Outcome of patients with acquired aplastic anemia given first line bone marrow transplantation or immunosuppressive treatment in the last decade: a report from the European Group for Blood and Marrow Transplantation

Anna Locasciulli, Rosi Oneto, Andrea Bacigalupo, Gerard Socié, Elisabeth Korthof, Albert Bekassy, Hubert Schrezenmeier, Jakob Passweg, Monika Führer
on the behalf of the Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (SAA-WP, BMT)

From the Severe Aplastic Anemia Working Party of the European Blood and Marrow Transplant Group (SAA-WP, BMT).

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Correspondence:
Anna Locasciulli, M.D., Ematologia e Trapianto di Midollo, Ospedale San Camillo, Circonvallazione Gianicolense 87, 00152 Rome, Italy.
E-mail: alocasciulli@scamilloforlanini.rm.it

ABSTRACT

Background and Objectives

The treatment of acquired aplastic anemia (AA) is based on allogeneic bone marrow transplantation (BMT) and immunosuppressive therapy. The aim of this study was to assess the outcome of children and adults with AA treated in the last decade, and to determine whether results have improved in two sequential time periods: 1991-1996 and 1997-2002.

Design and Methods

We studied 2479 consecutive patients with AA, classified according to first-line treatment, BMT (n=1567) or immunosuppressive therapy (n=912), and stratified according to two sequential time periods. Analyses included variables related to the patients, disease and transplant.

Results

The actuarial 10-year survival was 73% and 68% for patients treated with BMT or immunosuppression, respectively (p=0.002). BMT outcome improved significantly with time (69% and 77%, p=001) for both matched sibling donor (MSD) (74% and 80%; p=0.003) and alternative donor (38% and 65% p=0.0001) transplants, and was better in children (79% versus 68%, p<0.0001). In multivariate analysis favorable predictors (p<0.001) were younger age, transplant after 1996, a MDS, ashort diagnosis-transplant interval, and no irradiation. There was no significant improvement over time for patients receiving immunosuppressive therapy (69% and 73% p=0.29). Survival was significantly better in children (81% versus 70%, p=0.001), especially in those with severe AA (83% versus 62%, p=0.0002). Combined immunosuppression was superior to single drug treatment (77% versus 62%, p=0.002). In multivariate analysis significant predictors of survival following immunosuppressive treatment were age ≥16 years (p=0.0009), longer interval between diagnosis -treatment (p=0.04), and single drug versus combined immunosuppression (p=0.02).

Interpretation and Conclusions

Outcome has improved in subsets of AA patients: those receiving first-line BMT and children with very severe AA treated with immunosuppression. Age remains a major predictor of outcome following both treatments. Early intervention is associated with a significantly better outcome and is strongly recommended, whatever the first-line therapy.

Key words: acquired aplastic anemia, immunosuppression, BMT.

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Acquired aplastic anemia (AA) is a serious hematologic disorder characterized by pancytopenia and bone marrow aplasia or hypoplasia.[1] Bone marrow transplantation (BMT) and immunosuppressive therapy are the main therapeutic modalities currently used to treat both children and adults, with success rates ranging from 60% to 80%.[2-5] The choice between immunosuppression or BMT is largely based on the availability of a sibling donor and on age. In many centers patients over 45-50 years old are not considered for BMT as first-line therapy,[6-9] while there is no age limit for immunosuppressive treatment: the decision of whether to treat older patients is currently based on their performance status.[10] Procedures for transplants from matched sibling donors (MSD) are based on the original Seattle protocol:[11] cyclophopshamide 200 mg/kg, anti-lymphocyte globulin, a high dose of bone marrow cells (>3.5×10^8/kg) and cyclosporine A and methotrexate for graft- versus-host disease (GvHD) prophylaxis.[11,12] The current consensus is that radiation (either total lymphoid or total body) in the conditioning regimen should be discouraged in patients receiving a MSD BMT, due to the high risk of secondary cancer.[13] and long-term sequelae such as infertility and chronic GvHD.[14] Similarly, peripheral blood transplant is discouraged because of the high risk of chronic GvHD.[15] For alternative donor transplants the outcome has been less encouraging, although modified conditioning regimens have recently been proposed.[16]

