Towards responsible cord blood banking models

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Abstract

On 31 May 2010, 14 072 567 bone marrow/apheresis donors registered in 44 countries and 426 501 cord blood units banked in 26 countries for public use were available to treat candidates to haemopoietic stem cell transplant lacking a family related compatible donor. Despite these impressive numbers, additional efforts are required to ensure that all patients, including those from ethnic minorities, can promptly find a suitable donor. Governments, clinicians, scientists, patients and stakeholders should share the responsibility to develop haemopoietic stem cell donation and cord blood banking models able to fully match all patient needs. In this regard, current scientific evidence and prevalent opinions among expert clinicians support solidaristic cord blood donation for public use against the alternative option of commercial autologous cord blood storage.

Introduction

This article is based on a presentation given at the 2nd International Congress on Responsible Stem Cell Research, Monaco, 26–28 November 2009. Therefore, the topics discussed here do not relate primarily to technical, organizational and managerial aspects of different models for cord blood (CB) banking, but rather focus on responsibilities carried by CB bankers, stem cell scientists and health administrators in supporting different CB banking models. For the purpose of this discussion, the term 'responsible' is used as defined with a number of examples

applicable in different settings at <http://www.thefreedictionary.com> (Table 1). CB banking models are categorized in relation to alternative characteristics such as allogeneic versus autologous, public versus private, altruistic versus commercial, and not-for-profit versus for-profit, which are not necessarily mutually exclusive (1) (Table 2).

The ultimate purpose of this discussion is to share rational elements of decision with professionals involved in CB banking and with families considering altruistic CB donation versus autologous CB conservation.

The solidarity chain

Commonly agreed principles from consolidated fields of blood transfusion and organ transplantation and from the nascent field of cell therapies emphasize the central role of health professionals and organizations involved in blood procurement, cell manipulation and cadaver organ allocation, as links between donors and recipients in the so-called 'solidarity chain' (Fig. 1). Several areas of jurisdiction limit these activities to public sectors and exclude for-profit organizations from their management and control, based on a prevalent opinion among stakeholders that biological materials such as blood – hence, including CB – and organs are 'common goods' rather than 'commodities' and on evidence that their 'life saving' availability is limited. Accordingly, equal rights of access to benefits of blood transfusion, cell therapy and organ transplantation must be ensured for all individuals in need.

Worldwide cord blood inventory

On 31 May 2010, the Bone Marrow Donors Worldwide website (<http://www.bmdw.org>) reported a worldwide inventory of 14 072 567 bone marrow/apheresis haemopoietic stem cell donors from 63 registries in 44 countries and 426 501 CB units in 44 CB banks or banking networks from 26 countries, that is, a total of 14 499 068 globally available sources of therapeutic haemopoietic stem cells.

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Table 1. Responsible: some definitions from <http://www.thefreedictionary.com>

1. Liable to be required to give account, as of one's actions or of the discharge of a duty or trust
2. Involving personal accountability or ability to act without guidance or superior authority: *a responsible position within the firm*
3. Being a source or cause
4. Able to make moral or rational decisions on one's own and therefore answerable for one's behaviour
5. Able to be trusted or depended upon; reliable
6. Based on or characterized by good judgment or sound thinking: *responsible journalism*
7. Having the means to pay debts or fulfil obligations
8. Required to render account; answerable: *The cabinet is responsible to the parliament*

Table 2. Alternative features of CB banking models

1. Allogeneic versus autologous
2. Public versus private
3. Altruistic versus commercial
4. Not-for-profit versus for-profit

Is the worldwide CB inventory sufficient to cover current and future needs of patients requiring allogeneic unrelated haemopoietic stem cell transplantation? Although the more permissive compatibility of CB compared to bone marrow cells currently allows identification of CB units with reasonable HLA match (at least 4/6) and cell dose (at least 20–25 million total nucleated cells/kg recipient body weight) for most recipients lacking a family-related donor, the landmark study by Eapen *et al.* (2) shows that paediatric CB transplant recipients with high cell dose and HLA match (of note, a small group of 35 out of 503 CB recipients evaluated in that study) experienced 5-year probability of leukaemia-free survival of 60%, compared to lower values after 1-mismatched CB transplant (45%), HLA-matched bone marrow transplant (38%), mismatched bone marrow transplant (37%), one mis-

matched CB transplant with low cell dose (36%) and two mismatched CB transplants (33%).

These data support a previous report published by the Institute of Medicine (<http://www.nap.edu>) recommending expansion of current CB allogeneic inventories to increase the proportion of recipients transplanted with high cell doses and optimal HLA match. Considering higher cell doses required by adult recipients, it is evident that such expansion would benefit not only paediatric recipients, but also – and particularly so – adult patients.

Therefore, the frequent argument used to support commercial autologous CB conservation programmes as a form of 'biological life insurance' should be contrasted with evidence that there is currently more 'insurance' in depositing one's family CB into an altruistic repository – accessible to anyone in need and actually used for several thousand patients every year – rather than storing it for currently undefined, future personal therapeutic applications.

