厚生労働科学研究費補助金
（厚生労働科学特別研究事業）

造血幹細胞移植の制度に関する国際比較分析に関する研究

平成24年度 総括研究報告書

研究代表者
小　寺　良　尚
愛知医科大学医学部教授

平成 25 年 3 月

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別紙３

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研究代表者　　小 寺 良 尚　　愛知医科大学医学部教授

研究要旨
世界造血細胞移植ネットワーク（WBMT）を介して、海外主要国の造血幹細胞移植に関わる法律・規定の有無とその運用の実情、造血幹細胞移植の世界サーベイ、患者・ドナーの成績・安全担保の仕組みにつき研究した。法律を有する国はまだ少なく、その必要性を提唱する国は多かった。世界の造血幹細胞移植は累積100万例を超えることが示されるとともに、我が国を含むアジアの成績は欧米と遜色ないことが明らかになった。移植療法に必要な造血幹細胞ドナー数は世界で2000万人（件、臍帯血を含む）に到達していた。こうした患者・ドナーの世界レベルでの補足システムは、世界保健機関(WHO)の提唱する“移植医療における警戒と監視”の具現化であり、実践モデルと考えられた。

A．研究目的

造血機能障害等に対する有効な根治的治療である造血幹細胞移植は、 我が国において年間約5,000件前後が行われており、重要な医療技術の１つである。今般、移植に用いる造血幹細胞の適切な確保と、造血幹細胞移植の円滑かつ適正な実施を目的として、造血幹細胞移植に係る法律（議員立法）が、今国会への提出を見込まれている。

我が国の造血幹細胞移植は、 海外との比較においてもその成績は優れており、 我が国の造血幹細胞移植の普及率は世界的にもトップクラスにあると言われている一方、 法的な基盤が十分でない中、 現場の努力や工夫によって、 これを発展させてきた。

現在、造血幹細胞の提供は、国内に対するものにとどまらず、中国、米国、欧州各国等の海外に対して相互の連携がより活発化しており、我が国に対する国際的な期待は大きい。 更に現在知られている造血機能障害や、悪性腫瘍に対する治療としての役割のみならず、 国内外において、脳性麻痺やＩ型糖尿病など、 現在根治することが困難な疾病に対する治療としての研究が進められるなど、 今後発展の余地が大きな分野である。

このような状況において、 造血幹細胞移植の諸外国の制度の特徴や、 諸外国政府の政策的・経済的関与の現状を知ることにより、我が国の造血幹細胞移植制度・政策に関する基準等に反映することが期待できる。

また現在、 造血幹細胞のあっせんや供給は、骨髄移植推進財団や臍帯血バンクによって行われているが、 あっせんに時間がかかること、 適切なドナーが見つからない場合があること、 また臍帯血バンクの整備の必要性等の課題が指摘されている上に、 今後は高齢化等に伴い、 造血幹細胞移植の重要性はますます高まるものと予想されている。

本研究は、 我が国で初めて、 諸外国における造血幹細胞移植の位置づけや、 国の関与、 費用の分配方法、 あっせんの方法や移植成績等を比較検討することによって、 我が国における造血幹細胞移植のさらなる発展と、 国際協力を推進するにあたっての諸課題について検討しようとするものである。

B．研究方法

本研究は、 造血幹細胞移植に関連し、 先進国並びに新興国を対象と して国内及び諸外国の造血幹細胞移植における文献、 及び必要に応じて諸外国の関連学会 ・ 関連団体等に対して調査を行い、 可能な限り詳細に現状を把握するために以下の研究を行う。

1）APBMT/WBMT/WHOを介した、造血細胞移植に関わる情報収集

我が国同様、造血細胞移植先進国（米国、英国、ドイツ、フランス）を中心として、中国、韓国などアジアを含めた諸外国における、造血細胞移植療法の普及率、骨髄・末梢血バンク、臍帯血バンクの在り方と公費による助成の実態、患者、ドナー登録・フォローアップの仕組みと公費による助成の実態、造血幹細胞の値段、造血幹細胞採取・移植施設の認定基準、造血幹細胞移植療法と他の細胞療法や再生医療との関係につき情報収集を行い、今般新たに立法化が予定されている造血幹細胞移植法（仮称）に基づく諸施策に反映させる。

なお、米国、スイス等においては造血細胞移植関連法案が一部施行されているが、特に日本と造血幹細胞移植の相互協力が進んでいる米国、ドイツについては、現地調査を行う。

また、WHOでは関連法案の基本的考えや法案が対象とすべき領域等につき、近年一定の見解を出しつつある。これらに対するWHOの意向等についても、APBMT / WBMT / WHO を介して資料収集するとともに、各国・地域における制度との相互比較を行う。

2）患者・ドナーの安全性や臨床成績に関するデータの、世界規模での集計と解析

APBMT / WBMTが保有している患者データ、またドナーデータについて、比較検討できる形式への変換を委託し、データを収集する。これを用いて、各国における造血幹細胞移植の対象疾患や人数、臨床成績などの現状を比較する。

更に、世界の非血縁ボランティアドナーの安全性担保状況を検証する。それと並行し、我が国の末梢血幹細胞ドナーを例外として、こうした仕組みの枠外にあった、世界血縁ドナーの安全性担保状況についても調査を行う。

これをもって、各国制度における造血幹細胞移植の実態を検証し、更なる移植成績の向上につながることを示すとともに、我が国で行われているような、血縁者も含めた、全ての造血細胞ドナー事前登録・適格性チェックシステムが、ドナーの安全を担保する上で有用であることを証明する。

（倫理面への配慮）

患者、ドナーの情報は関与する全ての組織・機構において匿名化されており、且つそれらのデータセンターへの登録・利用に関しては関与する全ての組織・において倫理審査委員会又はそれに相当する委員会において承認を受けている。

C．研究結果

1）APBMT, WBMT の概要と WHO との関係:

WBMT は表-1 に示す造血細胞移植関連 18 国際組織即ち、APBMT (Asia-Pacific Blood and Marrow Transplantation Group)、ABMTRR (The Australasian Bone Marrow Transplant Recipient Registry)、EBMT (European Group for Blood and Marrow Transplantation)、CIBMTR (Center for International Blood and Marrow Transplant Research), WMDA (World Marrow Donor Association), AABB (American Association of Blood Banks), EMBMT (The East Mediterranean Blood and Marrow Transplantation Group), Netcord, Eurocord, ESH (The European School for Haematology), EFI (The European Federation for Immunogenetics), ISCT (The International Society for Cellular Therapy), JACIE (Joint Accreditation Committee-ISCT), BMDW (Bone Marrow Donors Worldwide), FACT (Foundation for the Accreditation of Cellular Therapy), ASBMT (American Society for Blood and Marrow Transplantation), ASHI (American Society for Histocompatibility and Immunogenetics), EMBIDS (European Marrow Donor Information System)、を束ねる

連邦であり、2006 年に設立された。APBMT（現在アジア 19 カ国/地域；日本、韓国、台湾、中国、ホンコン、モンゴル、インドネシア、マレーシア、フィリピン、シンガポール、ベトナム、タイ、バングラデシュ、ミヤンマー、インド、パキスタン、イラン、オーストラリア、ニュージーランド、が参加）もその一員である。WBMT は 2013 年 1 月、WHO の公認 NGO となった。

２）APBMT/WBMT/WHO を介した、造血細胞移植に関わる情報収集:

造血細胞移植の世界における普及率：

WHO 基準の世界区分、アジア・太平洋地域、南北アメリカ地域、ヨーロッパ地域、アフリカ・東地中海地域毎に、国別造血細胞移植年間実施数を WBMT として調査した。人口 1000 万人当たり 300 件以上の造血幹細胞移植を実施している国はアジアでは我が国とオーストラリア/ニュージーランド、南北アメリカでは米国、ヨーロッパではドイツ、イギリス、フランス、イタリア、北欧等の欧州内での先進国諸国、アフリカでは未だ存在していなかった。次に上記区分地域別の造血細胞移植累積実施数並びに、それらを全て合わせた世界での累積実施数を調査した。世界の総累積数は 2013 年初頭に 100 万例を超え、地域別では欧州 53%、南北アメリカ 31%、アジア 15%、アフリカ・東地中海 1％の順であった。従ってアジア地区で行われた累積数は約 15 万例であり、内我が国が約 7 万例を実施している。

３）骨髄・末梢血バンク、 臍帯血バンクの在り方と公費による助成の実態

造血幹細胞バンクの状況は、WBMT のメンバー組織の一つである BMDW を介して知ることが出来る。現在 HLA 情報を有する骨髄・末梢血ドナー及び保存臍帯血の総数は 53 カ国、116 レジストリー（バンク）からの合計で 21,650,000 人/件を超えている。116 バンクの内 46 バンクは臍帯血単独バンク、明らかになっているところで 1 バンク（米国骨髄バンク：NMDP）のみが骨髄・末梢血・臍帯血を扱っているが、これは米国内で他の臍帯血バンクが存在しないことを意味しているわけではない（後述）。残り 70 は骨髄・末梢血バンクでそれが 53 カ国に渡っているから、骨髄・末梢血バンクにかぎってみても 1 国内に 2 つ以上のものを有する国があることになる。以下国ごとに骨髄・末梢血バンク数：臍帯血バンク数を示す；アルゼンチン 1：1、アルメニア 1：0、オーストラリア 1 ： 1 、オーストリア 1：1、ベルギー1：1、ブラジル 1：0、ブルガリア 1：0、カナダ 1：1、中国 2：0、クロアチア 1：1、キプロス 2：1、チェコ 2：1、デンマーク 2：1、フィンランド 1：1、フランス 1：1、ドイツ 1：2、ギリシャ 2：2、ホンコン 1：0、ハンガリー1：0、インド 2：0、イラン 1：2、アイルランド 1：0、イスラエル 3：2、イタリア 1：1、日本 1：1（東京臍帯血バンクが唯一 BMDW へ加盟登録している）、韓国 0：2（韓国のソウル大学を中心とした骨髄・末梢血バンクと KMDP は最近統合に近い状態にあると聞くが、なぜか BMDW には登録していない）、リトアニア 1：0、マケドニア 1：0、メキシコ 1：1、オランダ 1：1、ニュージーランド 1：0、ナイジェリア 1：0、ノルウェイ 1：0、ポーランド 3：1、ポルトガル 1：0、ルーマニア 1：0、ロシア 3：1、セルビア 1：0、シンガポール 1：0、スロバキア 1：1、スロベニア 1：1、南アフリカ 1：0、スペイン 2：1、スウェーデン 1：1、スイス 1：1、台湾 1：5、タイ 1：1、トルコ 2：1、英国 3：2（Anthony Nolan 臍帯血部門を含む）、アラブ連合 1：0、ウルグアイ 1：0、

合衆国 3：7（NMDP 臍帯血部門を含む)。公費の助成に関してであるが、米国骨髄バンク（NMDP）は法に基づく政府助成を受け、英国骨髄バンク（Anthony Nolan Bone Marrow Donor Trust）も政府補助金を得ている。フランスの骨髄バンクは政府内組織である。ドイツ骨髄バンクは米国 NMDP に次ぎ世界第二位の規模であるが民間団体である。

４）造血幹細胞移植法（造血幹細胞の値段、造血幹細胞採取・移植施設の認定基準、 造血幹細胞移植療法と他の細胞療法や再生医療との関係を含む）に関する世界アンケートの実施

諸外国における造血幹細胞移植の位置づけをあきらかにする目的で、１）関連する法律や通達の有無、２）ＨＬＡ情報の管理の仕方（単一、公的、アクセス)、３）研究目的での造血細胞の転用の可否、４）費用の配分方法、５）価格が設定されているか（採取料、移植料)、６）患者負担の割合、７）斡旋の方法　（単一アクセス、移植チームの仕事、搬送（特に臍帯血)、８）患者負担金の有無、９）症例適格基準（制限の有無)、１０）ドナー適格基準、等に関する国際アンケートを、WBMT を介して行った。計１８カ国から回答を得たが、それらはＷＢＭＴ構成主要国際組織である CIBMTR の米国，EBMT のオーストリア、スウェーデン、ポーランド, APBMT の中国、香港、韓国、インド、パキスタン、フィリピン，オーストラリア/ニュージーランド、EMBMT のサウジアラビアを含み、回答者はそれぞれの地域を代表する人たちで、その地域の現状を、国をまたいで回答したものとなっている。以下にアンケート回答結果の要点を記す；

