Australian Government

Department of Health and Ageing

Australia and New Zealand Horizon Scanning Network

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Horizon Scanning Technology

Prioritising Summary

HLA mismatched and NIMA-matched unrelated cord blood transplants for patients who require a haematopoietic stem cell transplant to treat haematological malignancies

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AHTA

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Health Technology
Assessment

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PRIORITISING SUMMARY

REGISTER ID:	**000436**
NAME OF TECHNOLOGY:	**HLA MISMATCHED AND NIMA-MATCHED UNRELATED CORD BLOOD TRANSPLANTS**
PURPOSE AND TARGET GROUP:	**TO INCREASE THE DONOR POOL FOR PATIENTS WHO REQUIRE A HAEMATOPOIETIC STEM CELL TRANSPLANT TO TREAT HAEMATOLOGICAL MALIGNANCIES**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☒ Yet to emerge   ☐ Established

☐ Experimental   ☐ Established *but* changed indication or modification of technique

☐ Investigational   ☐ Should be taken out of use

☐ Nearly established

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐ Yes   ARTG number

☐ No

☒ Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
The Netherlands	✓		

IMPACT SUMMARY:

Human leukocyte antigens (HLA) matched haematopoietic stem cell transplantation is a common method to treat haematological malignancies. However, many patients fail to find a suitable matched donor. By using cord blood unmatched for HLA the donor pool may be increased. This technology would be made available through specialist tertiary hospitals for patients requiring a haematopoietic stem cell transplant to treat haematological malignancies.

BACKGROUND

For many haematological malignancies such as leukaemia, the only available treatment option is allogeneic[1] transplantation of immunologically naive stem cells.

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[1] Allogeneic stem cell transplantation is a procedure where stem cells are taken from a genetically non-identical member of the same species as the recipient (Wikipedia 2010).

Once a patient's immune system is depleted using chemotherapy and immunosuppressive therapy, donated stem cells are infused back into the patient and the haematopoietic cells repopulate the bone marrow (Wall & Chan 2008). Stem cells can be sourced from matched donor bone marrow but are more commonly isolated from peripheral blood. The umbilical cord at delivery is a rich source of haematopoietic stem cells, which have the ability to differentiate into lineages of all types of blood cells as well as the capacity for indefinite self-renewal (Sullivan et al 2005). The advantage of using cord blood stem cells is the immediate access to banked cord cells with no associated risk to the donor. In addition, there can be a greater HLA[2] disparity between donor and recipient when compared to using unrelated (allogeneic) donors of bone marrow (van Rood et al 2009). The disadvantage of cord blood transplants are, however, a higher incidence of graft failure compared to conventional bone marrow transplants. This is slightly offset by a reduced risk of acute and chronic graft-versus-host disease[3] (Wall & Chan 2008). Some cord blood units contain insufficient cells to perform a transplant for an adult, however ex-vivo expansion may be used to increase the number of stem cells. Current data suggests that cord blood can be frozen successfully for at least 15 years (Blacklock et al 2005).

Cord blood cells are used in approximately 22 per cent of all stem cell transplantations worldwide. According to the Bone Marrow Donors Worldwide (BMDW) network, the number of banked cord blood units is approximately 380,000 compared to the potential 13 million registered bone marrow donors (van Rood et al 2009). To date, children have undergone the majority of cord blood transplants, however its use in adults is increasing (Atsuta et al 2009). Australia and New Zealand are members of the worldwide bone marrow network and both countries have established public cord blood banks from altruistically donated umbilical cords. It would be expected that most of the transplantations that would make use of this facility would be allogeneic. Private cord blood banks exist in both Australia and New Zealand, which are designed for the preservation of cord blood samples as an "insurance" against future illness which may require autologous[4] cord stem cell transplantation. Autologous transplantation is not indicated in the treatment of heritable genetic diseases, as these stem cells will contain the existing genetic defect (Sullivan et al 2005).