An additional consideration regards similarity of haemopoietic stemness present in CB cells (which can, of course, be collected and stored once in a lifetime) and in bone marrow cells, which can be an inexpensive autologous stem cell source naturally conserved and renovated – except for diseases characterized by bone marrow neoplastic development or cancer invasion – under ideal storage conditions, for decades.

Communication and advertising

Correct communication to the population is of paramount importance for health-related programmes such as CB banking and for choice between CB altruistic donation and autologous conservation. Stakeholders, health professionals and administrators need to carefully check accuracy of information provided to expectant families through the internet and lay press. Formal investigation of messages delivered through the internet by 19 websites concerned with 'stem cell clinics' yielded disappointing findings in terms of message clarity (only one website being 'very clear' and nine being 'very indeterminate'), risk relevance of 'novel stem cell procedures' (14 sites omitting careful risk description and 10 sites declaring very relevant benefits) and readiness of the novel procedures (10 sites declaring 'very routine' availability of the novel procedures in the near future) (3).

At a more technical level, detailed analysis by Sullivan (4) on clinical indications for allogeneic versus autologous CB transplant ended with the conclusion that 'commercial CB banks currently offer superfluous service', a statement which triggered hot debate in the literature but which seems to be supported by prevalent opinions of 93 paediatric haemopoietic cell transplantation physicians from

Figure 1. Solidarity chain linking donors and recipients.

57 centres in the US and Canada, who participated in a recent survey (5). Cost effectiveness of commercial autologous storage programmes has been evaluated by Kaimal *et al.* (6), who based their evaluations on several assumptions including cost of US\$ 3620 for CB banking and storage for 20 years and 1:2500 chance of requiring an autologous stem cell transplant. Authors of this study concluded that private CB banking is not cost-effective as it requires 'additional US\$ 1 374 246 per life-year gained'.

National versus international needs

The naïve expectation that national CB banking programmes could ensure self sufficiency is contradicted by consolidated experience of the past decade showing that no more than half of national CB inventories is used within the original country of donation and storage, while the rest is exported for benefit of foreign recipients. Here, the 2007 annual report from the Worldwide Marrow Donor Association (<http://www.worldmarrow.org>) indicates that 42% of CB units used in that year crossed an international boundary. Besides natural justification for the current exchange rate due to immunogenetic distribution of HLA phenotypes among populations resident in different countries, the international exchange rate may be expected to increase in the future, in parallel with expansion of immigration and emigration and development of new haemopoietic stem cell transplantation programmes in countries progressively increasing their socio-economic conditions (7,8).

Careful analyses of ideal national inventories in relation to specific HLA characteristics of the resident population and to balanced cost-to-benefit analysis, are not available from many countries. Elegant studies by Querol *et al.* (9,10) provide useful methodology and interesting information as applied to the United Kingdom. These studies show that high probabilities of good HLA matches (5/6) can be achieved with an inventory of around 1–2 units per 1000 population. For several large European countries (for example, Italy, Spain, France, Germany, UK), this would translate into national inventories between 50 000 and 100 000 units. Hence, based on currently available units, governments should support at least triplication of national inventories, in agreement with the original recommendation of the Institute of Medicine report published in the US (11).

With regard to cost and yield of these programmes, Querol and co-workers (9) estimated that developing a national inventory of 50 000 units with cell dose threshold of 1250 million nucleated cells per CB unit, would cost GBP 68 million in the UK. This inventory would yield a 59–83% probability of finding at least one unit (median

number 9 units) within the 5/6 match category for 50 kg body weight recipients. Of note, many patients unable to achieve ideal cell doses with single unit transplantation, should become candidates for double CB transplantation, based on the very encouraging results published by the Minnesota and other CB transplantation groups, using this procedure (12–15).

Italian CB banking model

In Italy, CB banking belongs to the field of transfusion medicine. Two recent national decrees, both published on 31 December 2009, regulate the Italian CB banking model (16,17).

Ministerial decree 18 November 2009 entitled 'Implementation of a national network of CB banks' (16) established the Italian Cord Blood Network (ITCBN), which links 18 banks located in different Regions. Each of the 18 banks has to be authorized and accredited by the Regions in agreement with a set of minimum requirements and with guidelines described in article 6 of Legislative Decree no. 191 of 6 November 2007. Accreditations and authorizations are notified by the Regions to the National Blood Centre and National Transplant Centre in Rome, which act as national competent authority for their respective areas of competence and coordinate regional programmes. Primary objectives of ITCBN are collection, storage and distribution of CB for haemopoietic transplantation through implementation of (i) CB banking organization in agreement with national and international haemopoietic transplant criteria and requirements; (ii) regular data flow to the Italian Bone Marrow Donor Registry, which acts as national hub for haemopoietic stem cell procurement; (iii) specific staff training programmes; (iv) CB donation campaigns, developed in cooperation with volunteer associations, aimed to achieve optimal inventories; and (v) cooperative programmes to document CB recipients' follow-up.