Antilymphocyte globulin and cyclosporine is now regarded as the standard combination immunosuppressive therapy against which new treatment modalities need to be tested.[17] The addition of granulocyte colony-stimulating factor (G-CSF) has been reported to accelerate neutrophil recovery and improve failure-free survival, but has failed to reduce early mortality or increase response rates and survival.[18-20] A more accurate screening at diagnosis aimed at excluding hypoplastic myelodysplasia with specific chromosomal disorders, such as monosomy 7, may further improve the long term outcome of patients treated with immunosuppressive therapy. Several important issues in the treatment of severe AA are still unsettled. In a previous analysis reporting results in children treated with severe AA in Europe from 1970 to 1988 and evaluated in 1990, we showed that 10-year survival following BMT from an HLA-matched sibling was superior to that following immunosuppression (63% versus 48%, p=0.002). Results in children treated with immunosuppression were dependent on the degree of severity of the AA (actuarial 10-year survival 37% versus 57% in cases with very severe and severe AA respectively; p=0.001) and age (survival: 35%, 63% and 40% in children younger than 5, 5-10 years old and older than 10 years of age, respectively). When stratified for both age and severity, survival was 11% in children under 5 years old with very severe AA versus 43% in older children (p=0.03). Based on these results, we concluded that an early search for an unrelated matched donor was recommended upfront for children younger than 5 years who had very severe disease.[21]

In the present study we analyzed a large series of patients with severe AA treated in Europe between 1991 and 2002 with BMT or immunosuppression as first-line therapy. The aim of this analysis was to test for changes in outcome with time, and for potential predictive variables.

Design and Methods

Design

This retrospective cohort study used data provided by 257 centers from 29 countries reporting to the European Group for Blood and Marrow Transplantation (EBMT) Severe Aplastic Anemia Working Party (SAA-WP) between 1991 and 2002. Collected data included demographic information, pre-treatment blood values, date, type, source and protocols for transplant group and date, type of immunosuppressive therapy, response to therapy, status at latest follow-up, causes of death, and type and date of late complications. Follow-up was completed by December 2004. The analysis of data was then carried out according to first-line therapy (BMT or immunosuppression), time periods of treatment (1991-1996 and 1997-2002), age and other variables related to each treatment.

Patients

A total of 2739 patients with severe AA diagnosed according to current criteria[1] were treated in Europe from 1991 and 2002 and reported to the SAA-WP Registry. Adequate information at the time of treatment was available for 2479 receiving either BMT (n=1567) or immunosuppression (n=912) as first line treatment and this cohort formed the basis for this study (Table 1). The median age of the patients at diagnosis was 23.5 years (range, 1-94 years) and 18.7 years (range, 1-67 years) for those treated with immunosuppression and BMT, respectively; 1479 patients were male and 1105 female, while in 5 cases gender was not specified.

Bone marrow transplantation

A total of 1567 patients with severe AA received allogeneic BMT as first line therapy. The male/female ratio was 1.6 (959 /605). The degree of severity was specified in a minority of cases: 264, 120 and 125 transplanted patients suffered from very severe, severe and moderately severe AA, respectively, while this information was not provided for 1058 patients. The median interval between diagnosis and BMT was 81 days (range, 1-3661) (Table 1). The majority of patients were transplanted with a graft from a matched sibling donor

Table 1. Patient, disease and treatment characteristics of 2479 patients treated in Europe for acquired aplastic anemia between 1991 and 2002.

