Subject: HAEMATOL/2009/007583 – Unrelated donor stem cell transplantation…; supplementary appendix

Table S1. Multi-source search strategy

| Categories | Sources |
|---|---|
| Bibliographic databases* | MEDLINE via Ovid |
| | The Cochrane Library via Wiley InterScience |
| | EMBASE via Ovid |
| | PubMed Clinical Queries |
| Congress proceedings | Annual Meetings 2003, 2004 and 2005: ASH American Society of Hematology; Washington, District of Columbia, United States |
| | Annual Meetings 2004, 2005, 2006: EBMT European Group for Bone and Marrow Transplantation; London, United Kingdom |
| Online trials registers | ClinicalTrials.gov. National Institutes of Health, Bethesda, Maryland, United States |
| | National Research Register, Department of Health, London, United Kingdom |
| | Current Controlled Trials Ltd; London, United Kingdom |
| Institutions | AA & MDSIF Aplastic Anemia & Myelodysplastic Syndrome International Foundation; Annapolis, Maryland, United States |
| | AAMAC Aplastic Anemia and Myelodysplasia Association of Canada; Richmond Hill, Ontario, Canada |
| | Aplastic Anaemia Trust, St. George's Hospital Medical School; London, United Kingdom |
| | Catholic University of Korea; Seoul, South Korea |
| | Children's Hospital of Philadelphia; Philadelphia, Pennsylvania, United States |
| | Children's Memorial Hospital; Chicago, Illinois, United States |
| | CIBMTR Center for International Blood and Marrow Transplant Research; Milwaukee, Wisconsin, United States |
| | Columbus Children's Hospital; Columbus, Ohio, United States |
| | DKMS Deutsche Knochenmarkspenderdatei; Tübingen, Germany |
| | EBMT-AAWP European Group for Blood and Marrow Transplantation Aplastic Anaemia Working Party; London, United Kingdom |
| | Dr. von Haunersches Kinderspital; München, Germany |
| | Fred Hutchinson Cancer Research Center; Seattle, Washington, United States |
| | Great Ormond Street Hospital for Sick Children; London, United Kingdom |
| | Hadassah Medical Organization; Jerusalem, Israel |

HAS Haute Autorité de Santé; Paris, France
Hopital Saint Louis Groupement Hospitalier Universitaire Nord; Paris, France
Hopitaux Universitaires de Geneve; Geneve, Switzerland
Hospital for Sick Children; Toronto, Ontario, Canada
Karolinska University Hospital, Huddinge; Stockholm, Sweden
Kinderklinik München Schwabing; München, Germany
Medical College of Wisconsin; Milwaukee, Wisconsin, United States
Medizinische Universitätsklinik; Ulm, Germany
Nagoya University Graduate School of Medicine; Nagoya, Japan
NHLBI National Heart, Lung, and Blood Institute; Bethesda, Maryland, United States
Ospedale S. Camillo-Forlanini; Rome, Italy
Ospedale San Martino; Genova, Italy
Princess Margaret Hospital; Toronto, Ontario, Canada
Sidney Children's Hospital; Randwick, New South Wales, Australia
St. George's University of London; London, United Kingdom
St. Jude Children's Research Hospital; Memphis, Tennessee, United States
Universitäts-Kinderklinik; Tübingen, Germany
Universitätsspital Basel; Basel, Switzerland
University of California at Los Angeles's Jonsson Comprehensive Cancer Center; Los Angeles, California, United States
WMDA World Marrow Donor Association; Leiden, Netherlands

