UK NEQAS
International Quality Expertise

Histocompatibility
& Immunogenetics

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# Interpretive Educational Scheme (iED)
# Clinical Scenario 2/2019 – Haematopoietic Stem Cell Transplantation

Dispatched on 17th September 2019

## Summary of Results

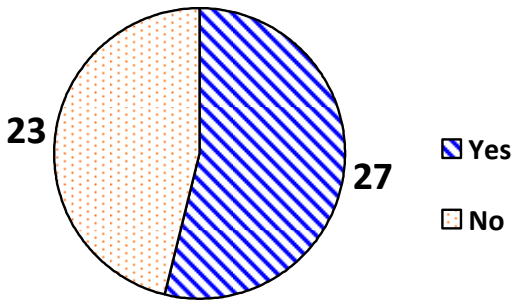
A total of 50 responses were received.

**1) What aspects of the patient's HLA type make this a challenging unrelated donor search?**

**Responses included:**

| |
|---|
| Likely African descent, which is underrepresented on donor registries |
| Low frequency alleles e.g. B*14:03, DRB1*15:03, A*34:02 |
| Uncommon DR-DQ association (DRB1*11:04-DQB1*05:02, would expect DQB1*03) |
| B*51:01 has a number of HLA-C associations, reducing the chance of a C match |
| Rare haplotypes |

**2) Would you consider selecting any of the mismatched unrelated donors listed in Table 1?**




| | UK&I | % (n=19) | RoW | % (n=31) | Total (n=50) |
|---|---|---|---|---|---|
| **Yes** | 11 | 57.9% | 16 | 51.6% | 27 |
| **No** | 8 | 42.1% | 15 | 48.4% | 23 |

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**Reasons for answers included:**

| | |
|---|---|
| **No** | All donors very likely to have >1 HLA mismatch due to patient's low frequency alleles/linkage and donor low resolution/missing typing data |
| | All donors have also a mismatch in class I so at best , they will be 8/10 |
| | Would need to carry out too much additional testing to consider potential MUDs with likelihood of finding a match unlikely, given the unusual HLA type of the patient. Majority of donors are older than 25. |
| | Our transplant centre would prefer a haploidentical donor over a mismatched MUD for AML patients |
| **Yes** | All sub-optimal on age, registry, HLA resolution, ethnicity data, ABO/CMV data. However, depending on patient disease status and clinical direction we would select donors that may potentially be 9/10 or 8/10 HLA matched. |
| | Yes if the urgency of the case permitted. They may be worth a try particularly if the ethnicity of the donors is provided on the searches and those where the presence of an allele might indicate matching across the extended haplotype. In addition because these donors are longshots we would look at other options simultaneously such as haplo and cord. |
| | No guarantee there is not a match, in our experience, the consultants would request we attempt to call in and type donors rather than assuming no matches available. We would however ensure the transplant team were aware of the unliklihood of finding a match |
| | There are some donors that have a small potential to be mismatched at only one antigen. 9/10 match still acceptable and preferable over haplo transplant. May be worth performing the confirmatory typing at the same time as looking at the potential family donors. |
| | We would consider other options as well, however the donor options for the patient are limited and (mismatched) unrelated donors may be considered by the clinical team |

The following table summarises the responses given by participants for those that selected unrelated donors (n=29)

| Donor | UK&I | RoW | Total | Reasons for Selection |
|---|---|---|---|---|
| **First Choice Donor:** | | | | |
| B | 12 | 7 | 19 | Potential 9/10<br>Has B*14:03 allele<br>CMV Neg<br>Age ok<br>Male<br>Reputable registry |
| C | 0 | 4 | 4 | Already typed for HLA-C<br>1 antigen mismatch at HLA-A<br>Male |
| A | 0 | 3 | 3 | Male<br>Age<br>HLA-B mismatch |
| G | 0 | 1 | 1 | HLA A*02 mismatch and this allele has shared epitopes to HLA A*68 |
| I | 0 | 1 | 1 | If this is a B*44:03 there is a LD with -C*16:01 |
| J | 0 | 1 | 1 | Identity for HLA DRB1*, A and one B |