N. of patients	*Total 2479*
Bone Marrow Transplantation	1567
Sex	
Male	959
Female	605
Interval diagnosis-treatment (days)	81 (1-3661)
Donor type	
HLA identical sibling	1275
Syngenic	29
Matched related	63
Mismatched related	48
Unrelated	149
Conditioning regimen	
Cyclophosphamide	1567
+ ALG	319
+ Irradiation (TBI,TLI,TAI)	282
No conditioning	9
Immunosuppressive Treatment	912
Sex	
Male	520
Female	390
Severity of the aplasia	
very severe AA	317
severe AA	227
moderately severe AA	368
Interval diagnosis-treatment (days)	23 (1-1375)
Treatment	
CSA+ALG	266
ALG+CSA+G-CSF	429
ALG	66
CSA±G-CSF	151

Very severe AA: neutrophils <0.2×10⁹/L; severe AA: neutrophils 0.2-0.5 ×10⁹/L; moderately severe AA: neutrophils >0.5×10⁹/L; ALG: antilymphocyte globulin; TBI: total body irradiation; TLI: total lymphoid irradiation; TAI: thoraco-abdominal irradiation; CSA, cyclosporin A; G-CSF, granulocyte colony-stimulating factor.

(MSD) (1275); 29 had a twin donor, while a transplant from an alternative donor was given as first-line therapy in 260 recipients (Table 1): in these cases no detailed information was provided on the level of HLA matching. The conditioning regimen was based on cyclophosphamide (with or without other drugs) in all cases. while irradiation (total body, total lymphoid or thoraco-abdominal) was included in a minority of patients (Table 1). GvHD prophylaxis consisted mainly of cyclosporine alone (182 patients) or in combination with methotrexate (540 patients). In 845 cases, GvHD prophylaxis was not specified.

Antilymphocyte globulin was included in the conditioning regimen in 319 patients (Table 1). The median follow-up at the time of analysis was 41 months (range 24-155 months) for living patients and 3 months (range 1-96) for those who had died.

Immunosuppressive therapy

A total of 912 patients with severe AA received immunosuppression as first line therapy. The male/female ratio was 1.3 (520/390). Details on the severity of the aplasia were available in all cases: 317 (35%) had very severe aplasia, 227 (25%) suffered from severe AA and 368 (40%) from moderately severe AA. Interestingly, the great majority of children (younger than 16 years) had severe or very severe disease, while adults suffered mostly from a moderate form of AA (p=0.000001). In detail, 176, 83 and 48 children had very severe, severe and moderately severe AA respectively. In the older group, 141 patients had very severe AA, 144 had severe AA and 320 moderately severe aplasia. The median interval between diagnosis and immunosuppressive treatment was 23 days (range, 1-1375) (Table 1). Immunosuppressive therapy mainly consisted on antilymphocyte globulin and cyclosporine (695 out of 912 cases); 429 patients also received G-CSF as part of the immunosuppressive protocol (Table 1). The median follow-up at the time of analysis was 54.5 months (range, 14-144) for those alive and 12 months (range, 0.5-91) for those who had died.

Statistical analysis

The Student's T and Mann Whitney tests were used for continuous variables, the χ^2 test for 2×2 tables and the log-rank test for time-dependent variables. Kaplan Meier curves were used for the analysis of actuarial survival. The number cruncher software (NCSS, version 5.0; JL Hintze, Kaysville, UT, USA) was used to perform the analyses.

Results

The overall outcome of the 2479 patients with severe AA, divided according to their first line treatment, is shown in Figure 1: 10-year survival was significantly superior in patients treated with BMT than in those in whom immunosuppression was used (73% versus 68%, p=0.002).

Bone marrow transplantation: univariate analysis

Figure 2 shows survival curves in patients treated with BMT in the two sequential time periods, 1991-1996 and 1997-2002: results have improved significantly over time (69% versus 77%, p=0.001), and this was true for transplants from both for MSD and alternative donors. Indeed, survival in patients receiving a graft from a MSD was 74% during 1991-1996 and 80% from 1997-2002 (p=0.03) while the corresponding figures for

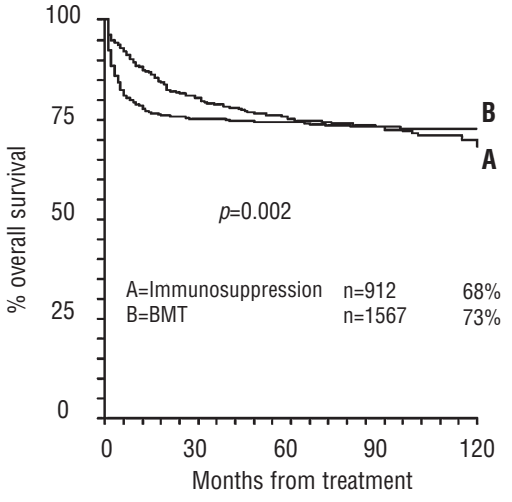

Figure 1. Actuarial survival of 2479 patients with acquired severe aplastic anemia according to whether their first-line treatment was BMT or immunosuppression: the 10-year survival is 73% in BMT recipients and 68% in those treated with immunosuppression (p=0.002).