When using unrelated donors, HLA matching is considered to be the most important factor for transplantation success. To maximise graft survival high resolution matching at the HLA-A, HLA-B, HLA-C and HLA-DRBI loci is recommended (8/8

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[2] HLAs are proteins expressed on the surface of cells which are used by the immune system to differentiate self from non-self (Wikipedia 2010).
[3] Graft failure= loss of function of transplanted cells. Graft-versus-host disease= transplanted cells are recognised by the body as foreign and an attack is launched by the immune system.
[4] Autologous stem cell transplantation is a procedure in haematopoietic cells from which all blood cells develop, are removed, stored, and later transplanted back into the same person (Wikipedia 2010).

matching alleles with each loci having 2 alleles). Matching of seven of the eight alleles results in increased mortality (RR 1.25) and reduced one-year survival (43%) compared to an 8/8 match (52%). Single mismatches at HLA-B and HLA-C are better tolerated than mismatches at HLA-A and HLA-DRB1 (Wall & Chan 2008). The majority of donors on the worldwide register have a north western European genetic background and in addition to the HLA loci mentioned above, HLA-DQB1 is considered important to type for and match. However, in terms of survival, if donors cannot be matched for all of these five loci, mismatching at the HLA-DQB1 is preferable. For patients with a similar genetic background to registered donors, the chances of finding a matching donor are approximately 70 per cent. However, for those patients with a different genetic background less than 30 per cent will successfully find a matching donor (van Rood & Oudshoorn 2009).

During pregnancy there is a two-way flow of cells and molecules, including soluble HLA antigens, between the mother and the foetus, with the foetus subsequently developing immunity and tolerance. Studies have demonstrated that some patients who have antibodies against a large number of HLA antigens have not formed antibodies against maternal HLA antigens that the patient *did not* inherit as part of their genetic make-up, that is the non-inherited maternal antigens (NIMA). Recent research into the use of unrelated cord blood for stem cell transplantation has investigated the role of NIMA. It has been suggested that a reduced level of graft-versus-host disease and hence improved transplantation outcomes, may occur despite HLA mismatches if donors are matched for NIMA (Scaradavou 2010; van Rood et al 2009). Using cord blood samples with NIMA mismatches may potentially increase the size of the potential donor pool, increasing the chances of finding a donor. van Rood and Oudshoorn (2009) illustrated this using a potential cord blood sample from a mother with the hypothetically acceptable NIMA mismatches of HLA-A2 and HLA-B8, which combined with HLA types yields eight new, acceptable HLA phenotypes (Table 1).

Table 1   Increase in virtual phenotypes, when NIMA are considered as acceptable mismatches (van Rood & Oudshoorn 2009)

Mother of cord blood	A1, A2–B7, B8	NIMA =A2 and B8
Cord blood	A1, A3–B7, B44	
Combining the NIMA A2 and B8 with the CB phenotype this cord blood unit results in the following acceptable phenotypes		
A1, A2/B7, B44	A1, A3/B8, B44	A2, A3/B7, B44
A1, A3/B7, B8	A2, A3/B8, B44	A1, A2/B7, B8
A1, A2/B8, B44	A2, A3/B7, B8	

The application of this reasoning to the 360,000 cord blood units stored in the BMDW database would create a potential of three million new "virtual" phenotypes (van Rood & Oudshoorn 2009). For examples of HLA mismatched recipient/donor pairs with and without a NIMA match see page two of the [supplemental](#) data from the van Rood et al (2009) paper.

CLINICAL NEED AND BURDEN OF DISEASE

In Australia during 2005, there were 2,591 registered cases of leukaemia, representing 2.6 per cent of all registered cancers. Of these 1,214 were lymphoid leukaemias (C91), 1,310 were myeloid leukaemias (C92-94) and 67 were leukaemias of an unspecified cell type (C95). The age-standardised incidence rate was 12.3 per 100,000 population. During this same period there were 1,417 recorded cases of mortality with leukaemia as the cause of death, with an age standardised mortality rate of 6.6 per 100,000 persons. The majority of these deaths were associated with myeloid leukaemias (866) (AIHW and AACR 2008). For the period 2005-06 there were a total of 51,187 public hospital separations for malignant neoplasms of the lymphoid, haematopoietic and related tissues (ICD-10 code C81-C96). Of these, 9,162 were lymphoid leukaemias (C91), 9,280 were myeloid leukaemias (C92), 204 were monocytic leukaemias (C93), 1,038 and 333 were other leukaemias of a specified and unspecified cell type (C94 and C95), respectively. The separations for these five leukaemias combined represent a total of 104,101 patient days with an average length of stay ranging from 4.0 (C91) to 8.8 (C93) days (AIHW 2010).

In New Zealand during the year 2005, leukaemias represented 3.1 per cent (577 cases) of all cancer registrations and accounted for 3.9 per cent (311 cases) of deaths from all cancers. The age standardised incidence rate per 100,000 population for multiple myeloma and malignant plasma cell neoplasms (C90) and leukaemia (C91–C95) for this period was 4.3 and 10.7, respectively. The age standardised mortality rate per 100,000 population for multiple myeloma and malignant plasma cell neoplasms (C90) and leukaemia (C91–C95) was 2.5 and 5.2, respectively (Ministry of Health 2009).

