrelated donor, have become valid alternatives, and are usually employed for young children and for patients transplanted from an adult donor, respectively. In particular, PB stem cell allograft have been performed with low frequency in children, mainly due to the ethical concerns related to the possible, still unknown, long-term side effects related to the administration of hematopoietic growth factors to a donor who is still a minor. In the Italian pediatric experience, allogeneic PB stem cells were used mainly for either patients experiencing graft failure and who received a second transplant or for children with an adult donor.[22] The use of CB progenitors from an unrelated donor offers the advantage of reducing the time needed to find a suitable source of hematopoietic progenitors[39-41] and preliminary evidence indicates that unrelated CB transplants can also be performed in the presence of a greater degree of HLA disparity between donor and recipient, as compared to BM transplants. In this regard, it is also noteworthy that in the last few years an increasing number of children have received a BM transplant from a PMUD, this tendency partially compensating the moderate reduction in the use of PMFD.

This analysis also provides information on patient outcome for each different diagnosis and stage of disease separately for each type of transplant. These data show that the vast majority of children given an allogeneic transplant for a non-malignant disease have been cured. Access to information on the five-year EFS probability obtained from data on a large number of patients treated with either *routine* or clinical research protocols is valuable for patient counseling.[42]

Our data confirm the well-known differences between North-Center and South of Italy, partially reflecting differences in organization of health cares and use of economic resources. The two major challenges for the future are to define rules for optimal allocation of resources based on health needs and qualification of available medical care, as well as to set up a system able to provide objective assessment of the performance of Centers.[43,44]

In conclusion, an exhaustive, reliable and updated database represents a useful tool for gathering information on the role of HSCT in children and for providing documented patient counseling. Knowledge of current activity and ongoing trends on a national basis allows establishment of more effective health-care planning, better definition of transplant indications and improvement of the quality of medical research.

Potential implications for clinical practice

AIEOP BMT Registry which represents a unique entity in the world as registry dedicated to transplant in childhood. An exhaustive, reliable and updated database represents a useful tool for gathering information on the role of HSCT in children and for providing documented patient counseling. Knowledge of current activity and ongoing trends on a national base allows establishing more effective health-care planning, better definition of transplant indications and improvement of the quality of medical research.

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AP, RR, AP, FL contributed to the study, data handling and interpretation and wrote the paper. PP, GD, FB, EM, FM, LZ, CU, MR, AU, PDB, CF, LBF, VP, RL, AD, FA, GLN and AA were involved in the recruitment and data handling. GP contributed to epidemiologic aspects of the work. We thank Dr. Piero De Stefano for his revision of the final version of the manuscript, and Mrs. Francesca Losito and Mrs. Barbara Negroni for data handling.

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Disclosures

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