回答結果の要点

１）造血幹細胞移植に関する法律/通達の有無：特化された法律あり；16.7%、他の関連する法律に組み入れられて存在；50%、なし；33.3%、２）法律の必要性：必要あり；66.7%、必要無し；33.3%、３）法律施行後貴国/地域の造血幹細胞移植領域は発展したか：発展した；50%、必ずしもそうではない；50%、４）法律は移植/採取施設レベルにおいて移植の発展に寄与したか：はい；58.3%、いいえ；33.3%、分からない；8.3%、５）法律は骨髄・末梢血幹細胞バンクレベルにおいて移植の発展に寄与したか：はい；75%、いいえ；16.7%、分からない；8.3%、６）法律は臍帯血バンクレベルにおいて移植の発展に寄与したか：はい；33.3%、いいえ；25%、分からない；41.7%、７）法律はドナーHLA データセンターレベルにおいて移植の発展に寄与したか：はい；66.7%、いいえ；25%、分からない；8.3%、８）法律は移植症例データセンターレベルにおいて移植の発展に寄与したか：はい；58.3%、いいえ；33.3%、分からない；8.3%、９）法律は新しい研究のレベルにおいて移植の発展に寄与したか：はい；16.7%、いいえ；50%、分からない；33.3%、１０）法律は医療費のレベルで移植の発展に寄与したか：はい 33.3%、いいえ；58.3%、分からない；8.3%、１１）貴国/地域には同種造血幹細胞移植の適格基準はあるか：はい；82.4%、いいえ；17.7%、１２）適格基準を満たす患者数を推定する上でどのようなデータを用いるか：国のデータ；33.3%、学会のデータ；46.7%、バンクデータ；13.3%、その他；6.7%、１３）貴国/地域は造血細胞移植領域の学会を有するか：特化された学会を有する；37.5%、他学会の一部として有する；25%、今のところ持っていない；37.5%、１４）誰が移植医療費を負担するか：公的健康保険；93.8%、私的健康保険；12.5%、他の支援基

金(研究費等);12.5%、患者が負担する;18.8%、その他;12.5%、１５）主治医が移植に用いることが出来る造血幹細胞を検索し最終的に入手に至るまでの過程で、アクセスポイントは幾つか：一つ；68.8%、複数；31.3%、１６）骨髄・末梢血幹細胞バンクや臍帯血バンクで保存されている細胞は研究用に用いることも許可されているか:はい;31.3%、いいえ;37.5%、その他;31.3%、１７）骨髄幹細胞の価格は設定されているか：はい；37.5%、いいえ；62.5%、１８）末梢血幹細胞の価格は設定されているか：はい；37.5%、いいえ；62.5%、１９）臍帯血の価格は設定されているか：はい；18.8%、いいえ；81.3%、２０）国際的にコンセンサスを得ている移植適応基準以外の基準があるか：はい（一部制限されている）；25%、いいえ；75%、２１）上記を制限しているものは：法律/規定；50%、保険；0%、その他；50%、２２）制限の要因が年齢の場合：50 歳まで；25%、65 歳まで；25%、70 歳まで；25%、無回答；25%、制限の要因が疾患状態の場合:いくつかの疾患においては特別申請が必要、治療抵抗性は制限あり、その他;移植施設の設備、２３）その他もし情報があれば：。

５）上記アンケートにおいて法律・規定ありとした国の主な法律・規定

a)米国：Public Law 109-129-Dec.20, 2005, “Stem Cell Therapeutic and Research Act of 2005”

b) Public Law 111-264-Oct. 8, 2010, “Stem Cell Therapeutic and Research Reauthorization Act of 2010”

c) Private Cord Blood Banking: Experiences and Views of Pediatric Hematopoietic Cell Transplantation Physicians. 2009

d) ＥＢＭＴ：On the issue of cord blood (CB) transplantation and private banking the EBMT.

e) 韓国：Enactment of a low for governmental support of the use of cord blood, and ethical issues.

f)韓国：The prospect of the government management for cord blood in Korea-At the time of enactment of the [Cord blood management and research act]-

これらの内、資料-３，４に示すものは、CW Bill Young Program と呼ばれ、我が国の“造血幹細胞移植推進法（略称)”に対応するものと考えられる。

６）米国の法律に関する識者招へい事業

上述の米国の法律(W Bill Young Program)に対する理解を深め、それの執行後の状況を把握する目的で、CIBMTR から J Douglas Rizzo 博士を招聘し公開討論会等を行った。本招聘は全項の米国の法律である CW Bill Young Program の概要と執行状況を把握する上で有益であった。ここに公開討論会（勉強会）のレジメを収録しておく。

「造血幹細胞移植の制度に関する国際比較分析」研究

Prof. Douglas Rizzo を囲んでの勉強会　レジメ

Summary of Presentation of CW Bill Young Cell Transplantation Program

ビルヤング移植プログラムの執行状況

January 15, 2013

The U. S. Stem Cell Therapeutic and Research Act of 2005 (Public Law 109-129) established the C.W. Bill Young Cell Transplantation

Program (the Program) to collect, analyze, and report on outcomes for all allogeneic transplants and on other therapeutic uses of blood stem cells. The Program was re-authorized in 2010 (Public Law #111-264).
2005 年に米国幹細胞治療・研究法（公法 109-129）に基づき、ビルヤング移植プログラム（以下プログラム）が全ての同種移植並びにその他の幹細胞を用いる治療に関わる情報の収集、解析、成績の報告を目的として定められた。プログラムは 2010 年に更新されている。
CIBMTR was awarded a contract with the Health Resources and Services Administration (HRSA) to administer the Stem Cell Therapeutic Outcomes Database (SCTOD) for the Program; National Marrow Donor Program (NMDP) was also awarded contracts to administer other portions of the Program.
CIBMTR（国際ＢＭＴ研究センター）がプログラム中の SCTOD（幹細胞治療成績データベース、以下データベース）を執行する組織として選ばれ厚労省と契約した。NMDP（米国骨髄バンク）はプログラムの他の部分を執行する組織として選ばれ同省と契約した。
The Program goals are to make information about HCT available to patients, families, health care professionals and the public; to help create better processes for identifying unrelated matched marrow donors, peripheral blood stem cell donors, and cord blood units through one electronic system; to increase the numbers of unrelated adult volunteer donors and cord blood units available; and to expand research to improve patient outcomes.
CIBMTR has grown to meet the needs of the SCTOD contract, which in turn enhances CIBMTR's ability to facilitate research conducted under U24-CA76518.
プログラムの目標は１）患者、家族、医療関係者、一般国民のための幹細胞移植情報を作成すること、２）非血縁骨髄、末梢血ドナー、保存臍帯血へ、単一の電子媒体システムを通じて検索できるより良いシステムを作ること、３）非血縁ドナーと臍帯血ユニットを増やすこと、４）移植成績向上のための研究を拡張すること、である。
CIBMTR は契約に基づくデータベースの要件を満たすべく拡大され、結果的に UA24－CA76518 で規定された研究を支える CIBMTR の機能が強化された。
Dr. Rizzo, Project Director for the SCTOD will provide an overview of the Program, describing each of the components, their responsibilities and relationships in the Program. These components include the Advisory Council to the Secretary of Health and Human Services, the SCTOD, the Cord Blood Coordinating Center, a Bone Marrow Coordinating Center, an Office of Patient Advocacy/Single Point of Access, and a National Cord Blood Inventory. The benefits of the Program will be described from the perspective of the HCT recipient, volunteer unrelated donors, transplant centers, researchers, the government, and third-party payers (insurers and employers). Limitations of the Program will also be addressed.
Dr.Rizzo はデータベースのプロジェクト責任者であるが、プログラムの概要とその内容、プログ

ラムとデータベースプロジェクトとの関係並びにプロジェクト側の責務について報告するであろう。内容の中には１）厚生科学審議会、２）プロジェクトの実態、３）臍帯血コーディネートセンター、４）骨髄（末梢血）コーディネートセンター、５）患者相談/単一アクセスのためのオフィス、６）国の臍帯血保存件数、が含まれる。プログラムの利点を１）移植患者、２）ボランティアドナー、３）移植センター、４）研究者、５）行政、６）経費に関わる第三者（保険会社や雇用主）の観点から述べるであろう。一方プログラムの限界についても言及する。

The impact of the Program on transplantation in the United States, especially increasing use of cord blood as a source of stem cells for transplantation will be briefly discussed. One particular benefit of the Program, research through the SCTOD, will be highlighted. The Outcomes database serves as a platform for public reporting, and robust tool to advance the field of HCT through research. CIBMTR has successfully leveraged the requirements of the SCTOD, funding from the National Institutes of Health, and the benefits of the collaborative academic environment to facilitate meaningful research to improve survival, access to HCT and understand late outcomes of HCT. The importance of the academic environment and the expertise it affords to stimulate collaborative research will be emphasized.

米国内の移植に対するプログラムの効果、特に臍帯血移植の増加についても述べる。更にプログラムの特筆すべき利点としての、データベースを介した研究について述べる。データベースは広報の基盤であり、研究活動を介して幹細胞移植分野を進展させる強力な手段でもある。CIBMTR はデータベースとして要求されているものを充足することに成功し、NIH からの資金を受け、又幹細胞移植の生存率向上、幹細胞移植に至るまでの道筋、幹細胞移植患者の長期予後への理解等のための有効な研究を実施する上で必要な研究機関（大学）との良き関係を確立している。アカデミックな環境と共同研究を推進する上での専門家の必要性についても強調したい。

７）CIBMTR/NMDP の視察

前項から得られた情報を基に、米国法律執行の中核的役割を果たす CIBMTR, NMDP の視察を実施した。視察項目は以下の如くである；

CIBMTR においては、ア）SCTOD のためのスペース、作業者の専門と人数、イ）将来今回の我が国の法律に基づいて作られた社団法人日本造血細胞移植データセンターが直にコンタクトが取れる要人との面会、ウ）SCTOD（CIBMTR）とＮＭＤＰ及び他のデータを必要とする組織間のデータ交換の方法（何かレギュレーションが在るか等も含め）。

NMDP においては、ア）The Office of Patient Advocacy/Single Point of Access (OPA/SPA)について、NMDP との関係、作業員の専門性と数、主任、OPA と SPA を同一部署として運営する背景思想、SCTOD が OPA/SPA とデータを共有する仕組み、同２者は距離的には離れているが、定期会合等を持つのか、もし患者がデータを要求した時直接渡すこともあるのか、主治医等を介してか、イ）米国内に多数ある臍帯血バンクと NMDP の関係、ウ）米国法律の NMDP への影響。

視察は研究協力者 P Watly の調整により２日間

という短期ではあったが極めて効率的に行われ、多くの情報を得ることが出来た。以下に主要なもののみ記載する；

CIBMTR において；

ア）SCTOD のためのスペース、作業者の専門と人数：即ち CIBMTR の規模。Chief Scientific Director である Mary Horowitz をトップとして組織図上名前の載っているメンバーだけで７１名である。イ）将来今回の我が国の法律に基づいて作られた社団法人日本造血細胞移植データセンターが直にコンタクトが取れる要人：Mary Horowitz, Douglas Rizzo。ウ）SCTOD（CIBMTR）と NMDP 及び他のデータを必要とする組織間のデータ交換の方法（何かレギュレーションが在るか等も含め）：（以下の NMDP の項に記載）

NMDP において；

ア）The Office of Patient Advocacy/Single Point of Access (OPA/SPA)について、NMDP との関係：IT システムを NMDP と共有する、NMDP 内のグループ。イ）作業員の専門性と数：看護師資格を有するもの、コーディネーター、研究者併せて 20 名以上が仕事をしている。ウ）主任：Elizabeth Murphy　エ）OPA と SPA を同一部署として運営する背景思想:　コーディネートという作業が両者を結びつけた。オ）SCTOD が OPA/SPA とデータを共有する仕組み：SCTOD がデータを作る。それを政府のウェブサイトに公開する。それを OPA/SPA が必要に応じて加工する。カ）同２者は距離的には離れているが、定期会合等を持つのか：初期には頻回に会合を持ったが、現在では関連する学会・会合を利用する。電話、電子媒体等による連絡は頻回である。キ）もし患者がデータを要求した時直接渡すこともあるのか、主治医等を介してか：CIBMTR(SCTOD)への患者からの問い合わせは多くあるが、その様な時には主治医を介してデータを渡す。CIBMTR に中に直接患者対応をする役割に医師はいない。ク）米国内に多数ある臍帯血バンクと NMDP の関係：（法律の基づき一元化中ではあるが、強制はしていないようである。）ケ）米国法律の NMDP への影響：（促進と規制双方を実感しているようであった。）

８）欧州骨髄バンク（英独仏）の視察報告

（資料提供：三田村真氏）

研究協力者2名による欧州骨髄バンクの視察報告を得たので収録しておく。

前文

全国協議会では、過去21 年間におよぶ患者支援、ドナーリクルート活動の実勢と、関連諸団体との連携を踏まえて新法施行後の、真に患者にとって有益な造血細胞移植医療環境を整備するための参考と資するために、 欧州先進国の造血細胞移植バンク訪問を企図し、英国（アンソニーノーラン財団）、ドイツ（ZKRD）、フランス（FGM）との面談を終えたので報告致します。

総括

１．　大きな成功を収めている欧州３カ国の造血細胞バンクに共通するポイント、特徴は以下の３点に集約される。① Web によるドナー希望者のオンライン登録制度の導入、ドナーDB への情報の自動転送、② 唾液検査キットによる DNA 簡易測定キット利用による幅広い層に対するリクルート活動の展開、③ ドナー登録年齢の低年齢化促進、ならびに男性ドナーの積極的登録の推進