*Executed on 21 April 2006 and last update on 19 November 2008

Table S2. Search strategy applied in MEDLINE/Ovid

| N | Searches |
|---|---|
| 1 | exp ANEMIA, APLASTIC/ |
| 2 | (aplast$ anem$ or aplast$ anaem$).tw,kf,ot. |
| 3 | or/1-2 |
| 4 | exp STEM CELL TRANSPLANTATION/ |
| 5 | exp BONE MARROW TRANSPLANTATION/ |
| 6 | exp TRANSPLANTATION, HOMOLOGOUS/ |
| 7 | transplant$.tw,kf,ot. |
| 8 | graft$.tw,kf,ot. |
| 9 | (allograft$ or allo-graft$).tw,kf,ot. |
| 10 | (homograft$ or homo-graft$).tw,kf,ot. |
| 11 | or/4-10 |
| 12 | RANDOMIZED CONTROLLED TRIALS AS TOPIC.sh. |
| 13 | RANDOMIZED CONTROLLED TRIAL.pt. |
| 14 | random$.tw,kf,ot. |
| 15 | CONTROLLED CLINICAL TRIAL.pt. |
| 16 | RANDOM ALLOCATION.sh. |
| 17 | DOUBLE BLIND METHOD.sh. |
| 18 | SINGLE BLIND METHOD.sh. |
| 19 | (ANIMALS not HUMANS).sh. |
| 20 | exp CLINICAL TRIALS AS TOPIC/ |
| 21 | CLINICAL TRIAL.pt. |
| 22 | (clin$ adj25 trial$).tw,kf,ot. |
| 23 | ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw,kf,ot. |
| 24 | PLACEBOS.sh. |
| 25 | placebo$.tw,kf,ot. |
| 26 | RESEARCH DESIGN.sh. |
| 27 | COMPARATIVE STUDY.pt. |
| 28 | exp EVALUATION STUDIES AS TOPIC/ |
| 29 | FOLLOW-UP STUDIES.sh. |
| 30 | PROSPECTIVE STUDIES.sh. |
| 31 | (control$ or prospectiv$ or volunteer$).tw,kf,ot. |

32 (metaanaly$ or (meta and analy$) or ((review or search$) and (medical database$ or medline or pubmed or embase or cochrane or systemat$))).tw,kf,ot.
33 META-ANALYSIS AS TOPIC.sh.
34 META-ANALYSIS.pt.
35 exp REGISTRIES/
36 (registr$ or register$ or ibmtr$ or ebmt$).tw,kf,ot.
37 ((group or regist$) and (blood or stem cell or marrow) and transplant$ and (europ$ or international)).tw,kf,ot.
38 or/12-37
39 (ANIMALS not HUMANS).sh.
40 and/3,11,38
41 40 not 39

Table S3. Study characteristics

| Study | Design | Research question | Diagnostic inclusion / exclusion | Number of centers / country | Observation period (years) |
|---|---|---|---|---|---|
| Bacigalupo 2005 [15] | Prospective case series | Impact of radiation-free pretransplantation conditioning on survival of patients with SAA treated with stem cell transplants from unrelated or family mismatched donors and who had failed pretransplantation IST | | 13 / Europe | 1998 – 2004 |
| Bunin 2005 [16] | Prospective case series | Survival of patients transplanted for SAA with unrelated donors who have been treated with partial T-cell depletion and who had failed pretransplantation IST | Shwachman-Diamond-Syndrome included (1 patient) | 1 / United States | 1992 – 2003 |
| Deeg 1999 [17] | Retrospective case series | Survival of patients transplanted for SAA with unrelated donors and who had failed pretransplantation IST | Fanconi anemia excluded | 36 / United States | 1988 – 1995 |
| Deeg 2006 [20] | Prospective case series | Impact of deescalating doses of total body irradiation to use for pretransplantation conditioning on survival of patients with SAA treated with stem cell transplants from unrelated donors and who had failed pretransplantation IST | Fanconi anemia excluded | 17 / United States, United Kingdom, Germany | 1994 – 2004 |
| Hows 1992 [21] | Retrospective case series | Survival of patients transplanted for SAA with unrelated donors and where most of the recipients had failed pretransplantation IST | Acquired versus constitutional SAA not differentiated | 5 / United States, United Kingdom, France | 1981 – 1990 |
| Inamoto 2008 [22] | Retrospective case series | Impact of a conditioning regimen with total lymphoid irradiation pretransplantation conditioning on survival of patients with SAA treated with stem cell transplants from unrelated or family mismatched donors (in a subgroup) | Moderate form of aplastic anemia may be included; the exact number was indicated only for the whole study population | 1 / Japan | 1984 – 2006 |
| Kennedy-Nasser 2006 [23] | Retrospective case series and consecutive patients | To compare the survival of matched sibling donor recipients with the survival of unrelated or family mismatched donor recipients of stem cell transplants for SAA where all but one of the unrelated or family mismatched donors recipients had failed pretransplantation IST | Fanconi anemia excluded | 1 / United States | 1997 – 2005 |
| Kim 2007 [24] | Prospective case series | Impact of deescalating doses of total body irradiation to use for pretransplantation conditioning on survival of patients with SAA treated with stem cell transplants from unrelated donors and who have not received IST or had failed pretransplantation IST | | 1 / Korea | 1998 – 2006 |
| Kojima 2002 [25] | Retrospective case series and consecu- | Impact of high-resolution genotyping on survival of patients with SAA treated with stem cell transplants from unrelated donors and who had failed IST | | 68 / Japan | 1993 – 2000 |