The Australian Bone Marrow Donor Registry (ABMDR) has the details of 170,000 people who have registered and whose tissue typing details are available for patients needing a transplant. In addition, the ABMDR cord blood network has 20,000 cord blood samples stored with 2,218 donations of umbilical cord blood banked in 2008. In 2008 the ABMDR provided transplants for 337 patients, of whom 182 received a cord blood transplant. Sixty-one patients in Australia received a cord blood transplant while the remaining 121 cord blood transplants from the ABMDR went to patients living in other countries, five of whom lived in New Zealand. Of the 61 patients who received a cord blood transplant in Australia, 37 cord blood units originated in Australia with the remaining 24 originating from overseas. In 2008, 455 new Australian patients requested a search of the register with 270 (60%) of these patients finding a donor. A transplant has already been performed on 134 (30%) of these patients and 136 are still waiting to be transplanted (ABMDR 2009). Similarly, the New Zealand Bone Marrow Donor Registry exists to facilitate stem cell transplants and store cord blood units for patients in New Zealand and as part of the worldwide network of registries, Bone Marrow Donors Worldwide.

Private cord blood banks such as Cryosite (Australia) and CordBank (New Zealand) charge a fee for parents to store their child's cord blood to guard against future illness

and the possible need for *autologous* stem cell transplantation. Cryosite currently charge A\$2,995 for storage of cord blood until the child is 18 years old, however CordBank charge NZ\$ \$2,750 for initial storage and a further \$200 per year. Interestingly, in 2005, New Zealand legislation restricted the use of privately collected umbilical cord blood to the child from whom it was collected. An application would have to be made to the Ministry of Health for an exemption if the use of a privately banked cord blood was required for the treatment of a sibling (Sullivan et al 2005).

DIFFUSION

In Australia and New Zealand unrelated cord blood stem cell transplantation has been increasingly used over the past decade for patients with haematological malignancies who lack a HLA-matched bone marrow donor. It has been estimated that 20 per cent of all allogeneic transplantations performed in young patients (less than 20 years) use unrelated cord blood as the source of stem cells. Between 1995 and 2005, in Australia and New Zealand, a total of 135 paediatric patients underwent unrelated cord blood transplantation. HLA typing was performed on all cord blood units for HLA-A, HLA-B and HLA-DRB1, however matching for NIMA is not routinely performed. A perfect 6/6 match occurred on 12 per cent of these patients, 46 per cent had a 5/6 match, 41 per cent had a 4/6 match and one per cent had a 3/6 match. Transplant centres in both countries would have the ability and resources to type for NIMA (Petterson et al 2009).

COMPARATORS

Conventional stem cell transplantation using either HLA matched or unmatched stem cells sourced from bone marrow, peripheral blood or cord blood is the comparator.

SAFETY AND EFFECTIVENESS ISSUES

Although several studies were identified which reported on patient outcomes for stem cell transplantation using unrelated cord blood cells (Atsuta et al 2009; Kurtzberg et al 2008; Petterson et al 2009), none of these studies reported on the use of matching for NIMA.

Only one study using matching of NIMA was identified (van Rood et al 2009). This large retrospective case series conducted by the New York Blood Center National Cord Blood Program reported on the outcomes of 1,121 patients transplanted with a single cord blood (CB) unit (level IV intervention evidence). The primary endpoint reported was transplant-related mortality with secondary endpoints including neutrophil and platelet engraftment, acute and chronic graft-versus-host disease, relapse and treatment failure.

Patients did not receive CB with *a priori* matching of NIMA, however some patients did receive CB with matched NIMA and unmatched HLA serendipitously. The database records of the Cord Blood Program were retrospectively searched to collate

information on the NIMA and HLA typing status of patients who received an unrelated cord blood transplant (URCBT). Supplementary patient information is available from the following link. Some patient information is summarised in Table 2. The majority of patients had not received a prior transplantation. At the same HLA mismatch level (1 or 2), patient characteristics did not differ between the matched and unmatched NIMA transplant groups with the exception of a slightly greater proportion of high-risk leukaemias in the 2-HLA mismatch group (41% vs 32%, p=0.038).

Only a total of 62 patients (5.5%) received a matched CB transplant. Of the remaining 1,059 patients, 79 had a mismatched antigen that was identical to a donor NIMA, 25 (2.2%) of whom received CB with one HLA mismatch and 54 (4.8%) had two HLA mismatches. Of the NIMA mismatched patients there were 363 (32.4%) patients with one HLA mismatch and 617 (55.0%) with two HLA mismatches.