２．今回、日本で制定されたような“縛り”とも、“促進法”とも言える移植に関する基本法は、基本的に欧州３カ国には存在しない。また、レギュレーションとしての規制とも言える、日本で言う

ところの薬事法に類する法、ガイドラインなどは一部存在するが、それでも原則、“移植を推奨するための”性質のものであり、日本のような規制法ではない。

３． 一方で、欧州３カ国のバンク組織の運営、事業目標などは、明確にドナー登録拡大と、移植機会提供という観点であり、患者支援、或いはドナーフォローアップと言った側面は実質存在しない。 それ故、きめ細かな患者およびドナーのニーズ、安全性に考慮した日本の基本スタンスとはまったく異なる状況であった。

４． また、３カ国それぞれ隣同志の国家であるにも関わらず、その国民性の違い、歴史的背景などからそれぞれ独自の特徴を有していることは興味深い。

５．今回、新法制定に漕ぎ着けた日本であるが、欧米の造血細胞バンクとの比較では、単純に劣っているという括りになるのではなく、むしろ日本人特有のち密さ、慎重さなどが発揮されてむしろ先進事例となっている項目も散見された。 そのため、全てを海外バンクに学ぶのではなく、日本の国土、国民気質などに合致した独自のバンク構想を策定してもよいのでは、という印象を持った。

以下に、視察3バンク及び対象として我が国の、バンク名、ドナー登録者数・登録年齢、組織形態を記す；Anthony Nolan Trust （英国）、約46 万人・ 16～30歳（新規登録）、民間団体、政府補助金、ZKRD （ドイツ）、約450 万人、民間団体、FGM （フランス）、約20 万人・18～40 歳、政府内機関、JMDP/JCBBN （日本）約45 万人 18～55 歳公益法人、政府補助金

＜各国訪問記＞

１． 英国 Anthony Nolan Trsut （ロンドン北西部）

面談日時： 2012 年10月29 日

面談者 ： Richard Davidson, Director of Communications and Marketing
Ann O'Leary, Head of Register Development, Manager of R&Be

(1) 概要

・現在、ドナー登録者数約46 万人。 日本と丁度同規模。男性約20 万人、女性26 万人。 目標とするドナープールは70 万人。 特に、 HLA 学的見地から示しているのではなく、あくまでも数値目標として設定した。・新規のドナー登録年齢は、以前は16 歳から40 歳までであったが、この10月から30 歳までとする変更を実施した （！）。実際に提供ドナーの平均年齢は29 歳であるというから驚きだ。 現在の登録済みドナーの世代別頻度でいうと、19 歳がピークで7.3%を占める。・ドナー年齢の切り下げは、順調なドナー確保が実現できている背景と合わせて、やはり移植成績、主治医側からの要望が、「若い男性ドナーを！」 と、少し誤解を受けかねない希望を表明するための施策実施だという。その影響により、今年末だけで登録抹消となるドナー登録者 （現59 歳） が8,000 人にも及ぶという。 以降、かつての上限だった60 歳の段階で自然減につながるという。 因みにイギリスの献血年齢は18 歳から49 歳。・さい帯血バンクに関しては、４病院プラスNHS （英国厚生省） ７機関で保存実施、現在、保存数が少ないが、2020 年までに1 万5 千保存を目指しているという。・ HLA 検査方式は従来A, B, DP であったが、2012 年に入り DQ を追加し、 DNA４ケタ化。 血清学的検査からの転換は2000 年代初頭。 ということで、やはり登録ドナーの大半は血清データのままだが、追加検査等は実施せず、あくまで適合してから再検査

する体制・ HLA の分布ならびに適合度から言うと、現在では登録患者の約90%に適合ドナーは見つかるらしい。 日本が約95%と説明すると頷きつつも、羨ましいという表情だった。 特に、見つからな場合の多くの理由は、やはりHLA の多様性に依存するようで、白色人種以外にも、アフリカ系の血液が流れていることから、多様な分布を示すという。・ドナーリクルート活動による、登録者の内訳では、大別すると２種類に分けられ、すなわち ANT のスタッフ・リードと呼ばれる、職員が関係団体と協力するなりして、実際に手がける活動の結果、得られるドナーの確保数が Staff Leads 案件。中でも、その名も「Marrow」と呼ばれる医学系大学生中心の自主ボランティア・サークルによる登録会が29%で最も多いという。 Marrow は、90 年代後半に発足し、現在40団体、18 歳から21 歳までの３年間の活動。 ３年次には、人材確保し、引退するという。世代交代は順調に推移している。次いで、陸軍による協力が最も盛んで全体の約10%、 さらに Patients Appeal と言い、いわゆる患者さん自身による露出、広報手段による影響が9.5%（日本で言う、かつての AC もえちゃん）、大学での登録が5.5%となっている。 ５番目としてはイベント関連。 100 から200 人規模の若者向けのイベント、特にMusic Festival が最も効果ありらしいがそれによる登録が近年増加傾向にある。

NAVY/AirForce （海軍/空軍） による協力も最近始めたばかり。 最近脚光を浴びているのが、R&Be というグループによる登録活動。これは、もともとライフサイエンスに興味関心があった団体が、骨髄バンク支援に走るようになったということで、今回Mtg で面談したAnn も、この R&Be 担当のマネージャという肩書を持っていた。・一方、 Marketing Lead と呼ばれる登録方式では、圧倒的な割合が、 Online登録。つまり、ネット登録。 Webサイトからの申し込み者に対して、 Spit Kit を郵送することでの登録が全体の32%を占める。 唾液採取キット（１セット７ポンド、約1,000 円）は、これほど手間がかからずに登録に寄与できる方法もなく、非常に効率的で特に若い世代の獲得に役立つという。・ドナー登録に地域制、偏在があるのかと聞いたところ、ロンドン周辺が大半を占めると思われたが、決してそうではなく、全土に分布しているという。・因みに、英国では患者自身が登場し積極的にアピールしているが （図２女児写真）、欧州各国でもそのスタンス、考え方が様々で、 ドイツでは容認しているが、それほど積極的ではない。一方、 フランスでは Patients Appeal は法律により禁じられている。 但し、英国でも様々な影響、患者さんの状態を考慮して最長３年で露出を止めにするという。・様々な登録活動において推進に寄与しているのが、唾液中DNA採取方法。かつて、 NMDP （全米骨髄バンク）などでは口腔内粘膜採取方法を採用していたが、ANT ではより進化、簡便化したキットを採用。 この簡易キットがあるために、 不特定多数が集まるイベント等での一斉登録が可能になる。HLA 検査精度に関しては、やはり再検査の必要な検体もあるという。 これは、十分な DNA 量を採取できなかった場合に起こるという。・課題としては、効率追求と、コスト削減。唾液採取キットの無駄で終わっているキットの低減へ。・ブランドイメージとしては、以前は 「花」 をテーマにしてロゴを使用していたが、2010 年からコンサルタントを入れて CI（Corporate Identity） を検討し、現在の黒と緑を基調としたイメージカラーに変

更。・ ANT の運営、基本方針となるガイドライン、法などが存在するかと確認したら、まずは WMDA Standard に準拠しているということだが、他には英国内の HTA, Human Tissue Authority という組織が、ヒト細胞を用いた移植に関する合意文書、 といった内容があり、 これらに準拠しているが、いずれにしても厳しいレギュレーションではないという。・ Patients Adovocate （患者擁護） に関しては、現時点ではまったくアクションがない。せめて Patients Appeal という関連で、患者が普及啓発にアピールするための活動に患者を起用する程度という。但し、 ANT の内部でも、患者支援の活動も同時に実施しないと不十分であるという認識は最近出始めているという。・因みに、アンソニー（患児）の母親のシャイリー・ノーランは、５年前に死去。現在、一部の理事が家族とコンタクトを取っているが、事業には一切関知していないという。また、公的骨髄バンクであるにも関わらず、個人名、固有名詞でいつまでもバンクの名称が残存していることが問題無いか、確認したところ、確かに好ましくない、 という意見もある一方、今さら変更できないという肥大化した組織が抱える課題に直面しているようだった。

２．ドイツ ZKRD; Zentrales Knochenmarkspender-Register Deutschland （ウルム市）

面談日時： 2012年10月31 日

面談者 ：Hans-Peter Eberhard,PhD, Head of Search and Transplant Services

・ ZKRD （ドイツ骨髄中央バンク） の所在地は、ドイツ南部の小都市ウルム市に位置する。丁度、ミュンヘンとシュツットガルトの中間点辺り。・ ZKRD は、唯一の公的骨髄バンク。 政府からの補助金等は一切受けていない、完全に独立したバンク組織。よって、法的規制もガイ ドライン等も特に存在しない。・ 医療保険についても、短期入院、 長期入院で異なるが、いずれにしても患者の経済事情によって支払が滞る、不明なようにならないように社会のセーフティネットは存在している。具体的には、医療費の支払いが年間所得の2%を超えてはならない、縛り、上限がある。・ ZKRD の現在のドナー数ン実績は約500 万人。ざっと日本の10倍。なぜ、これほどまでに成長、成功したのかと確認したところ、幾つかの理由は見当たるものの、「自然にそうなった」、というコメントが帰ってきた。・ ZKRD の本部が、ドイツ南部の小都市ウルムに決まった経緯について尋ねると、政府が当初中央バンクの公募を1990 年頃に実施した際、３か所のバンク母体が手上げをしたという。 それは、エッセン、ドレスデン、ウルムが名乗りをあげたらしい。 当時ベルリンは、ベルリンの壁崩壊で東西冷戦雪解けの時期であったために、混乱を極めており見送られた。 また、他の候補都市との勝負では有力な大学教授が存在していたこと、既に大学を中心とした地域バンクでの実績があったことなどから最終的にウルムが当確となった。・現在のバンク組織の構成としては、ドナーセンターが29 か所、採取センターが45 か所、移植センターが61 か所（成人・小児別）サーチセンターが12 か所ある。（移植とサーチC は別）・役員は、CEO ２名制。一人は純然たるビジネス経験者、もう一人はMedical Director という称号。今回、お世話になった Hans-Peter は、 Head of Search Transplant Services ということで、コーディネート、移植調整などを含む総括的部署の責任者であり、実質運営部門の最高責任者と言える。 ・

いわゆるコーディネーター活動を行う担当者は40 人。このメンバーは、 DRK （Deutsch Red Kross） ドイツ赤十字社。・ Online登録は、ZKRD 自身は実施していないが、各DC（ドナーセンター）レベルで実施されている。ベルリンのDKMS など。やはり、唾液採取検査方式の採用とセットで。DC からは、ドナー情報が１週間で届き、サーチが始まる。・最近話題になった大規模なイベントとしては、「ミュンヘン・ブレードナイト」 というものに新しく協賛した、これはミュンヘン市内の通りを、歩行者天国としたローラースケートのイベントでやはり若年者層へのアピールの機会になったという。・移植患者とドナーとの対面については、２年後に双方が会いたいと希望した場合、当事者間での決定に任せるというもの。およそ移植ペアの４組に１組が何らかの対面を実現しているという。 記者会見をする場合も、式典での場合も。日本ではネガティブな想定から万一のトラブルを懸念する意見がいまだ多数をしめる。そこで、かつて実際にトラブルが発生した事例を聞いたが、ドイツ国内では聞いておらず、スイスで金銭授受の問題が発生して以来禁止しているという。

３． フランス FGM：France Greffe de Moelle（パリ市北部）

面談日時： 2012年11 月2 日

面談者 ：Dr.Francoise Audat, Donor's Department, Director, Physician,
GFM Registry Dept. Operations Medical Chief Officer, Agence De La Biomedecine

・フランスの骨髄バンクは、完全に国の機関の一部。仏厚生省ビル内に、３つの組織が共存 ・France Greffede Moelle は直訳するとフランス移植・骨髄機関。 職員40 人。コーディネーター約200 人移植施設約50 機関。・ドナー登録者数約20 万人、ドナー年齢40 歳以下・非血縁移植 年間1,000例、血縁も含めると、骨髄移植1,100例、PB,CB はそれぞれ500例・唾液検査方式は、フランスも実施。同検査方式を実施する国としては再検査率として、英、独、スイス、 US など5%以下とされているが、仏では5-10%程度。精度は、DNA 量が足りないと必要になる。・ PB と BM の選択。最初は患者側、ドナーに血栓症があればPB を選択することがある。ドイツはPB 比率高い。・仏の造血細胞の提供は骨髄、末梢血、 DLI 含めて２回までだが、それも同一の患者だけという。何故こうした縛りがあるのか責任者も不可解・統計解析の専門家を職員に抱えていて、年報を発行している。 医師との連携を常に取り、学会発表などもFGM としても積極的に行っている。患者とドナーの対面に関しては、FGMの方針として「禁止」している。理由については、職員の間でもよく理解していない・ “Ce aue tu Donnes aux autres, tule Donnes A toi-meme ” アフリカのことわざ「あなたが与えたのと同じものを、あなたは与えられるのです」このメッセージが記載されたしおりを、 Thank you Letter と一緒に採取後のドナーに、記念品の砂時計と一緒にドナーにプレゼントしている。