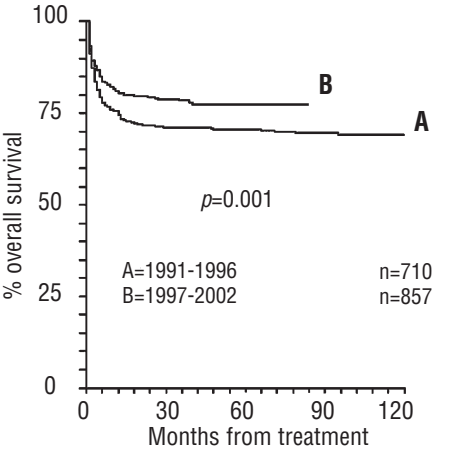

Figure 2. Actuarial survival of patients treated with BMT in two sequential time periods: 1991-1996 and 1997-2002: results have improved significantly over time (69% versus 77%, p=0.001).

alternative donor transplants were 38% and 65% (p=0.0001, Figures 3A and 3B) . According to age-groups (1-15, 16-30 and ≥31 years) crude survival rates were 82%, 81% and 63% respectively. Survival in children (<16 years) was significantly better than in adults (79% versus 68%, p>0.0001, Figure 4). Current survival in MSD transplants is 91% for children and 74% for adults. For transplants from an alternative donor, the survival rate is 75% in children and 63% in adults.

The addition of antithymocyte globulin, given to 319 /1567 patients (20%) as part of the conditioning regimen, produced a non-significant improvement of survival: 81% versus 73% in MSD transplants (p= 0.06) and 66% versus 52% in transplants from alternative donors (p=0.32).

In patients receiving marrow from an HLA identical sibling, the type of GVHD prophylaxis (cyclosporine A alone or in combination with methotrexate) did not affec survival in either children or older patients (<16 years: 81% and 83%, p=0.96; ≥16 years : 67% and 67%, p=0.56 respectively).

The use of irradiation in the conditioning regimen has become less frequent with time. Total body, total lymphoid or thoracoabdominal irradiation was given to 24% of patients undergoing a MSD transplant before 1996 and to 8% after (p<0.0001). The same was seen for transplants from an alternative donor, although to a lesser degree (65% versus 30%, p=0.001).The 10-year survival was significantly inferior in patients receiving irradiation in both age-groups : 62% versus 83% in children (p<0.001) and 56% versus 71% in adults (p<0.001).