Table 2   Characteristics of transplanted patients

Patient characteristics	Matched CB n=62	1 HLA mismatch, NIMA		2 HLA mismatch, NIMA	
		NIMA match n=25	NIMA mismatch n=363	NIMA match n=54	NIMA mismatch n=617
Mean patient age (years)	12.4	13.1	11.5	18.1	17.1
Range patient age	1mth – 61 yrs	4 mths- 48 yrs	10 mths- 67 yrs	1yr - 58 yrs	3 mths- 65 yrs
Ethnic background	%	%	%	%	%
Asian	3	8	3	8	4
African	3	4	10	21	21
Hispanic	20	21	19	26	20
Caucasian	73	62	62	40	50
Other	0	4	5	6	4
Unknown	5	4	2.5	2	3
Diagnosis	%	%	%	%	%
ALL	44	32	42	33	40
AML	31	32	35	41	32
CML	6	4	6	13	13
Other leukaemia	10	4	4	6	4
Lymphoma	2	16	5	7	4
Myelodysplasia	10	12	8	0	7
Total nucleated cell dose transplanted (x 10^7/ kg)					
	%	%	%	%	%
0.7 - 2.4	19	20	20	26	24
2.5 – 4.9	29	48	38	43	41
5.0 – 9.9	31	20	26	26	25
≥ 10	22	12	17	6	10
Mean	4.3	4.2	4.7	3.8	4.1
Range	0.7-19.4	1.2 -19.6	0.7 – 23.1	1.3 -15.9	0.9 – 28.0

ALL = acute lymphoblastic leukaemia, AML = acute myeloid leukaemia, CML = chronic myeloid leukaemia

A multivariate analysis of the relative risk of all the study endpoints was conducted in patients undergoing transplantation with zero, one or two HLA mismatches, by match for a non-inherited maternal antigen. A great deal of data was generated by this analysis and the full table can be viewed in the [supplemental online data](). An abbreviated version of the results of patient outcomes is presented in Table 3. Despite low patient numbers in each of the sub-analyses groups, there were some significant differences between HLA mismatched patients with NIMA matching compared to those without NIMA matching.

The three-year cumulative probability of transplant-related mortality was 46 per cent and was lower in the NIMA matched patients than in the non-NIMA matched pairs (relative risk 0.7, 95% CI [0.5, 0.97], p=0.034). This effect was strengthened when patients were stratified for age, as there was a significant decrease in transplant-related mortality in patients older than 10 years who had one HLA mismatch (RR 0.6, 95% CI [0.4, 0.99], p= 0.048) or zero or more HLA mismatches (RR 0.6, 95% CI [0.3, 0.9], p=0.012). A similar improvement was reported in patients older than 10 years for overall mortality (RR 0.6 95% CI [0.4, 0.9], p=0.022) and transplant failure (RR 0.6 95% CI [0.4, 0.9], p=0.02).

COST IMPACT

Although no cost data was provided for this new technique, it would be envisaged that typing for NIMA would increase the cost of transplantation minimally as HLA typing is already conducted. However, a future cost-effectiveness analysis may identify areas of cost savings if the technique proves to be effective in the reduction of graft-versus-host disease.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

Stem cell transplantation may not be a treatment option for some patients on the grounds of religious beliefs.

OTHER ISSUES

No issues were identified/raised in the sources examined.

SUMMARY OF FINDINGS

Clinicians often have to resort to using unrelated stem cells in transplantation procedures. Attempts are made to ensure that the number of HLA mismatches between donor and recipient are kept to a minimum to ensure the success of the transplant. Allowing HLA mismatches whilst ensuring non-inherited maternal antigens are matched appears to lower transplant-related mortality and the incidence of treatment failure. As the matching and mismatching of both HLA and NIMA was by chance and not by selection, further prospective studies are required to ascertain whether or not these preliminary findings can improve survival in patients who undergo unrelated cord blood stem cell transplantation.