9）WHOの動向：

WHO は造血幹細胞移植関連法案の基本的考えや法案が対象とすべき領域等につき、 近年一定の見解を出しつつある。即ち、WHO は、WHO GUIDING PRINCIPLES ON HUMAN CELL, TISSUE AND ORGAN TRANSPLANTATION （The sixty-third World Health Assembly in May 2010）において、臓器、組織、細胞（ここに造血

幹細胞が含まれる）移植・提供に際し、“絶えざる警戒と監視(Vigilance and surveillance)”が必要である旨記載したわけであるが、我が国、APBMT、WBMT がこれまでも行ってきた造血幹細胞移植世界調査及びこれから記す患者、ドナーのアウトカムレジストリ（移植・提供例における予後調査）は、この警戒と監視の具現化として他の領域のモデルと目されている。

患者･ドナーの安全性や臨床成績に関するデータの、世界規模での集計と解析

１）患者の安全性並びに臨床成績の世界規模での集計と解析に関してであるが、集計に関しては先述の世界サーベイに記した。解析はより詳細なデータを集める必要があり、それが患者アウトカムレジストリであるが、APBMT, CIBMTR, EBMT はWBMT内の三大患者アウトカムレジストリの機構である。この三つのレジストリで集約する患者情報の内共通項目を Least Minimum Dataset として設定、2012 年度に初めて先発の CIBMTR, EBMT と同じ基準でアジア・太平洋地域における造血幹細胞移植全体の移植後生存曲線を作成し、この地域の成績が CIBMTR, EBMT のそれと比べ、遜色ないことを示した。

２）造血幹細胞ドナーの安全性に関しては、WBMT の構成メンバーの一つである WMDA が非血縁ボランティアドナー並びに臍帯血に関わる安全情報を捕捉・世界発信する SEAR (Severe Event and Adverse Reactions), SPEAR (Severe Product Event and Adverse Reactions)と呼ばれる仕組みを構築している。我が国では、2000 年 4 月から血縁末梢血幹細胞ドナーの、2005 年 4 月からは血縁骨髄・末梢血幹細胞ドナーの全件事前登録・フォローアップ事業を実施しており、血縁ドナーの安全性にも着目したことは世界的にも評価されつつある。骨髄バンクでも 1991 年発足当初より非血縁ドナーの安全情報を捕捉している。こうした血縁・非血縁ドナー並びに臍帯血の安全性に関する世界的な注目の高まりの中で、WBMT は 2012 年度に、同種造血幹細胞提供に関する WBMT の統一見解 ”Allogeneic hematopoietic stem cell donation :standardized assessment of donor outcome data-A WBMT consensus document. (Bone Marrow Transplant 2012, 1-6)”を発表した。この中には血縁、非血縁を問わず幹細胞提供直後に報告されるべき項目、長期フォローアップで報告されるべき項目が記載されている。

「移植に用いる造血幹細胞の適切な提供の推進に関する法律」及び「同法率概要」の英訳

国際情報収集をする上では、本研究の背景即ち上記法律を理解してもらうことが必要であるので、英訳を本研究の一環として行い、国内外に配布するとともに、日本造血細胞移植学会ホームページ上に開示した。

Ｄ．考察

1） APBMT/WBMT/WHOを介した、造血細胞移植に関わる情報収集に関しては、WBMTのそれまでの造血細胞移植世界サーベイに加え、同機構として初めての世界アンケートを実施、発送先が世界ほぼすべての地域に及んだこと、回答率はともかくも一つの領域における世界レベルでの比較的迅速な情報収集の仕組みが作動することが確認できたことは、本研究が世界レベルで評価されても良い大きな成果であったと考える。こ。そしてアジアを含めた諸外国における、造血細胞移

植療法の普及率、 骨髄・末梢血バンク、臍帯血バンクの在り方と公費による助成の実態、法律施行後の実情等がある程度明らかになったと考える。そしてこれらは、今般新たに立法化された“造血幹細胞移植推進法（略称）”に基づく諸施に反映されるであろう。

２）なお、米国、スイス等においては造血細胞移植関連法案が一部施行されているが、特に日本と造血幹細胞移植の相互協力が進んでいる米国について、同国識者の招聘と現地調査を行った。その結果米国法がそれまで存在したCIBMTRとNMDPをそのまま認定し法の保護と規制を与えた所が印象的であった。従ってCIBMTRは今もウイスコンシン大学に属し、データセンター作業者は同大学の教官でもあり続けているわけであるが、そしてそのためにCIBMTRのアカデッミクアクティビティーが維持され、発展し続けているわけであるが、我が国の場合新たなデータセンターはそれまでの大学帰属を廃し、独立した組織であることが求められているので、アカデミックアクティビティーを維持、発展させるために新たな仕組みの構築が求められることになろう。

3） 招聘・視察事業によりもう一つ明らかになったのは、骨髄バンク、臍帯血バンクの関係とSPA/OPAの実態である。米国法は、その当初から既に多く存在していた民間臍帯血バンクの統合をNMDPに嫁している。一方我が国ではこの点については明記が無い（骨髄移植推進財団の仕事とは明記されていない）。只、使用者にとって使い勝手の良いバンク機構にするように、ということなので、米国の実態を参考にしつつ作業を進めることが必要であろう。

４）WHOが他領域のモデルと考えている造血幹細胞移植世界調査（サーベイとレジストリ）の精度を上げるには、新法に基づく我が国の造血細胞移植データセンターの機能を向上させ、データ収集・解析機能をさらに向上させることが、国内のみではなく、アジアレベル、世界レベルでも重要である。

5）患者・ドナーの安全性や臨床成績に関するデータの、 世界規模での集計と解析に関しては、2013年度APBMT, WBMTサーベイを実施した。アジア地区で造血幹細胞移植累計数が10万例、世界全体で100万例をそれぞれ突破したことが明らかになるとともに、更に全ての地域で増加の一途をたどっていることが示された。APBMT / WBMTが保有している患者データ、 またドナーデータについて、 比較検討できる形式への変換に関しては、米国、欧州、アジアでの共通項目を設定し（Outcome Registry Form, Minimum Essential Data ase）,APBMTとして初めて、アジア人における移植後生存曲線を描いた。各国における造血幹細胞移植の対象疾患や人数に関しては、先述の世界アンケート結果において記載した。

6）世界の非血縁ボランティアドナーの安全性担保状況は、我が国の骨髄移植推進財団もそのメンバー組織の一つであるWBMTによって補足されており、特に緊急有害事象を世界レベルで発信しているSEAR/SPEARシステムは有用である。我が国でこれまで日本造血細胞移植学会（血縁ドナー）/骨髄移植推進財団（非血縁ドナー）のドナー安全補足システムは血縁ドナーをも対象としている点、一日の長があるが、国際標準であるSEAR/SPEARとの整合性を取り、そこへの情報提供をしてゆく必要があろう。尚、血縁ドナーをも対象とする我が国発の考えは、WBMT Consensus Document（先述）のみならず、WBMTにある5つの常設委員会の一つであるドナー委員会のテーマにも取り入れられている。

Ｅ．結論

造血幹細胞移植の制度に関する国際比較分析の

ために主として世界造血細胞移植ネットワーク（WBMT）を介して行った国際情報収集・解析並びに国際意見交換は、我が国で新たに制定・施行される”造血幹細胞移植推進法（略称)”の実践に有意な情報をもたらした。

Ｆ．健康危険情報

患者並びにドナーに関わる健康危険情報は、国内では日本造血細胞移植学会、骨髄移植推進財団により、海外ではWMDAにより捕捉され、電子媒体等により逐次全国、全世界へ発信されている。

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Ｈ. 知的財産権の出願・登録状況 （予定を含む。）

１. 特許取得

特に無し

2. 実用新案登録

特に無し

3.その他

別紙４

研究成果の刊行に関する一覧表

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Quantitative and qualitative differences in use and trends of hematopoietic stem cell transplantation: a Global Observational Study

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ABSTRACT

Fifty five years after the first publication, hematopoietic stem cell transplantation has become an accepted treatment option for defined hematological and non-hematological disorders. There is considerable interest in understanding differences of its use and trends on a global level and of the macroeconomic factors associated with these differences

Data on HSCT numbers for the 2006-2008 3- years period were obtained from WBMT member registries and from transplant centers in countries without registries. Population and macroeconomic data were collected from the World Bank and from the International Monetary Fund. Transplant rates were analyzed by indication, donor type, country, and World Health Organization (WHO) regional offices areas and related to selected health care indicators using single and multiple linear regression analyses.

A total of 146,808 patients were reported by 1,411 teams from 72 countries over 5 continents. Annual number of transplants increased worldwide with the highest relative increase in the Asia Pacific region. Transplant rates increased preferentially in high ($p=0.02$), not in low or medium income countries. Alllogeneic transplants increased for myelodysplasia, chronic lymphocytic leukemia, acute leukemias, and nonmalignant diseases but decreased for chronic myelogenous leukemia. Autologous transplants increased for autoimmune and lymphoproliferative diseases but decreased for leukemias and solid tumors. Transplant rates ($p< 0.01$), donor type ($p< 0.01$) and disease indications ($p < 0.01$) differed significantly between countries and regions. Transplant rates were associated with Gross National Income/capita ($p < 0.01$) but showed a wide variation of explanatory content by donor type, disease indication and WHO region.

HSCT activity increases worldwide. The preferential increase in high income countries, the widening gap between low and high income countries and the significant regional differences suggest that different strategies are required in individual countries to foster HSCT as an efficient and cost effective treatment modality.

Key words: Hematopoietic stem cell transplantation, autologous, allogeneic, global perspective, transplant rates, leukemia, lymphoma, solid tumors, non-malignant disorders, unrelated donors.

INTRODUCTION

Quantitative differences in transplant rates of hematopoietic stem cell transplantation (HSCT) have been well described in the recent past: more patients are transplanted in countries with a higher national income. HSCT requires a specific infrastructure, depends on a network of specialists and remains associated with significant morbidity and mortality; it is a prime example of costly specialized medicine. Broader use of HSCT has therefore long been limited to high income countries (1, 2). This has changed over the last decade, for several reasons. Transplantation of autologous or allogeneic bone marrow, peripheral blood or cord blood stem cells has become treatment of choice for many patients with defined severe congenital or acquired disorders of the hematopoietic system. Unrelated donor registries have expanded to more than 20 million HLA-typed (Human Leukocyte Antigen) volunteer donors worldwide and increased the likelihood to find a suitable matched donor. Results have improved, including those for elderly patients and for those with co morbidities. As a consequence, novel indications are being explored and transplant numbers have increased worldwide (3-9).

Furthermore, the World Health Organization (WHO) has recognized transplantation as an important global task. Transplantation of cells, tissues and organs has extended the lifespan of hundreds of thousands of patients worldwide and enhanced their quality of life; it has become standard of care for many patients with single organ failure and should no longer be restricted to affluent countries or individuals. The guiding principles of the WHO declare regulation of transplantation on a national level as a governmental responsibility. Regulation includes harmonized data collection on use and outcome as an essential tool to improve results and to achieve efficient and cost effective use of resources (10, 11). Information on use and trends is therefore a prime prerequisite for any health care agency. The Worldwide Network for Blood and Marrow Transplantation (WBMT), an umbrella organization of HSCT and a non-governmental organization recognized by WHO has taken up the task of facilitating HSCT. It previously identified availability of resources, governmental support and access of patients to the therapy as key factors associated with *quantitative* differences in transplant rates (12). It presents now an in-depth assessment of factors associated with *qualitative* differences in use and trends on a global level.

METHODS

Study design

This retrospective survey followed the principles of the WBMT through data collection by its network of international or regional member organizations (12). Main outcome measures were the assessment of transplant rates by indication and donor type for each country, the changes

over the three years period from 2006 to 2008 and their associations with defined macroeconomic factors.

Data collection and validation

Data were obtained from 1,411 teams in 72 countries over 5 continents on their numbers of HSCT performed in the years 2006, 2007 and 2008 by indication and donor type (Table 1). Data were reported via the mandatory worldwide compatible reporting system of initial transplant data (ABMTRR, CBMTG, and CIBMTR) or by a separate survey data form (APBMT, EBMT, EMBMT, and SBTMO) (9, 13-16).

Data were pooled, validated through confirmation by the reporting team, which received a computer printout of the entered data, by selective comparison with MED-A data sets in the EBMT ProMISE data system or by crosschecking with National Registries. Double reporting was excluded. Onsite visits of selected teams are part of the quality control program within CIBMTR and EBMT teams.

Definitions

Transplant rates

Transplant rates were computed as the number of patients treated with a first HSCT per 10 million inhabitants (2). Patients with a re-transplant or a second or third HSCT were not included.

Population data and data on Gross National Income/capita (GNI/cap), Health Care Expenditures/cap, Governmental Health Care Expenditures, and World Bank Category (by GNI/cap) were obtained from the World Bank (www.worldbank.org) and from the International Monetary Fund (www.imf.org).