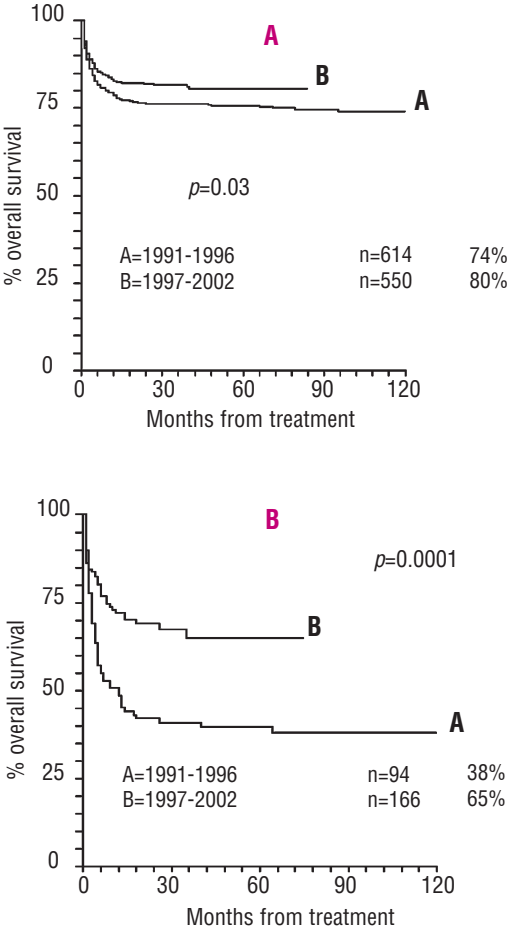

Figure 3. Actuarial survival of patients undergoing BMT from HLA identical siblings (3A) or from alternative donors (3B) according to time periods (1991-1996 and 1997-2002): results have improved significantly over time for patients transplanted from both MSD (74% versus 80%, p=0.03) and alternative donors (38% versus 65%, p=0.0001).

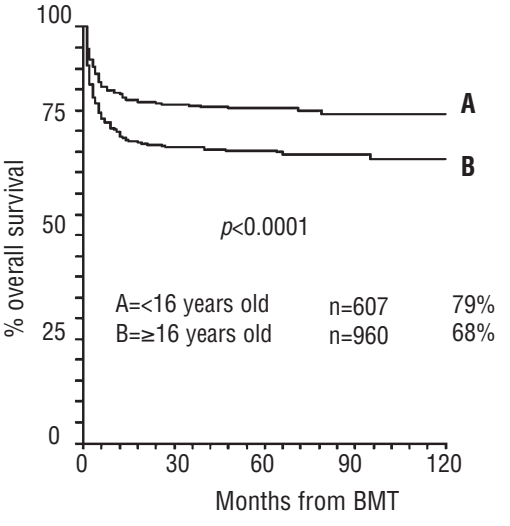

Figure 4. Actuarial survival in patients undergoing BMT, according to age (<16 years and ≥16 years): the outcome is significantly better in children (79%) than in adults (68%, $p<0.0001$).

Bone marrow transplantation: multivariate analysis

In multivariate analysis year of transplant, donor type, patient's age, interval between diagnosis and transplantation and the use of radiation were all independent predictors of survival. Favorable predictors were younger age (p=0.00001), transplant after 1996 (p=0.001), an HLA identical donor (p=0.00001), a short interval between diagnosis and BMT (p=0.00006) and no radiation in the conditioning regimen (p=0.001) (Table 2). We also ran a multivariate analysis on patients stratified according to type of donor (MSD and alternative donor): among patients receiving a graft from an alternative donor, the only significant predictor was year of transplant (p=0.001, RR=-0.74), while among those transplanted from a MSD, other significant variables besides transplant year (p=0.09, RR=0.77) were younger age (p=0.0001, RR=2) and interval between diagnosis and transplantation (p=0.0001, RR=1.91).

Immunosuppression: univariate analysis

Figure 5 shows survival curves in all patients treated with immunosuppression in the two sequential time periods 1991-1996 and 1997-2002: results were comparable over time (69% versus 73%, p=0.29) with no significant improvement in the last decade. However, there were differences when patients were stratified for degree of severity of their underlying disease: the actuarial 10-year survival in 1991-1996 and 1997-2002 was 69% versus 73% (p=0.2) for patients with very severe AA, 77% and 77% for patients with severe AA (p=0.1), and 70% versus 56% (p=0.01) for patients with moderately severe AA. The interval between diagnosis and immunosuppressive treatment was comparable in the two time periods for very severe and severe AA, but was significantly longer in the most recent era for patients with moderately severe AA (57 vs 102 days, p=0.04).

When age groups were considered, overall survival was 81% in children (<16 years old) and 70% in adults (≥16 years old) (p=0.001). The difference in overall survival was highly significant in patients with very severe aplasia (83% vs 62%, p=0.0002) (Figure 6A) but not so in patients with neutrophil counts >0.2×10^9/L (74% vs 61%, p=0.2) (Figure 6B). The survival of patients treated with the combination of antilymphocyte globulin plus cyclosporine A was 77%, compared to 62% for those receiving either antilymphocyte globulin or cyclosporine A alone (p=0.002). G-CSF was given to a large

Table 2. Multivariate analysis.

