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Meta-analysis of HLA matching and the outcome of unrelated umbilical cord blood transplantation (CBT)

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ABSTRACT

Objective: The aim of this meta-analysis is to compare the HLA disparities and the outcome of UCBT, i.e. the disease-free survival (DFS), engraftment, graft-versus-host disease, (GVHD), and transplantation related mortality (TRM).
Methods: We electronically searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Pubmed, IBMTR and critically appraised all relevant articles (1989.01–2008.12). Comparative studies are carried on HLA typing and cord blood transplantation with research on stem cells engraftment, GVHD, TRM, and DFS. A meta-analysis is performed using Review Manager 5.0 software and adopted funnel plot regression assessed the publication bias.
Results: We got 882 records, and 10 trials totaling 1589 patients assessed. Pooled comparisons of studies of outcomes found that the incidence of neutrophil and platelet engraftment failure increased with HLA-mismatched antigen increased, ≥2-Ag mismatched group had a higher risk of ≥II degree GVHD and a lower DFS rate than the HLA matched group.
Conclusions: Our meta-analysis confirmed that with the HLA-mismatched antigen increased, the rate of graft failure, severe GVHD and TRM increased, and the DFS decreased. We cannot fully exclude the possibility of center biases in treatment and selection of patients and well-designed trials need to carry out.

Umbilical Cord blood (UCB) is increasingly used as a source of haematopoietic stem cells in both related and unrelated recipients [1–4] and preliminary data indicate that they may have some immunological advantages over bone marrow [5]. Hematopoietic stem cells in UCB from an HLA identical donor were first used to transplant a patient with Fanconi's anemia in 1988 by Gluckman et al [6]. The successful use of partially HLA-mismatched unrelated UCB donor as a source of hematopoietic stem cells was first reported by Kurtzberg et al [7] in 1996. Since then, the number of UCBT has increased very quickly and, to date, preliminary multicenter analyses show encouraging results in hematologic patients receiving related or unrelated CBT. Compared with unrelated donor bone marrow, major advantages of UCB include the speed of availability and less stringent requirements of HLA typing between the donor and recipient because of a low risk of severe GVHD [8,9]. The accepted level of mismatching in cord blood transplant is generally 4/6 or better, so the role of HLA is difficult to ascertain if everyone has the same degree of mismatch because of the limited number of patients. Relationships between CBT outcome and HLA disparities have not clearly identified. The aim

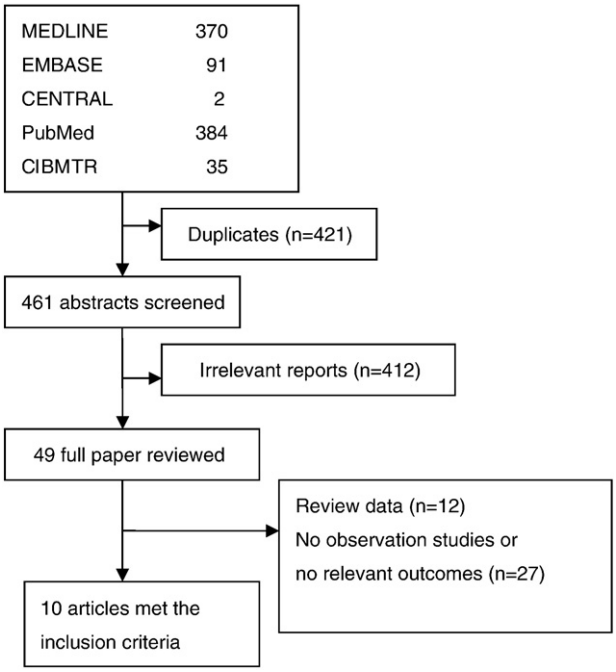

Fig. 1. Flow chart of study inclusion process.

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Table 1
Characteristics of included studies.

Author	Publication year	Age (year)	diseases	No patients	Follow-up
Eapen [14]	2007	0–16	Leukemia	503	5 years
Liao C [15]	2007	1.2–34	Malignant non-malignant	65	6 years
Kögler [16]	2005	0.3–48.4	Malignant non-malignant	122	2 years
Gluckman [17]	2004	4.5–21.2	Malignant non-malignant	550	3 years
Nishihira [18]	2003	0–56	malignant	216	2 years
Abu-Ghosh [19]	1999	1.25–21	Malignant non-malignant	11	0.3year
Gluckman [20]	1997	0.3–45	Malignant non-malignant	65	1 year
Elia [21]	1999	2–16	AML, ALL, CML	14	3 years
Wagner [9]	1996	0.1–21.3	Malignant non-malignant	18	0.5 year
Kurtzberg [7]	1996	0.8–23.5	Malignant non-malignant	25	1 year

of this meta-analysis is to compare the HLA disparities and the outcome of CBT, i.e. the DFS, engraftment, GVHD, and TRM.