World Health Organization regional offices areas

The allocation of individual countries to a region followed the WHO regional offices classification (www.who.int/about/regions/en/) and the previously reported restriction to four regions (11): 1) the Americas; 2) Asia; 3) Eastern-Mediterranean and Africa; and 4) Europe (Figure 1).

Statistical analysis

The association of macroeconomic factors with HSCT rates and the changes from 2006 to 2008 were estimated by single and multiple linear regression analyses using the least squares method. The significance of relationships was measured using τ statistics; a level of 5% was considered significant. The goodness of fit was calculated using the coefficient of

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determination (R^2), the square of the Pearson's correlation coefficient. For single and multiple regression analyses, the dependent variables were transformed to be closer to an underlying linear model. For the multiple regression analyses, all factors were assessed for their multicollinearity.

The t test was used to evaluate significant differences between the WHO regions. All statistical analyses were performed with EViews version 5.1 (Quantitative Micro Software, Irvine, California).

RESULTS

Numbers of HSCT for the years 2006-2008, indications, donor type and stem cell source

There were 146 808 patients (45% allogeneic and 55% autologous) with HSCT during this three years period (Table 1). The analysis showed substantial heterogeneity in indication and donor type by WHO region. Main indications were *lymphoproliferative disorders with* 53%; *leukemias* 36%; *solid tumors* 5% and *non-malignant disorders and others* 6%. There was, however, a distinctly different pattern for allogeneic and autologous HSCT. Main indications for allogeneic HSCT were leukemias (72%), lymphoproliferative disorders (15%) and non malignant disorders (12%), while main indications for autologous HSCT were lymphoproliferative disorders (84%), solid tumors (9%) and non malignant disorders (1%; see Table 1).

Information on stem cell source was available on a total of 142,822 patients. Peripheral blood was used predominantly in related and unrelated HSCT (64%) and in autologous HSCT (98%). Bone marrow remained an important source for allogeneic HSCT (26%), specifically for *non malignant disorders* (56%); its use was minimal for autologous HSCT (2%). Allogeneic HSCT (in patients with information on stem cell source available) were performed from family donors in 51% (43% matched, 7% mismatched/haplo, 0.5% twins and 0.43% cord blood) and from unrelated donors in 49%. Of the 49% unrelated HSCT, 54% were obtained from peripheral blood, 27% from bone marrow and 19% from cord blood.

The highest number of HSCT was reported from Europe (51% of which 39% allogeneic HSCT) followed by the Americas (29%; 46% allogeneic HSCT), Asia (18%; 60% allogeneic HSCT) and Eastern Mediterranean/Africa (3%; 63% allogeneic HSCT) as shown in Table 1. The distribution was asymmetric concerning the proportion of autologous and allogeneic HSCT with a significant difference between America and Europe from Asia and Eastern Mediterranean/Africa ($p < 0.05$) and concerning the repartition of main indications with a higher proportion of non malignant indications in Eastern Mediterranean/Africa ($p< 0.01$) and a higher proportion of acute leukemia in Asia ($p< 0.01$). This asymmetric distribution was primarily influenced by the World Bank category of the participating countries (Figure 2). Low income countries preferentially used

allogeneic compared to autologous HSCT, low and middle income countries preferentially used family donors compared to unrelated donors and showed a higher proportion of non malignant indications.

Transplant rates

Over the three years period the average absolute number of HSCT in the participating countries ranged from 1 (Philippines) to 11,228 HSCT (USA; Figure 1). Transplant rate ranged from 0.1 to 732 per 10 million inhabitants (median 119) for total HSCT, from 0 to 397 (median 49) for allogeneic and from 0 to 412 (median 81) for autologous HSCT. There were no autologous or allogeneic transplants in countries with less than 300,000 inhabitants or with a GNI/cap below $US 690; there were no unrelated donor transplants in countries with a GNI/cap below $US 850.

Transplant rates were significantly associated with common health care indicators, lnGNI/cap (R^2 = 61%) (Figure 3), Health Care Expenditures/capita (R^2 = 64%) or Governmental Health Care Expenditures/capita (R^2 = 63%) (Data not shown). These associations were similar for 2006, 2007 and 2008. They differed significantly for donor types, indications and by the World Health Organization regions.

The association was stronger and with a greater explanatory content for autologous (R^2 = 55%) than allogeneic HSCT (R^2 = 49%) as shown for lnGNI/cap (Figure 3a). Explanatory content was higher for unrelated than for family donor HSCT. It was highest for acute leukemia (R^2 = 49%), lower for non malignant disorders (R^2 =15%) (Figure 3b) and nonexistent for non malignant disorders with HSCT from family donors (R^2 = 4%).

Unrelated donor transplant rates were also associated with lnGNI/cap (R^2 = 48%), with the presence of an unrelated donor registry in the respective country (R^2=30%) and the number of donors in the respective donor registry (R^2=15%). The combined effect of these three factors in a multiple regression reached an extent of even R^2=59. If only countries performing unrelated donor transplants were included in the analysis, explanatory content reached R^2=72% (Figure 3c). Unrelated cord blood transplant rates were weakly associated with lnGNI/cap (R^2 = 24%) and with the presence of a cord blood bank in the respective country (R^2=10%). The 264 family donor cord blood transplants were minimally associated (lnGNI/cap: R^2=5%). The three factors lnGNI/cap, presence of an unrelated donor registry and the number of donors in the respective donor registry exerted as well a combined effect on total transplant rates (R^2=63%; all regions combined) but to a different extent in the different regions. Associations with lnGNI/cap were strongest in the Americas (R^2=94%), followed by Asia (R^2=67%), Europe (R^2=57%) and the Eastern Mediterranean /Africa region (R^2=25%).

Trends 2006 to 2008

Numbers of HSCT increased from 46 563 HSCT in 2006 to 51 536 HSCT in 2008 (+ 10%). The increase in reporting teams from 1327 teams in 2006 to 1407 in 2008 (+6%) was one reason, but even more was the increase of the median number of transplants/year (+26.3%) performed at each center [38 (range 3-180), to 46 (3-421) and 48 (1-389) in 2006, 2007 and 2008 respectively]. Changes differed between regions as well as for main indications, donor types and stem cell sources (Figure 4).

Relative increase was greater for related and unrelated allogeneic (+17%) than for autologous HSCT (+ 5%; see Figure 4A). The highest increase in absolute and relative numbers was observed in the Asia/Western Pacific region (see Figure 4B; +39%) for allogeneic (+50%) and autologous (+22%) HSCT, followed by Europe (+6%) for allogeneic (+10%) and autologous (+3%) HSCT, Americas (4%) for allogeneic (+9%) and autologous (+1%) HSCT, and EMRO/Africa (+19) for allogeneic (+11%) and autologous (+34%) HSCT. The relative increase in HSCT numbers was higher in low income countries (Figure 4C) but not in absolute numbers and in transplant rates (see below). The increase in HSCT numbers was predominantly accounted for by unrelated donor HSCT for patients with leukemia in America and Europe, by family donor HSCT for patients with non malignant disorders in Asia and EMRO/Africa.

Numbers of autologous HSCT increased for for lymphoproliferative disorders (+8%) and decreased for leukemia (-15%) and solid tumors (-2%) as shown in Figure 4D. Numbers of allogeneic HSCT increased for leukemia (+20%) and non malignant disorders (+26%; Figure 4E) with divergent trends for myelodysplasia (+26%), acute myeloid leukemia (+23%), acute lymphoblastic (+27%) leukemias and chronic lymphocytic (+24.6%) leukemia than for chronic myeloid leukemia (-17%). The numbers of allogeneic HSCT increased for bone marrow failure syndromes (+21%) and other non-malignant disorders (+27%). Changes in use of stem cell source are shown in Figure 4F with the highest relative but not absolute increase in cord blood HSCT. The relatively higher increase in transplant numbers in countries with lower income (R^2 = 11%) did not translate into a higher increase in transplant rates. In contrast transplant rates were weakly but positively associated with lnGNI/cap (R^2 = 3%) (Figure 3d). Linear trend analysis confirms this with a positive and increasing linear trend (p=0.02, total HSCT) for the absolute number of HSCT in high income countries but none for the middle (p=0.57) and low (p=0.35) income countries. The trend was most clearly underpinned for unrelated donor HSCT for acute leukemia in high income countries (p=0.004). There was no association of increase or decrease in transplant rates with change in lnGNI/cap over time (R^2 = 1%).

DISCUSSION

This global analysis shows that availability of resources impacts on use of HSCT in a quantitative *and* qualitative way. Transplant rates are higher in high income countries but the difference is not the same for all indications or all donor types. High income countries use autologous and allogeneic HSCT for more indications. They are more likely to use autologous than allogeneic HSCT and unrelated donors than family donors. Transplant rates for autologous HSCT are more likely to be influenced by GNI/cap as illustrated by the higher explanatory content for autologous HSCT. Countries with limited resources in contrast preferentially restrict use of HSCT to allogeneic transplants with stem cells from family donors for non malignant indications or chronic leukemia. The previously described differences between the WHO regional offices areas (11) might therefore rather reflect the differences in resources than in opinions. It is comforting to observe the continued increase in transplant numbers in low income countries; it remains of concern that transplant rates increased to a greater extent in high income compared to middle or low income countries: the gap remains widening.

Transplant rates were associated with GNI/cap for all indications and all donor types but with vast differences in explanatory content and impact. How can these findings be interpreted? A high explanatory content with a strong impact can be considered as a situation with increasing demand without saturation: more patients with acute leukemia will be transplanted in the coming years if the necessary resources, money and donors can be made available. A low explanatory content with a weak impact indicates a different situation. Transplant rates are no longer driven by a higher national income alone. Other factors than availability of resources must come into play. It could relate to different beliefs of the medical community on the value of a given therapy in different countries. However, the focus on matched family donor transplant for non malignant disorders and chronic leukemia in lower income countries is suggestive for prioritization in a cost effectiveness approach. HSCT might be less expensive and equally effective as lifelong treatment with supportive care or expensive drugs in selected patients. There is no need for intensive high cost pre-treatment as is the case for patients with acute leukemia and, the search for a matched family donor requires minimal resources (17-21).

Economic aspects of HSCT with its patient centered approach have traditionally concentrated on costs of the individual procedure for an individual patient. (17, 22-24). Studies on macroeconomic aspects or on cost effectiveness in individual countries have gained broader acceptance only recently (11, 21, 22, and 25). They were triggered in part by some rapid changes in use of HSCT, such as for breast cancer or chronic myeloid leukemia (18, 26) and by the raising awareness of the disturbing gap between unlimited requests and limited resources in any health care system (27, 28). Availability of resources, governmental support and access to therapy were identified as factors associated with use; availability of resources, evidence, external regulations and positive or negative expectations of transplant physicians as factors associated with diffusion (11, 25). These previous findings and the observations in this report

form an objective basis for recommendations or guidelines by professional organizations. They point to the different requirements within high or low income countries, hence different cost effectiveness considerations (20, 21, 26-28). Unrelated donor transplant rates were associated with GNI/cap, the presence of an unrelated donor registry and the number of registered donors. The association is likely reciprocal; high income countries perform more HSCT in general and are more likely to invest in an unrelated donor registry. Competent authorities will have to balance the advantages and costs of establishing and maintaining a national donor registry with its own local HLA-haplotype distribution with alternative strategies (24, 29, 30). The even representation of unrelated HSCT in high income countries documents the functioning worldwide exchange of graft material.

Some caveats remain. Data for this survey were collected for the years 2006 to 2008. Patterns might have changed since; differences in indications might reflect different disease prevalence or missing information. Some congenital non malignant disorders such as immune deficiency syndromes or hemoglobinopathies are highly present in some and absent in other countries (31, 32). Evidently, a few teams known to have performed HSCT did choose not to report (13). Data reporting is mandatory by law in some, limited to allogeneic HSCT or even absent in other countries. The discrepancy between performed and reported HSCT might be higher for autologous than for allogeneic HSCT (9, 14-16). There is, however, no indication for a systematic bias and more recent data from the European survey are consistent with a widening gap (13).

The report gives no information on outcome. This requires additional time and another framework. Outcome is influenced by many factors, including the disease, the pre-treatment, patient and donor characteristics, transplant techniques, the transplant team, its quality management system or the income of the respective country (3, 5, 33-36). Combined analyses on use *and* outcome are needed to ascertain that those patients with the highest need and the best likelihood to profit from a transplant procedure are selected within a given country. Transplant organizations and competent authorities worldwide are currently challenged to implement the WHO guiding principles. The present data provide a platform to begin with. They indicate that one size will not fit all. Regulatory aspects and recommendations on therapy should not only be transparent and consistent but as well be targeted according to the specific cost effectiveness considerations and needs in the individual countries (36, 37).