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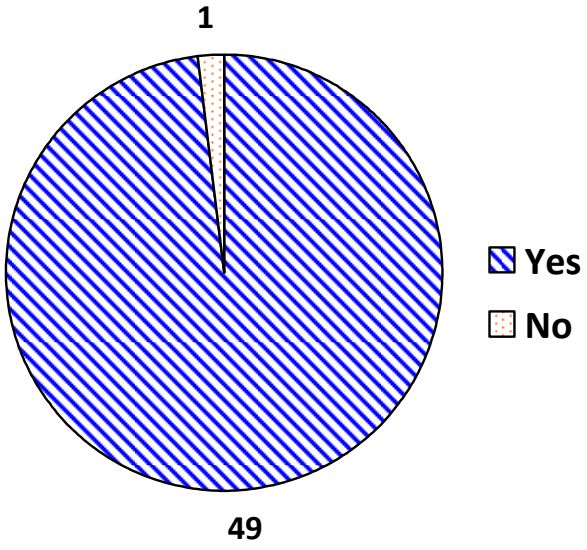
**3) Would you perform additional testing or require any further information to inform selection of a related donor?**




| | UK&I | % (n=19) | RoW | % (n=31) | Total (n=50) |
|---|---|---|---|---|---|
| **Yes** | 19 | 100% | 1 | 96.8% | 49 |
| **No** | 0 | 0% | 30 | 3.2% | 1 |

| | **Responses included:** |
|---|---|
| Donor | CMV |
| | ABO |
| | Donor Weight |
| | KIR Typing |
| | DPB1 Permissive mismatch tool |
| | Virology screening |
| | Confirmatory HLA typing |
| | PIRCHE |
| Patient | HLA Antibody testing |
| | Weight |
| | Confirmatory HLA typing |
| | ABO |

**4)** Based on the information provided so far, rank the top 2 related donors in order of preference and outline your reasons in the table below.

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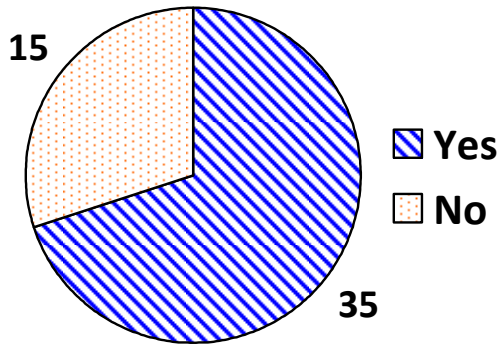
| Donor | UK&I | RoW | Total | Reasons for Selection |
|---|---|---|---|---|
| **First Choice Donor:** | | | | |
| Son | 8 | 13 | 21 | Young male<br>Haploidentical<br>Benefit of NIMA effect<br>Permissive DP mismatch<br>Likely to provide good cell dose |
| Half Sibling 2 | 8 | 8 | 16 | Haploidentical<br>Male<br>Likely to provide best cell dose<br>Reduced chance of pregnancy induced DSA<br>Permissive DP mismatch<br>Sibling preferred over parent or child donor |
| Daughter | 3 | 10 | 13 | 8/10 match<br>Young donor<br>More likely to be CMV Negative due to age<br>Haploidentical<br>Homozygous<br>Few mismatches in GvH direction<br>Permissive DP mismatch |

**5) Would the results of HLA antibody testing alter your ranking of related donors?**



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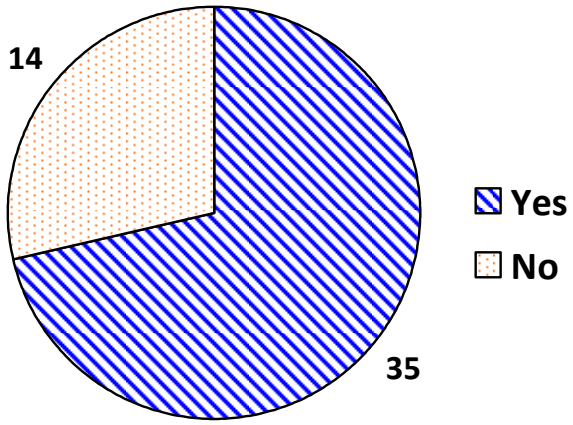
| | UK&I | % (n=19) | RoW | % (n=31) | Total (n=50) |
|---|---|---|---|---|---|
| Yes | 13 | 68.4% | 22 | 71.0% | 35 |
| No | 6 | 31.6% | 9 | 29.0% | 15 |