	Bone marrow transplantation	
	p	*RR*
Year of transplant (1991-1996/1997-2005)	0.001	0.69
Age (<16 years/≥ 16 years)	0.0001	1.66
Interval diagnosis-transplant (<median/>median)	0.0006	1.56
Donor type (MSD/alternative donor)	0.0001	1.97
Radiation (no/yes)	0.001	1.47
	Immunosuppressive therapy	
	p	*RR*
Year of treatment (1991-1996/1997-2002)	0.07	1.32
Age (<16 years/≥ 16 years)	0.0009	1.76
Interval diagnosis-treatment (<median/>median)	0.04	1.32
Severity of AA (very severe/other)	0.4	0.9
ALG+CsA (no/yes)	0,02	0.69
G-CSF (no/yes)	0.9	1.04

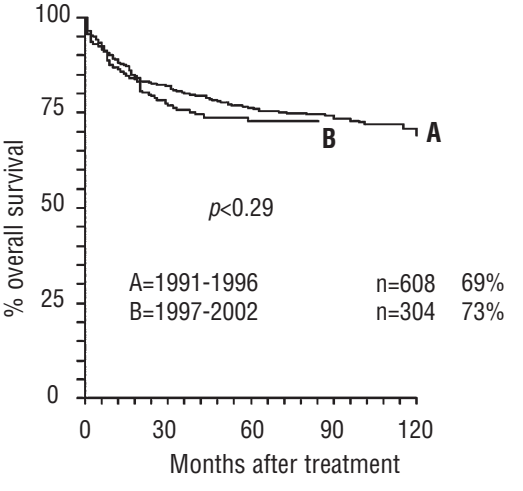

Figure 5. Survival curves in all patients treated with immunosuppression in the two sequential time periods 1991-1996 and 1997-2002: results are comparable over time (69% versus 73%; p=0.29).

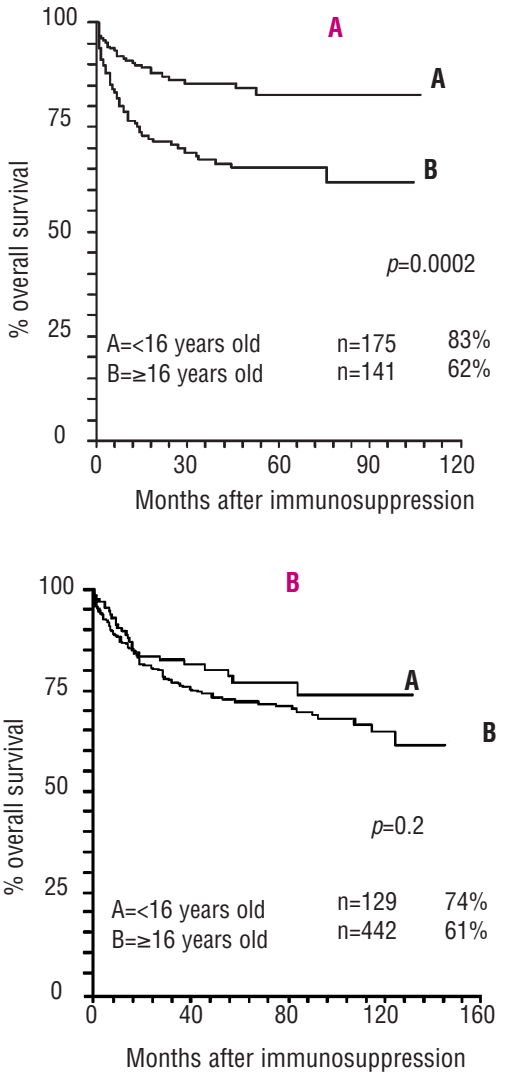

Figure 6. Actuarial survival in children and adults, according to the severity of the disease. Among patients with very severe AA, (Figure 6A) the outcome was significantly better in children than in adults (83% versus 62%; p=0.0002). In contrast, among patients with less severe aplasia (neutrophils >0.2×10^9/dL) results were similar (74% and 61%, p=0.2) (Figure 6B).

proportion of patients with very severe AA (80%), to 64% of patients with severe AA and to 30% of patients with moderately severe AA (p=0.00001).