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Authorship and Disclosures

Contributions to the manuscript are as follow:

Design: AG; DN; KF

Contributing data and data analysis: HB; AG; DN; KF; MG; MA; LFB; MH; YK; JL; MI; MCP; JP; JS; AM; KF

Manuscript processing: AG; DN; MG; MA; LFB; MH; YK;JL; MI; MCP;JP; JS; AM; KF; HB; AG; DN; KF

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Table 1: Population description of patients with HSCT by WHO regional offices area from 2006 to 2008

	East Mediterranean / Africa		SE Asia/ Western Pacific		Americas		Europe		Total	
	N	%	N	%	N	%	N	%	N	%
Donor type*										
Allogeneic HSCT	**2509**	***63***	**15547**	***60***	**19463**	***46***	**28707**	***39***	**66226**	***45***
Family donor	2474	*99*	7944	*51*	10034	*52*	14523	*51*	34975	*53*
Unrelated donor	35	*1*	7603	*49*	9429	*48*	14184	*49*	31251	*47*
Autologous HSCT	**1477**	***37***	**10384**	***40***	**23007**	***54***	**45714**	***61***	**80582**	***55***
Total **	**3986**	**3**	**25931**	**18**	**42470**	**29**	**74421**	**50**	**146808**	**100**
Main Indications Allogeneic*										
Leukaemias	**1455**	***58***	**1212 6**	***78***	**13620**	***70***	**20476**	***71***	**47677**	***72***
Acute Leukemia	1059	*73*	9585	*79*	9619	*71*	14271	*70*	34534	*72*
Chronic Leukemia	276	*19*	1086	*9*	1827	*13*	2259	*11*	5448	*11*
MDS/MPS	120	*8*	1455	*12*	2174	*16*	3946	*19*	7695	*16*
Lymphoproliferative disorders	**99**	***4***	**1463**	***9***	**3414**	***18***	**4868**	***17***	**9844**	***15***
Lymphoma	68	*69*	1280	*87*	2729	*80*	3347	*69*	7424	*75*
Plasma cell disorders	31	*31*	183	*13*	685	*20*	1521	*31*	2420	*25*
Non malignant disorders	**928**	***37***	**1747**	***11***	**2192**	***11***	**2954**	***10***	**7821**	***12***
Bone marrow failure	468	*50*	1094	*63*	1247	*57*	1359	*46*	4168	*53*
Other non malignant	460	*50*	653	*37*	945	*43*	1595	*54*	3653	*47*
Solid tumors	**3**	***0***	**132**	***1***	**65**	***0.3***	**199**	***1***	**399**	***0.6***
Other	**24**	***1***	**79**	***1***	**172**	***1***	**210**	***1***	**485**	***1***
Main Indications Autologous*										
Lymphoproliferative disorders	**1213**	***82***	**8156**	***79***	**20023**	***87***	**37999**	***83***	**67391**	***84***
Lymphoma	734	*61*	4279	*52*	9719	*49*	18994	*50*	33726	*50*
Plasma cell disorders	479	*39*	3877	*48*	10304	*51*	19005	*50*	33665	*50*
Solid tumors	**101**	***7***	**1347**	***13***	**1951**	***8***	**4260**	***9***	**7659**	***9***
Leukemias	**153**	***10***	**717**	***7***	**852**	***4***	**2926**	***6***	**4648**	***6***
Acute Leukemia	129	*84*	694	*97*	816	*96*	2453	*84*	4092	*88*
Chronic Leukemia	10	*7*	14	*2*	22	*3*	353	*12*	399	*9*
MDS/MPS	14	*9*	9	*1*	14	*2*	120	*4*	157	*3*
Non malignant disorders	**10**	***1***	**88**	***1***	**154**	***1***	**453**	***1***	**705**	***1***
Bone marrow failure	0	*0*	0	*0*	1	*1*	3	*1*	4	*0.5*
Other non malignant	10	*100*	88	*100*	153	*99*	450	*99.3*	701	*99*
Other	**0**	***0***	**76**	***1***	**27**	***0.1***	**76**	***0.1***	**179**	***0.2***

*column percentages; **row percentages; MDS/MPS, myelodysplastic syndrome/myeloproliferative syndrome

Legend to the Figures

Figure 1: Transplant rates for the total number of HSCT in participating countries by WHO regional offices area for the years 2006-2008. Regions are colored by WHO regional offices area code (see text). Shades of colors reflect transplant rates (numbers of HSCT, allogeneic and autologous combined, by 10 million inhabitants).

Figure 2: Indications and donor types of 146 808 HSCT by World Bank category in the years 2006-2008. The figure reflects the relative proportions of allogeneic (blue) or autologous (red) HSCT (left three columns), of allogeneic donor type [family donor (green) or unrelated donor (blue)] (central left three columns), main indications allogeneic HSCT (central right three columns), and main indications autologous HSCT (right three columns; for color code see figure) by low, middle of high income World Bank category. For definitions see methods section.

NM, non malignant disorders; ST, solid tumors; LPD, lymphoproliferative disorders; Leuk, leukemia;

Figure 3: Transplant rates and Gross National Income per capita (GNI/cap)

Figure 3a) Transplant rates for allogeneic and autologous HSCT by WHO regional offices area, donor type and GNI/cap. Symbols reflect transplant rates (TR; numbers of HSCT by 10 million inhabitants) in participating countries and the respective lnGNI/cap. Colors indicate WHO region (see figure 1); squares indicate allogeneic, triangles autologous HSCT. Vertical lines separate countries by World Bank category.

Figure 3b) Transplant rates for allogeneic HSCT for acute leukemia and non malignant disorders by WHO regional offices areas and GNI/cap. Symbols reflect transplant rates (TR; numbers of HSCT by 10 million inhabitants) in participating countries and the respective lnGNI/cap. Colors indicate WHO regional offices areas (see figure 1); squares indicate acute leukemia, triangles non malignant disorders. Vertical lines separate countries by World Bank category.

Figure 3c) Unrelated donor transplant rates by WHO regional offices areas, GNI/cap and presence of an unrelated donor registry. Symbols represent transplant rates; open symbols indicate absence of, full symbols presence of an unrelated donor registry and size of symbols numbers of its registered donors. Colors indicate WHO region (see figure 1). Only countries with unrelated donor HSCT are included.

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Figure 3d) Change in transplant rates (all transplants) from 2006 to 2008 by GNI/cap and WHO regional offices areas. Symbols represent increase or decrease in transplant rates (TR) from 2006 to 2008; colors indicate WHO regional offices areas (see figure 1).

Figure 4: Total HSCT in 2006 and relative increase or decrease (in %) in 2007 and 2008 according to (A) donor type, (B) WHO region, (C) World Bank Category (high, medium and low income by GNI/capita), (D) autologous transplant indication, (E) allogeneic transplant indication and (F) allogneic stem cell source