| | | | | | |
|---|---|---|---|---|---|
| | tive patients | | | | |
| Kosaka 2008 [26] | Prospective controlled clinical trial | To compare the survival of unrelated or family mismatched donor recipients of stem cell transplants with the survival of IST after failed first-line IST for SAA | Congenital forms of SAA excluded | 79 / Japan | 1997 – 2004 |
| Margolis 1996 [27] | Retrospective case series and consecutive patients | Survival of patients transplanted for SAA with unrelated donors and who had failed pretransplantation IST | Congenital amegakaryocytic thrombocytopenia included (1 patient); paroxysmal nocturnal hemoglobinuria included (1 patient); Fanconi anemia excluded | 1 / United States | 1986 – 1994 |
| Maury 2007 [11] | Retrospective case series | Impact of high-resolution genotyping on survival of patients with SAA treated with stem cell transplants from unrelated donors and who had failed pretransplantation IST | Paroxysmal nocturnal hemoglobinuria included (12 patients); congenital forms of SAA excluded | 25 / France | 1989 – 2004 |
| Passweg 2006 [10] | Retrospective case series | Survival of patients transplanted for SAA with donors other than HLA-identical siblings | | 112 worldwide (29 countries) | 1988 – 1998 |
| Perez-Albuerne 2008 [28] | Retrospective case series | Survival of children less than 21 years of age transplanted for SAA with unrelated donors<br>Sixty-one patients (31%) in this report were included in a previously published analysis (Deeg 1999) of 141 patients undergoing unrelated donor transplantation for SAA | Fanconi anemia excluded; other known congenital bone marrow failure syndrome excluded | Multiple / United States | 1989 – 2003 |
| Svenberg 2004 [29] | Retrospective case series | Survival of patients transplanted for SAA with matched unrelated donors and who had failed pretransplantation IST | Fanconi anemia included (1 patient) | 1 / Sweden | 1993 – 2003 |
| Viollier 2008 [30] | Retrospective case series | Survival of patients transplanted for SAA with unrelated donors and without precise information on the proportion of patients failing pretransplantation IST | | 142 / Europe | 1990 – 2005 |
| Yagasaki 2007 [31] | Retrospective case series | Survival of patients transplanted for SAA with mismatched unrelated donors and who had failed pretransplantation IST | | 1 / Japan | 2002 – 2006 |
| Yoshimi 2008 [32] | Retrospective case series | Survival of patients transplanted for SAA with unrelated cord blood | | Multiple / Japan | 1998 – 2006 |

HLA: human leukocyte antigen; IST immunosuppressive therapy; SAA: severe aplastic anemia

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Table S4. Patients' characteristics