Immunosuppression: multivariate analysis

In multivariate analysis age (≥16 years) was a highly significant risk factor (p=0.0009, RR 1.76), followed by a longer interval between diagnosis and treatment (p=0.04, RR=1.76) (Table 2). Combined immunosuppression including antilymphocyte globulin and cyclosporine A offered a significant advantage over the use of either agent alone (p=0.02, RR=0.69), while year of treatment, degree of severity of the underlying disease and the use of G-CSF were not predictive of the outcome.

Table 3. Causes of death in patients treated with BMT or immunosuppression, according to age group.

Age group	*<16 years*		*≥16 years*	
BMT: n. patients	607		960	
n. of dead patients (%)	110	18.1%	261	27.2 %
Causes of death:				
Infection	45	7.4%	107	11.1%
Lymphoproliferative disease	1	0.2%	1	0.1%
Multiorgan failure	0	0%	4	0.4%
Toxicity	1	0.2%	3	0.3%
Hemorrhage	5	0.8%	18	1.9%
Rejection	15	2.5%	30	3.1%
GvHD	13	2.1%	29	3.0
Late relapse/rejection	2	0.3%	9	0.9%
Secondary malignancy	1	0.2%	1	0.1%
Other and unknown	27	4.4%	59	6.1%
Immunosuppression: n. patients	307		605	
n. dead pts (%)	53	17.3%	175	28.9%
Causes of death:				
Infection	17	5.5%	50	8.3%
Hemorrhage	8	2.6.%	28	4.6%
Relapse	1	0.3%	5	0.8%
Secondary malignancy	0	0.%	7	1.2%
Transplant-related (after failed immunosuppression)				
Lymphoproliferative disease	1	0.3%	1	0.2%
Multiorgan failure	1	0.3%	0	0%
Toxicity	1	0.3%	2	0.3%
Rejection	4	1.3%	4	0.7%
GvHD	2	0.7%	6	1.0%
Other and unknown	18	5.9%	72	11.9%

Causes of death

Causes of death are outlined in Table 3. Infection was the single major cause of death, both in patients treated with BMT or immunosuppressive: infections were more frequent in adults than in children accounting for the higher mortality rate in the former (Table 3). Other causes of death were GvHD following transplants and hemorrhage following immunosuppression. Second malignancies were seen, especially in adults given immunosuppressive therapy. The group of patients treated with immunosuppression also included patients who died of transplant-related complications following transplants given after immunosuppression had failed although these accounted for less than 3% of the total patients.

Transplantation after failed immunosuppression

The proportion of patients receiving a transplant after failed immunosuppression was 13% and 17% of patients with very severe AA, before and after 1996, respectively (p=0.3), and 18% and 36% of patients with less severe aplasia before and after 1996, respectively (p<0.0001).

Discussion

This study shows that: (i) outcome has improved in subsets of AA patients, (ii) age remains a major predictor of outcome for both BMT and immunosuppressive treatment, and (iii) early intervention is associated with a significantly superior outcome.