Figure 1

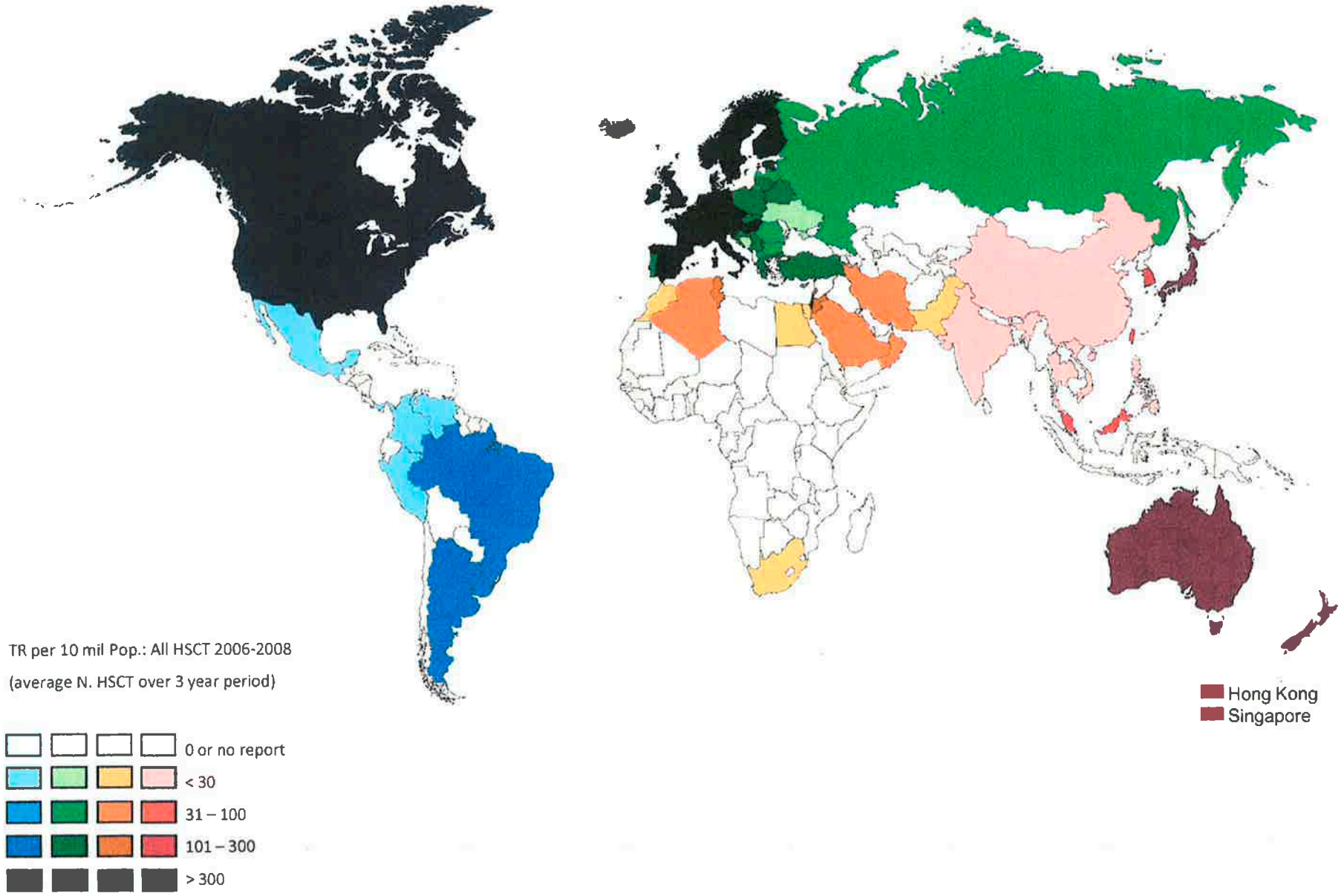

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Figure 2

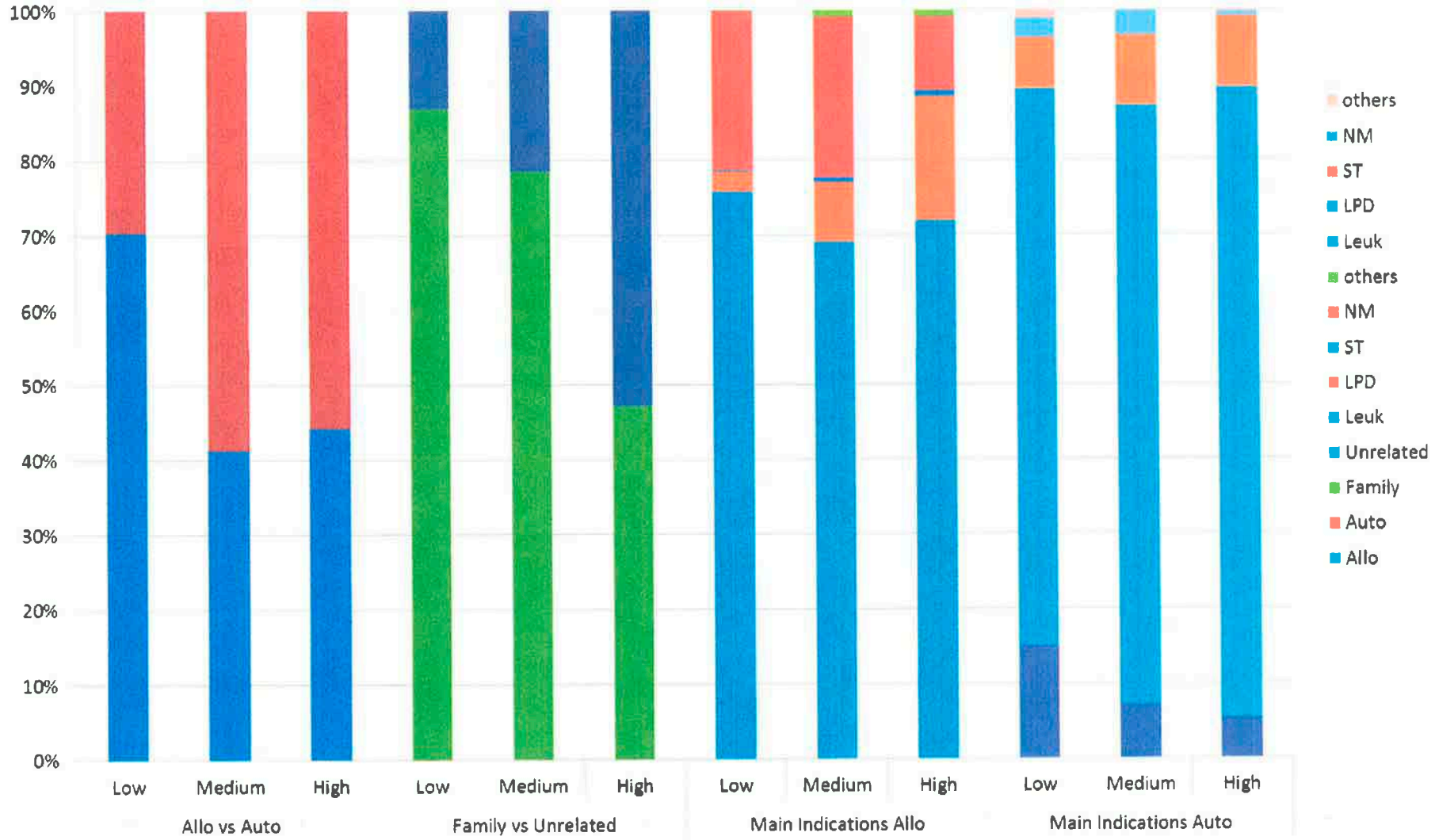

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Figure 3a

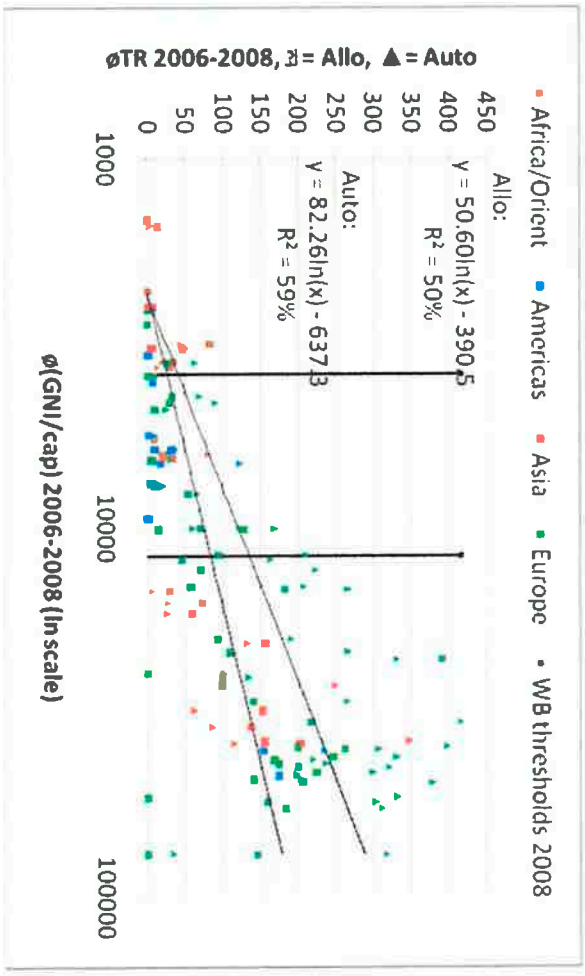

Figure 3b

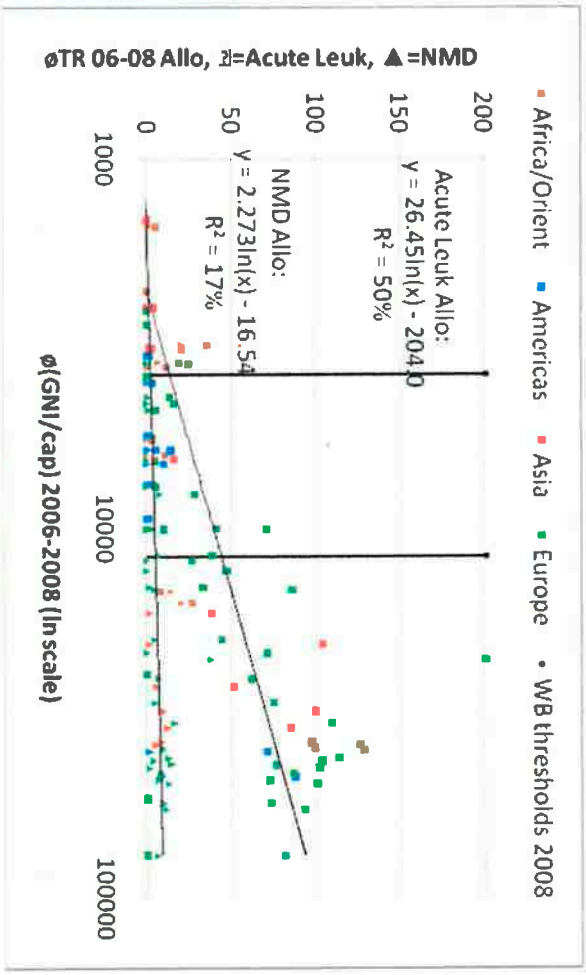

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Figure 3c

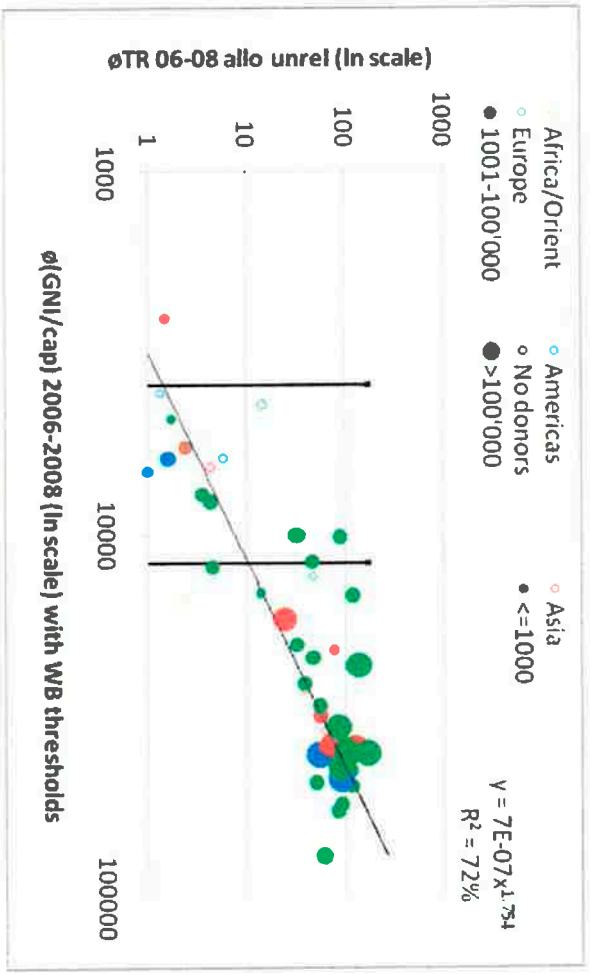
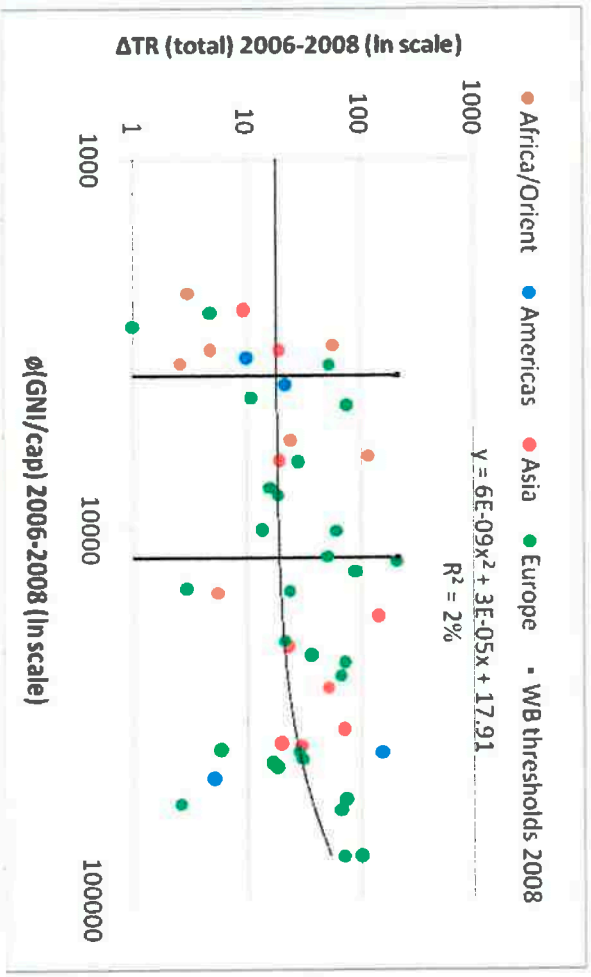


Figure 3d



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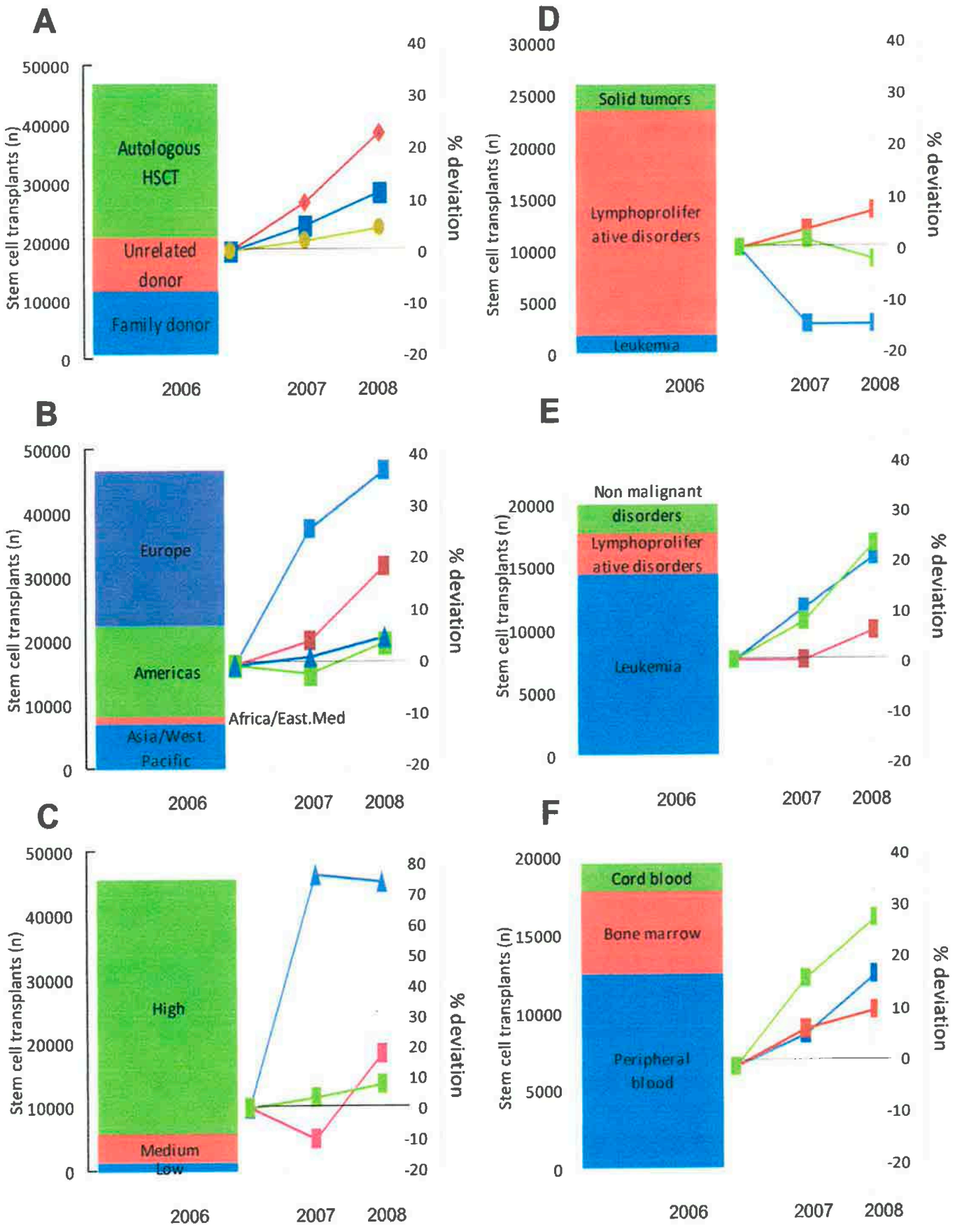

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METHODS

Study design

This retrospective survey followed the principles of the WBMT through data collection by its network of international or regional member organizations (12). Main outcome measures were the assessment of transplant rates by indication and donor type for each country, the changes over the three years period from 2006 to 2008 and their associations with defined macroeconomic factors.