| Study | Subgroup | N of evaluable patients[*] | Age of patients Median; range (years) | Gender of patients (male : female) | N of patients with pretransplant IST[†] (failed / recipients) | N of pretransplant IST courses | Interval from diagnosis to transplant Median; range (months) |
|---|---|---|---|---|---|---|---|
| Bacigalupo 2005 [15] | – | 38 | 14 (3-37) | 19 : 19 | 38 / 38 | – | 20 (1-100) |
| Bunin 2005 [16] | – | 12[‡] | 9[§] (1-20) | 5 : 7 | 12 / 12 | – | 16 (5-36) |
| Deeg 1999 [17] | – | 141 | 17 (1-47) | 82 : 59 | 141 / 141 | – | 13 (3-162) |
| Deeg 2006 [20] | < 20 years of age (Deeg 2006a) | 33 | –[‖] | –[‖] | 33 / 33 | –[‖] | –[‖] |
| | >= 20 years of age (Deeg 2006b) | 22 | –[‖] | –[‖] | 22 / 22 | –[‖] | –[‖] |
| Hows 1992 [21] | – | 40 | 19 (1-41) | 30 : 10 | "most" | – | 13 (2-157) |
| Inamoto 2008 [22] | – | 16 | – | – | unclear | – | 168 (11-336) |
| Kennedy-Nasser 2006 [23] | – | 22[¶] | 11 (1-18) | 11 : 11 | 22 / 22 | – | 6 (–) |
| Kim 2007 [24]8 | 800 cGy TBI (Kim 2007a) | 26 | –[**] | –[**] | 26 / 26 | –[**] | –[**] |
| | 1000-1200 cGy TBI (Kim 2007b) | 14 | –[**] | –[**] | 14 / 14 | –[**] | –[**] |
| Kojima 2002 [25] | – | 154 | 17 (1-46) | 86 : 68 | "most" | – | –[††] |
| Kosaka 2008 [26] | – | 31 | 8 (0-17) | 14 : 17 | 31 / 31 | 0 : 31 : 0[‡‡] | 8 (5-20) |
| Margolis 1996 [27] | – | 28[‡] | 8 (0-24) | 17 : 11 | 27 / 27 | – | 14 (4-84) |
| Maury 2007 [11] | – | 89[‡] | 17 (0-52) | – | 73 / 73 | – | 13 (2-145) |
| Passweg 2006 [10] | matched unre-lated donor (Passweg 2006a) | 181 | 16 (1-55) | 96 : 85 | unclear | – | 13 (2-245) |
| | mismatched unre-lated donor (Passweg 2006b) | 51 | 10 (2-44) | 35 : 16 | unclear | – | 11 (4-124) |
| Perez-Albuerne 2008 [28] | – | 195 | – | 109 : 86 | unclear | – | 13 (–) |
| Svenberg 2004 [29] | – | 12[‡] | 15 (1-39) | 6 : 6 | 12 / 12 | – | – |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Viollier 2008a [30] | before 1998 (Viollier 2008a) | 149 | 16 (1-48) | 89 : 60 | "majority" | – | 14 (3-167) |
| | after and in 1998 (Viollier 2008b) | 349 | 18 (1-65) | 202 : 147 | "majority" | – | 16 (2-209) |
| Yagasaki 2007 [31] | – | 11 | 11 (3-20) | 7 : 4 | 100% | – | 76 (12-136) |
| Yoshimi 2008 [32] | – | 31 | 27 (0-72) | 11 : 20 | unclear | – | 11 (1-167) |

–: information not stated in the publication; cGy: centi Gray; HLA: human leukocyte antigen; IST immunosuppressive therapy; TBI: total body irradiation. [*]SAA-patients who have received allogeneic HSCT from unrelated or mismatched related donors. [†]Failed = no response or refractory as well as relapse after initial response. [‡]Non-SAA patients are included in the following studies, number of non-SAA patients in brackets: Bunin 2005 (1); Margolis 1996 (2); Maury 2007 (12); Svenberg 2004 (1). [§]Bunin 2005 stated the number of 9 (6) patients in table (abstract). [‖]Deeg 2006 stated a median (range) age of 18 (1-53), the gender of patients (male : female) 50 : 37, the median (range) number of pretransplant IST courses of 3 (1-11), and a median (range) interval from diagnosis to transplant of 14 (3-328) months for the whole study population of 87 patients. [¶]Kennedy-Nasser 2006: 3 patients with mismatched related donor included. [**]Kim 2007 stated a median (range) age of 27 (16-50), the gender of 24 : 16 patients (male : female), the number of 8 : 19 : 13 patients who received 0 : 1 : >1 pretransplant IST courses, and a median (range) interval from diagnosis to transplant of 39 (2-192) months for the whole study population of 40 patients. [††]Kojima 2002: number of patients was 26 : 52 : 73 : 3 in the groups of <=12 : >12 to <36 : >= 36 : unknown months disease duration before transplantation. [‡‡]Kosaka 2008: number of patients who received 0 : 1 : >1 of pre-transplant IST courses.