Table 3   Patient outcomes

Endpoint	Zero or one HLA mismatch NIMA matched			Two HLA mismatches NIMA matched			Zero, one or two HLA mismatches NIMA matched		
		RR [95% CI]	p value		RR [95% CI]	p value		RR [95% CI]	p value
Transplant-related mortality in 3yrs									
Zero HLA mismatch	11/62	0.4 [0.2, 0.7]	**0.004**		NA		11/62	0.4 [0.2, 0.7]	**0.004**
HLA mismatch, NIMA match	7/25	0.6 [0.3, 1.3]	0.170	25/54	0.7, [0.5, 1.1]	0.101	32/79	0.7 [0.5, 0.97]	**0.034**
Subset ≥ 10 years old									
Zero HLA mismatch	4/22	0.3 [0.1, 0.8]	**0.016**		NA		4/22	0.3 [0.1, 0.7]	**0.011**
HLA mismatch, NIMA match	3/10	0.4 [0.1, 1.3]	0.131	17/31	0.6 [0.4, 0.99]	**0.048**	20/41	0.6 [0.3, 0.9]	**0.012**
Overall mortality in 3yrs									
Zero HLA mismatch	22/62	0.5 [0.3, 0.8]	**0.002**		NA		22/62	0.5 [0.3, 0.8]	**0.002**
HLA mismatch, NIMA match	10/25	0.5 [0.3, 1.02]	0.059	34/54	0.8 [0.5, 1.1]	0.180	44/79	0.7 [0.5, 0.97]	**0.029**
Subset ≥ 10 years old									
Zero HLA mismatch	8/22	0.4 [0.2, 0.9]	**0.021**		NA		8/22	0.4 [0.2, 0.8]	**0.011**
HLA mismatch, NIMA match	5/10	0.5 [0.2, 1.3]	0.151	21/31	0.7 [0.4, 1.04]	0.073	26/41	0.6 [0.4, 0.9]	**0.022**
Treatment failure (relapse or death) in 3yrs									
Zero HLA mismatch	25/62	0.5 [0.3, 0.8]	**0.003**		NA		25/62	0.5 [0.3, 0.8]	**0.002**
HLA mismatch, NIMA match	11/25	0.5 [0.3, 1.0]	0.051	38/54	0.8 [0.6, 1.2]	0.289	49/79	0.7 [0.6, 0.99]	**0.049**
Subset ≥ 10 years old									
Zero HLA mismatch	8/22	0.4 [0.2, .09]	**0.021**		NA		8/22	0.4 [0.2, 0.8]	**0.009**
HLA mismatch, NIMA match	5/10	0.5 [0.2, 1.2]	0.123	23/31	0.7 [0.4, 1.04]	0.072	28/41	0.6 [0.4, 0.9]	**0.020**
Absolute neutrophil count 500 by day 77									
Zero HLA mismatch	51/59	1.7 [1.2, 2.3]	**0.001**		NA		51/59	1.7 [1.2, 2.3]	**0.001**
HLA mismatch, NIMA match	18/21	1.3 [0.8, 2.1]	0.297	39/52	1.3 [0.95, 1.9]	0.094	57/73	1.3 [1.01, 1.7]	**0.043**
Subset ≥ 10 years old									
Zero HLA mismatch	14/15	5.2 [2.5, 11.1]	**< 0.001**				14/15	3.8 [2.0, 7.2]	**<0.001**
HLA mismatch, NIMA match	3/4	2.1 [0.5, 9.4]	0.319				14/18	1.9 [1.1, 3.3]	**0.031**
Chronic host-versus graft disease									
Zero HLA mismatch								0.9 [0.4, 1.8]	0.677
HLA mismatch, NIMA match								1.1 [0.6, 1.9]	0.839
Acute host-versus graft disease									
Zero HLA mismatch								0.3 [0.1, 0.9]	**0.028**
HLA mismatch, NIMA match								0.9 [0.5, 1.6]	0.693

HEALTHPACT ACTION:

This technology appears to be slowly diffusing into Australia and New Zealand. HealthPACT have agreed to disseminate this information to the relevant bodies including the Australian Bone Marrow Donor Registry's Cord Blood National Management Committee. No further review by HealthPACT is required.

NUMBER OF INCLUDED STUDIES

Total number of studies	1
Level IV intervention evidence	1

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SEARCH CRITERIA TO BE USED:

Cord Blood Stem Cell Transplantation
Fetal Blood/*immunology
Fetus/immunology
Maternal-Fetal Exchange/immunology
Graft Survival/*immunology
HLA Antigens/*immunology
Hematologic Neoplasms/immunology/therapy
Immune Tolerance/immunology
Donor Selection/methods
Hematopoietic Stem Cell Transplantation/*methods
Hematopoietic Stem Cells/cytology/*immunology
Histocompatibility Testing
Histocompatibility/*genetics/immunology
Antigens, CD34/blood/immunology
Graft vs Host Disease
Hematologic Diseases/prevention & control/*therapy
Hematopoiesis