As regards the first point, the improvement in outcome over time was seen in BMT patients overall in both univariate and multivariate analyses. Interestingly, improved survival was seen both in patients grafted from a MSD (from 74% to 80%) and those with an alternative donor (from 38% to 65%) suggesting that better supportive care and improved management of infections can still have an impact in a proportion of patients. In a multivariate analysis, run separately according to type of donor, the year of transplant proved to be the only favorable factor for BMT from unrelated donors, (p=0.001), possibly due to better matching and HLA typing, together with less toxic conditioning regimens.[16] In contrast, for patients treated with immunosuppression there was no overall improvement with time: survival was slightly increased in patients with very severe AA, was comparable those with in severe AA, and was significantly worse in the most recent time period for those with moderately AA. This suggests that, overall, immunosuppressive therapy has not improved to the same degree as BMT: reasons for this could be that Iimmunosuppressive regimens have not changed over time, and our ability to treat the disease itself has not, therefore, improved. In mitigation of this negative result, we mention that actuarial survival of children with severe AA treated in the decade 1991-2002 (83%) is significantly better, than that of children with very severe AA (37%) treated before 1990 (37%).[21] The message is that while improvements have not been seen with immunosuppression in the 1990s, we are doing better than in the 1980s. As to the second point, we found a strong effect of age of outcome, confirming the results of numerous previous studies:[12,20,21,22,23,24,25] this effect was present in patients treated with transplantation (79% survival in children versus 68% in adults) as well as for those receiving immunosuppressive therapy (81% vs 70%), and could be demonstrated in univariate and multivariate analyses. The explanation of the different outcome in children and adults is relatively straightforward for BMT: children tolerate the conditioning regimen, associated toxicity, and GvHD better graft and have faster immune reconstitution, possibly also as a consequence of having younger donors. Indeed, children had a lower rate of deaths caused by GvHD, infections and multiple toxicities. Survival of children undergoing a sibling BMT currently exceeds 90%, and this makes marrow transplantation mandatory in young patients with an HLA-identical sibling. Age also has a strong impact in patients receiving first line immunosuppression, with the survival rate being 80% in children and 70% in adults. This effect of age is particularly marked in patients with very severe AA since the survival rate exceeds 80% among children but is about 60% in adults. Similar outcomes were recently reported in two large cooperative pediatric studies by Kojima and Fuhrer.[25,20] Also among patients treated with immunosuppression, we found that infectious deaths, together with hemorrhages and other toxicities, were more frequent in adults. Furthermore, the adult group had a higher rate of second tumors. Age therefore remains a major predictor of outcome after both BMT and immunosuppression. One of the main problems in adults with AA is infection, which may be addressed by the advent of the new potent antifungal and anti-bacterial agents. It will be interesting to see whether there will be an improvement in the outcome of adults with AA in the next 5 years, as a consequence of new anti-infective agents.

The third message of this study is *the sooner the better*: the interval between diagnosis and treatment proved to be a highly significant predictor of outcome following both BMT and immunosuppression, with survival being better for patients treated early. It is interesting to note that the decreased survival for patients with non-severe AA treated with immunosuppression was associated with delayed treatment in the most recent years. We believe that this is an important message for the general practitioner who sees the patient first, as well as for the hematologist: AA is a rare, potentially fatal hematologic disorder, which requires immediate intervention, preferably in a center with experience in the treatment of marrow failure.

Additional treatment variables were irradiation: given as part of the conditioning regimen, irradiation was a negative predictor of survival in both sibling and unrelated donor transplants, in keeping with results from previous studies[5,22] which showed significantly more late events, such as second tumors, in irradiated patients.[14] Accordingly, we strongly discourage the use of irradiation in the conditioning regimen for patients with severe AA undergoing an HLA identical sibling transplant. For alternative donor transplants very small doses of radiation (2 Gy) are being tested, and should be investigated in clinical trials, as already done in Japan and the USA.[26–28] For patients receiving immunosuppressive treatment, combination regimens (antilymphocyte globulin and cyclosporine A) proved superior to the single drug regimens. In a multivariate analysis on all 2479 patients, year of treatment, age and the interval between diagnosis and treatment were the three significant predictors of outcome.

This study confirms the excellent results obtained in Europe in AA patients treated with BMT or immunosuppression. The outcome after BMT has improved

greatly, especially in cases of grafts from alternative donors and in young patients. Results with immunosuppression with antilymphocyte globulin and cyclosporine A are so good that this immunosuppressive regimen must be considered the standard protocol in children and adults. The role of G-CSF still needs to be assessed prospectively. Age remains a major predictor of outcome, as does early intervention, which should be recommended in all patients, whatever their first line therapy, given the very strong effect of the interval between diagnosis and treatment on survival.

Author Contributions

AL, AB, JP and MF gave substantial contributions to the conception and design of the study, analysis and interpretation of data, drafting the article and final approval of the version to be published; RO gave fundamental contributions to analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published; GS, EK, AB, HS contributed to the conception and design design of the study, critically revised the manuscript for important intellectual content and gave final approval of the version to be published.

Conflict of Interest

The authors reported no potential conflicts of interest.

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