Ministerial decree 18 November 2009 entitled 'Provisions on CB stem cells for autologous-related use' (17) regulates CB autologous conservation and donation for a specific actual or potential-related recipient. This decree defines CB storage as a primary interest for the national health service and limits this practice to specifically authorized public organizations. It explicitly prohibits private banking and any form of advertising. It allows and supports: (i) altruistic donation for allogeneic transplantation; (ii) dedicated storage for a relative affected by a disease curable with CB transplantation and with clinical indication to this type of transplant; and (iii) 'preventive' storage in case of delivery of healthy newborns in families at risk of transmitting genetic conditions treatable with CB transplant. The decree includes a useful attachment listing

Table 3. Technical issues relevant to different CB banking models

1. Minimum cell dose per unit in inventory
2. Technique for CB unit volume reduction
3. Number of aliquots per banked unit
4. Liquid versus vapour nitrogen storage
5. CB unit overwrapping
6. Proportion of ethnic minorities in inventory
7. Reimbursement fee per transplanted patient versus per distributed CB unit

clinical conditions of established use of CB haemopoietic stem cell transplantation. In addition, it provides instructions for CB exportation to private foreign CB banks.

Ancillary norms make primary reference to national blood transfusion law and its related decrees to define criteria for allogeneic CB donor selection.

Technical issues

Although not primarily addressing technical aspects of CB banking, this article would be incomplete without briefly discussing some critical issues that may be relevant to different CB banking models (Table 3).

Minimum cell dose per unit represents a basic characteristic of allogeneic CB inventories, which needs to be defined with particular attention to future clinical needs and prospective collections. Significant direct relationship between cell dose and haemopoietic transplantation outcome that has been documented in a large number of studies, prompts adoption of increased thresholds. It may be expected that this will translate into very high CB unit discard rates and adequate information on the reason for this choice should be provided to donors to prevent possible disappointment. Of course, different (lower) thresholds for storage should be defined for dedicated units, which may present unique compatibility characteristics. Other criteria are expected to be applied for commercial banking, where the banking decision may be taken with expectation or hope that even very small numbers of cells may be used for future transplantation programmes.

Considering the high cost of cryogenic space, techniques for CB unit volume reduction are and will be of paramount importance in large CB banking programmes. Although numbers of techniques have been developed and their *in vitro* evaluations have been published (18), comparative information on their impact on transplantation outcome is still limited.

In most current inventories, CB units are stored in single bags or in bags where a minor aliquot can be separated for additional processing at the time of transplantation. The latter option has been developed mainly in relation to

ex vivo haemopoietic stem cell expansion protocols, although no conclusive evidence on clinical value and practicality of these programmes has been gathered so far. At the Milano Cord Blood Bank, several thousand red cell and plasma reduced units processed in the last few years have been stored as three 25 ml aliquots (three bags per unit) with the expectation that CB donor leucocyte infusion could represent an interesting option for CB transplantation clinicians. This has not been the case so far.

Other important technical decisions to be taken before starting a CB banking programme regard CB unit overwrapping (a desirable option to reduce risks of cross-contamination) and storage in vapour versus liquid nitrogen. Recent technical improvements in tank construction ensure achievement of very low temperatures close to the upper lid, also in the nitrogen vapour phase, thus reducing cost of liquid nitrogen. Moreover, plans to develop a responsible CB banking model must take into account not only the most prevalent HLA haplotypes in the autochthonous population but also those of ethnic minorities, who currently find limited access to most CB inventories. A relevant issue in this regard is selection of CB collection centres with high or low prevalence of deliveries from ethnic minorities. Querol *et al.* (9) in their study suggest to 'pursue collection centres with the highest ethnic mixture (ideally achieving between 30% and 50% of the CB units from ethnic minority populations)'. Effective relationships with ethnic minorities may require availability of translators and cultural intermediaries.

Finally, any effort to develop a responsible CB banking model would be incomplete without appropriate cost recovery plans and procedures. Although economic models for definition of a CB release fee have been published (19), information on cost recovery of CB banking programmes based on current CB unit prices (20) is missing in the scientific literature. The current prevalent approach to request reimbursement 'per CB unit' should be considered with the possible reimbursement alternative 'per transplanted patient'. The latter approach may reduce an undesirable economic difficulty possibly hampering medically indicated uses of double CB transplantation, in the best interest of CB transplantation candidates.

Conflict of interest

The authors are the current Medical Director (PR) and Technical Director (LL) of the Milano Cord Blood Bank, a large public cord blood bank storing cord blood units donated for allogeneic altruistic transplant and for family-related use in case of current cord blood transplant indication in a family member or genetic risk of transmission of disease curable with cord blood transplant.

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