If Yes, what would be your new preferred donor

| Donor | UK&I | RoW | Total | Reasons for Selection |
|---|---|---|---|---|
| **First Choice Donor:** | | | | |
| Half Sibling 2 | 7 | 13 | 20 | Lower risk DSA to B41 MFI 2832 |
| Daughter | 4 | 8 | 12 | Low risk B45 DSA (2396) than Son |
| Son | 0 | 2 | 2 | No HLA antibodies detected |

6) Do you provide a clinical HSCT service?




7) Does your laboratory routinely perform haploidentical transplants?

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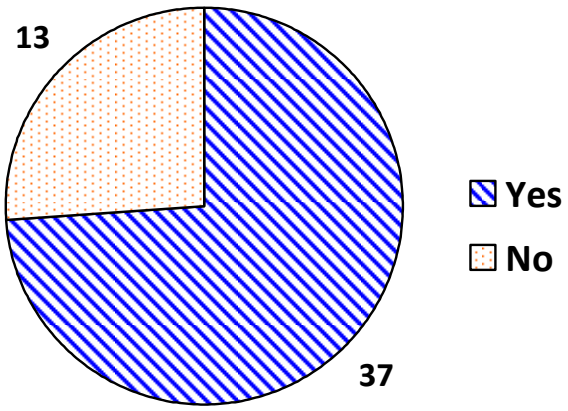


**Comments from Centre that set the scenario:**

Local donor selection policy will in most cases select a haploidentical related donor over mismatched unrelated donors. In selected cases HLA-C mismatched unrelated donor is considered, particularly if suitability of related haplo donors is an issue either due to medical fitness or social/family dynamic reasons.

HLA antibody status of patients is evaluated for all haplo-identical transplants on at least 2 separate samples. Levels (as indicated by MFI values in single antigen bead assay) of anti- HLA antibodies where present, are taken into consideration in selection the haplo-identical donor where choice is available.

Presence of HLA antibodies have been shown to constitute an increased risk to stem cell transplant outcome in multiple studies (e.g. Ciurea et al., 2017). Three rounds of Plasma exchange are carried out for patients with antibodies to mismatched HLA antigens as per centre haplo-identical transplant protocol.

Post plasma exchange samples are tested for HLA antibodies by Luminex single antigen bead assay after each round and results reported on the same day. If antibody levels to mismatched antigens are deemed clinically relevant (usually MFI greater than ~1000) after three rounds, additional rounds are recommended based on discussions at the BMT MDT and taking into consideration patient factors.

Haplo transplant programme is still evolving at the centre, and levels of antibodies to mismatched antigens are evaluated for their clinical significance on a case by case basis in consultation with the H&I lab.

Recently published guidelines from EBMT and soon to be published new version of BSHI BSBMT guidelines will help refine decision criteria going forward.

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**Centre Actual Donor Selection:**

Son was excluded as a donor due to presence of sickle cell trait.

Half sibling 2 was a potentially suitable donor (young age) but patient had higher MFI of antibodies to the mismatched B41 antigen (2800).

Half sibling 1 was ruled out as completely HLA mismatched.

Daughter was chosen as a haplo-identical donor as antibodies to B45 mismatched antigen had the lower MFI of 2400.

Patient underwent three cycles of plasma exchange. Post plasma exchange serum samples were tested for HLA antibodies with the results:

After 1st exchange -Luminex Single Antigen has detected Donor Specific antibody to HLA B45 -**470 MFI**
After 2nd exchange-Luminex Single Antigen has detected Donor Specific antibody to HLA B45 -**349 MFI**
After 3rd exchange-Luminex Single Antigen has detected Donor Specific antibody to HLA B45 -**861 MFI.**

A final sample from the a day before stem cell infusion (1 week post Plasma exchange ) was tested for antibodies by single antigen bead and found to be negative ( MFI < 500).