1. Methods

Unrelated donor search between 1989.01 and 2008.12 were eligible for analysis on HLA matching and UCBT outcome. We systematically reviewed all data on CBT and HLA typing in which survival was the key outcome measure. To obtain reliable evidence on the relative effect of different conditioning regimens in the primary treatment of children with malignant disorders, results from independent and comparable studies are integrated to increase statistical power. The primary outcome of interest for our analysis is survival, and the secondary outcomes studied included engraftment, GVHD, and TRM incidence.

1.1. Search strategy

Following established guidelines, we performed a literature search using the databases were Medline (1989.01–2008.12), CENTRAL, Pubmed, and IBMTR. The search terms used were "cord blood", "transplantation", and "HLA typing". For limited publications to randomized controlled trials, we expanded our search criteria to include all listed clinical trials. Full text papers were obtained to extract the data for this analysis. References of retrieved articles were also checked for any relevant trials.

According the HLA typing based on HLA-A and HLA-B low-resolution typing and HLA-DRB1 high resolution typing, the patients divided into 3 groups, i.e: the HLA matched group, 1-Ag (antigen) mismatched group and ≥2-Ag mismatched group. Selection Criteria: (1) All studies on CBT and HLA typing selected. (2) Patients requiring CBT mainly to treat for malignant disorders (3).The articles should be published in English journals. Studies published in languages other than English were also translated and included. (4). Data for any of the outcome such as neutrophil and platelet engraftment, TRM, GVHD, overall or event-free survival is available. Two independent reviewers (T XH, X HQ) examined the titles and the articles of all identified trials to confirm that they fulfilled the inclusion criteria. They examined and recorded the trial characteristics and outcomes independently, using a predesigned data abstraction form. This abstraction form was used to

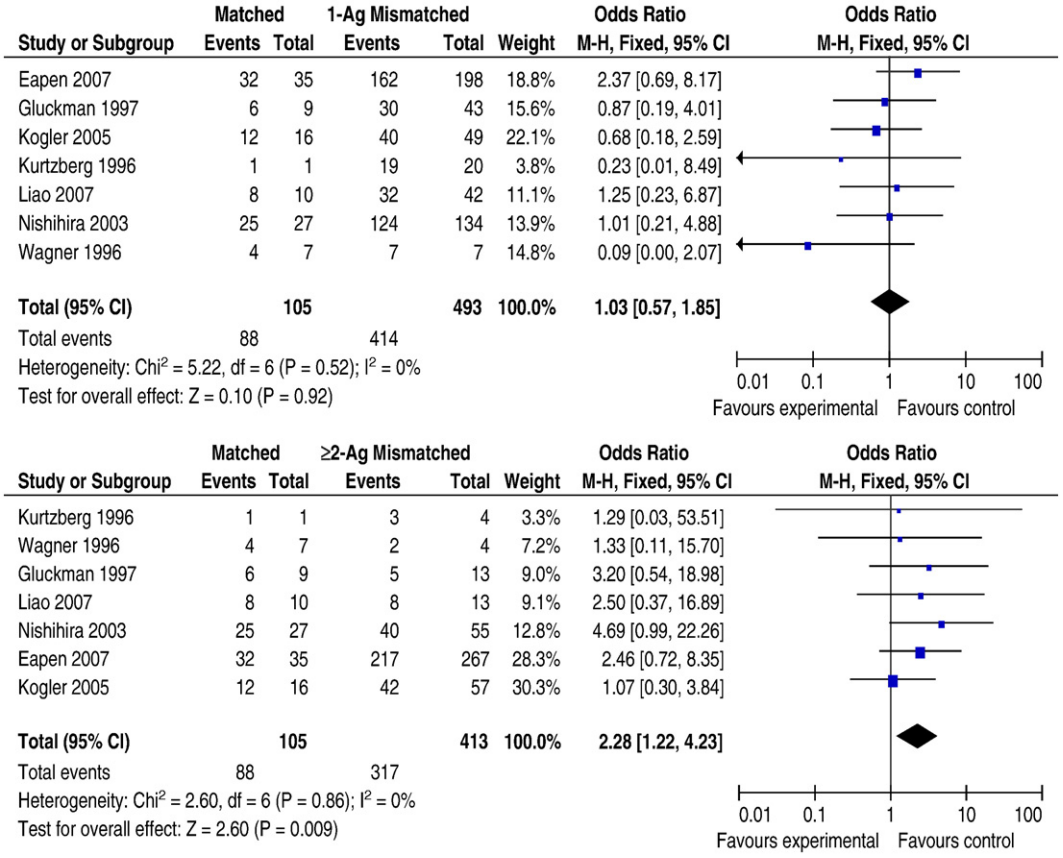

Fig. 2. The rate of neutrophil engraft in HLA matched group compared with the 1-Ag mismatched or 2-Ag mismatched CBT group. CI indicates confidence interval. Each study is shown by the point estimate of the odds ratio (square proportional to the weight of each study) and 95% confidence interval for the risk ratio (extending lines), the summary risk ratio and 95% confidence interval by fixed-effects calculations are shown by diamonds. For all figures, odds ratio values higher than one indicate that HLA mismatch has a risk effect.