Data collection and validation

Data were obtained from 1,411 teams in 72 countries over 5 continents on their numbers of HSCT performed in the years 2006, 2007 and 2008 by indication and donor type (Table 1). They were contributed by the Asian Pacific Blood and Marrow Transplant Group APBMT, the Australasian Bone Marrow Transplant Recipient Registry ABMTRR, the Canadian Blood and Marrow Transplant Group CBMTG, the Center for International Blood and Marrow Transplantation CIBMTR, the Sociedade Brasileira de Transplante de Medula Ossea SBTMO, the Eastern Mediterranean Blood and Marrow Transplant Group EMBMT and the European Group for Blood and Marrow Transplantation EBMT. Data were reported via the mandatory worldwide compatible reporting system of initial transplant data (ABMTRR, CBMTG, and CIBMTR) or by a separate survey data form (APBMT, EBMT, EMBMT, and SBTMO) (9, 13-16).

Data were pooled, validated through confirmation by the reporting team, which received a computer printout of the entered data, by selective comparison with MED-A data sets in the EBMT ProMISE data system or by crosschecking with National Registries. Double reporting was excluded. Onsite visits of selected teams are part of the quality control program within CIBMTR and EBMT teams.

Definitions

Transplant rates

Transplant rates were computed as the number of patients treated with a first HSCT per 10 million inhabitants (2). Patients with a re-transplant or a second or third HSCT were not included. Transplant rates were computed by donor type, irrespective of stem cell source. This did relate to cord blood transplants as well. There was no adjustment for patients who crossed borders and received their HSCT in a foreign country.

Population data and data on Gross National Income/capita (GNI/cap), Health Care

Expenditures/cap, Governmental Health Care Expenditures, and World Bank Category (by GNI/cap) were obtained from the World Bank (www.worldbank.org) and from the International Monetary Fund (www.imf.org).

World Health Organization regional offices areas

The allocation of individual countries to a region followed the WHO regional offices classification (www.who.int/about/regions/en/) and the previously reported restriction to four regions (11): 1) the Americas (the corresponding WHO regional offices areas are North and South America); 2) Asia (South-East Asia and Western Pacific Region which includes Australia and New Zealand); 3) Eastern-Mediterranean and Africa; and 4) Europe (which includes Turkey and Israel; Figure 1).

Statistical analysis

The association of macroeconomic factors with HSCT rates and the changes from 2006 to 2008 were estimated by single and multiple linear regression analyses using the least squares method. The significance of relationships was measured using τ statistics; a level of 5% was considered significant. The goodness of fit was calculated using the coefficient of determination (R^2), the square of the Pearson's correlation coefficient. For single and multiple regression analyses, the dependent variables were transformed to be closer to an underlying linear model. For the multiple regression analyses, all factors were assessed for their multicollinearity.

The t test was used to evaluate significant differences between the WHO regions. All statistical analyses were performed with EViews version 5.1 (Quantitative Micro Software, Irvine, California).

Allogeneic hematopoietic stem cell donation—standardized assessment of donor outcome data: A consensus statement from the Worldwide Network for Blood and Marrow Transplantation (WBMT)

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Abstract

The number of allogeneic hematopoietic SCTs performed globally each year continues to increase, paralleled by an increased demand for donors of therapeutic cells. Donor characteristics and collection procedures have undergone major changes during recent decades, and further changes are foreseen. Information on short- and long-term donor outcomes is of crucial importance to ensure maximal donor safety and availability. Current data, predominantly from unrelated donors, give reliable information on the frequent early events associated with donation—most of them of mild-to-moderate intensity. Information on the type and relative risk of serious adverse reactions is more limited. Moreover, only few data exist on long-term donor outcome. On the basis of this need, recommendations for a minimum data set for prospective donor follow-up were developed in a workshop with the participation of an international group of investigators actively involved in allogeneic stem cell donation under the auspices of and approved by the Worldwide Network for Blood and Marrow Transplantation. Establishment of a standardized global follow-up for both, related and unrelated, donors will enable monitoring of the short- and long-term safety profiles of hematopoietic cell donation and form a solid basis for future donor selection and counseling.

Keywords:

donor outcome; global donor follow-up; serious adverse reactions; minimal data set; WBMT

Introduction

During recent decades, the number of allogeneic hematopoietic SCTs (HSCTs) has steadily increased by, up to, 10% annually on a global scale.[1, 2, 3] Furthermore, several new trends in transplantation have emerged: the introduction of reduced-intensity conditioning (RIC) regimens has led to an increase in the number of HSCT performed in older patients and those with comorbidities and G-CSF-mobilized PBSC have in part replaced BM as the main source of hematopoietic stem cells (HSC) in adult and pediatric patients.

These developments are accompanied by a parallel increase in the number of donors involved in transplantation and substantial changes in the donation process. The rapid expansion of the unrelated donor registries, with more than 19 million HLA-typed unrelated donors worldwide, has allowed for an increase in unrelated HSCT activity, now surpassing the number of related donor transplants in some regions.[1, 3] The median age of related donors has increased with the increasing age of the recipients, leading to potentially more donors with occult or manifest comorbidities at the time of donation. As a consequence of RIC, an increasing number of donors becomes involved in multiple donations of therapeutic cells. It is likely that this trend will continue for the next decade; it might even increase further with future progress in transplant regimens. Furthermore, if the use of stem cells for non-hematopoietic indications and/or organ repair is confirmed as a useful therapeutic tool, this may accelerate the demand for stem cell donations.

Since the beginning of HSCT, donor safety has been recognized by the community as an important issue.[4, 5, 6, 7] Today, numerous donor outcome registries exist in different countries or in individual institutions but only the World Marrow Donor Association (WMDA) collects donor outcome data from unrelated donors on a global level. The serious events and adverse reactions (SEAR) and serious product events and adverse reactions (SPEAR) are collected centrally.

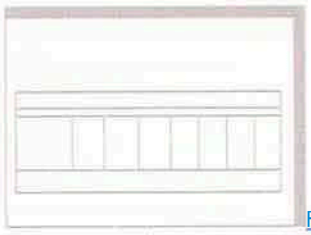
Very rare events may become apparent when the number of donations increases, but only if a large amount of the collected data can be analyzed. Such events may have detrimental effects on donation, if they become public without the benefit of coherent investigation and explanation by the scientific and transplant community.

Hence, the need for collection of donor data has been underlined by the recent release of the guiding principles on human cell, tissue and organ transplantation by the World Health Organization (WHO) in Resolution WHA63.22, endorsed in May 2010. Donor safety and follow-up are specifically expressed as principles with data collection and analysis as integral part of any therapy.[8] This need has not yet been completely addressed yet by other regulatory bodies like FACT-JACIE (www.factwebsite.org, www.jacie.org).

Today, large registry studies in unrelated donors[9, 10, 11] form the basis for the current knowledge on the frequent side effects during BM and PBSC donation, which are usually of mild or moderate severity. Smaller studies from related donors suggest that these frequent side effects occur with the same pattern in related donors.[12, 13, 14, 15]

Sporadic case reports and a recent large survey among transplant teams demonstrate that the donation procedure can be associated with a small but real risk for serious adverse events and reactions (SAE/R).[16, 17, 18, 19] Current experience suggests that risks seem to be higher for related than for unrelated donors with the caveat of reporting bias and lack of an adequate amount of prospective follow-up data in the related donor setting.[9, 10, 11, 18] These rare SAE/R that occur with estimates of about 1 in 3–5000 for serious and 1 in 10–20000 for lethal events are still incompletely understood.[9, 10, 11, 16, 17, 18, 19] Hence, there is urgent need for better understanding of short-term SAR and to identify donors at risk. Because of the rarity of the events, progress can only be achieved by large international collaborations that include both unrelated and related donors. Despite the fact, that related and unrelated donors might differ for many basic characteristics (Table 1), the quality of adverse reactions associated with stem cell donation is not expected to be different between related and unrelated donors forming the rationale for a uniform donor follow-up for all types of donors. Generally, donor eligibility criteria for related donors are less strict with only a few definite criteria[20] and may vary significantly between different centers. In contrast, eligibility criteria for unrelated donors are summarized by WMDA recommendations[21] resulting in somewhat more homogenous donor selection criteria. Together with the unequal basic characteristics, this may lead to differences in the incidence and/or severity of adverse events in related vs unrelated donors but large data sets to support this hypothesis have first to be set up.

Table 1 - Differences between related and unrelated donor characteristics.



Full table

The question of long-term effects of donation is even less understood. Despite an intensive discussion on hematological malignancies in donors after exposure to growth factors a few years ago, data to assess reliably long-term SAE are still lacking.[22, 23, 24, 25] The fact that these issues have already been raised almost 15 years

ago[5] underlines the ongoing urgent need to standardize short- and long-term donor follow-up.

Methods

The recently founded Worldwide Network for Blood and Marrow Transplantation (WBMT; www.wbmt.org), recognized the need for global cooperation in the field of HSCT and defined donor issues as one of its prime tasks. In August 2009, a workshop of an international group of representatives involved in related or unrelated HSC donation developed a consensus for such a donor follow-up on a global level, taking into account that resources for new tasks are limited in most teams. These collected data should form the basis to address donor risks in public discussions to safely maintain allogeneic HSCT as an important treatment for many patients in need. Hence, two main topics were identified that should be addressed with priority:

- Prospective data collection should include all SAE/SAR during the donation procedure from all types of donors in the same way, that is, unrelated and related donors.
- Prospective data collection on potential long-term complications should focus on a minimum data set, that is, incidence and type of malignancies and autoimmune disorders only, and include all donors as above.

Results

Currently available data and experience have been reviewed in detail to form the rationale for this consensus. It has been observed, that most immediate or short-term SAR, related to the donation procedure, occur either before (during mobilization, induction of anesthesia) or within the first 30 days after donation. Hence, this time period needs to be analyzed carefully for all donation procedures. It follows the convention for a 30-day post-intervention period, which is currently established for other surgical and medical interventions. Beyond this point, follow-up and data collection will focus on a few potential late events. While they have been selected based on the biologic action of mobilizing agents currently in use, both PBSC and BM donors will be followed on long term. The reason to also follow BM donors is twofold: Some of them may get EPO and/or G-CSF before or after collection of therapeutic cells and BM donors who did not get any mobilizing drug may represent the best available

control group for evaluating late effects in donors. Long-term follow-up will be more time consuming for centers. Therefore, we propose an approach that should be achievable with a minimum of resources.

For more specific questions, clinical studies are needed with a separate funding and predefined donor populations and follow-up.

Immediate/short-term SAR associated with the donation procedure

SAR, in the context of HSC donation, have been described for both BM and PBSC donation,[4, 26] including rare fatal events, mainly of cardiac or cardiovascular origin.[17, 18, 19, 27] Currently, it is suggested that related donors could be more frequently affected, because of less strict donor eligibility criteria in this group. SAR may occur during mobilization, before cell collection, during the collection or shortly thereafter. Most cases have been reported as case reports or by retrospective studies, hence causality is frequently not conclusive and relative risks cannot be estimated. Some of these SAR, such as thrombotic and cardiovascular events or splenic rupture, might be explained by the biological effects of G-CSF that have recently been reviewed in detail[26, 28] or are associated with an inherent risk of the collection procedure used (anesthesia, central venous catheter related complications, anticoagulation during apheresis, human error). Preexisting comorbidities of the donors are likely to have contributed to other SAR (for example, precipitation of sickle cell crisis or inflammatory diseases).

Late SAE/SAR associated with the donation procedure

Late SAE/SAR are defined as SAE/SAR possibly related to the donation procedure with onset more than 30 days after completion of the donation. Chromosomal changes and changes in microarrays have been described after G-CSF stimulation raising concern on an increased long-term risk for hematological neoplasms.[29, 30] These concerns have not been substantiated so far.[31] Chromosomal changes seem to be transient and do not affect $CD34^+$ stem cells. Observational data from unrelated donor registries do not show an increased risk for secondary malignancies,[32] but the number of donors followed is still limited, given the large number needed to detect an even considerable increased risk for hemato-oncological neoplasms.[33, 34] Furthermore, epidemiologic studies are required for comparison of neoplastic events observed in healthy stem cell donors and representative control populations. It is important to realize that G-CSF, PEG-G-CSF and CXCR-4 antagonists recruit different cell populations according to global gene and mRNA expression levels.[34, 35, 36] Finally, it is possible that biosimilars of G-CSF and EPO will also be applied in healthy donors although recent statements

from the European Group for Blood and Marrow Transplantation (EBMT) and WMDA do not recommend it outside of the context of well set up safety studies. This emphasizes the need to include all current mobilizing agents as well as any new agents that will be introduced into clinical practice in the future in a prospective follow-up.

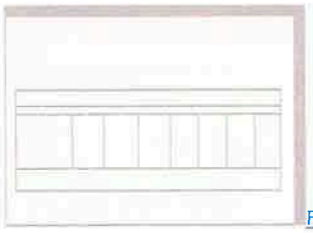
In related donors, an increased risk for hematological malignancies might be expected owing to the same genetic background as the patient and the known association between HLA and malignancies.[37] The degree of risk increase is difficult to estimate from available data. Epidemiological studies in families of patients with hematological neoplasms suggest that the risk to develop any malignancy is at least twice that of a normal population.[38] Some of these donor characteristics may also apply to unrelated donors. So far it is not known how many volunteers joined the unrelated donor registries because of close relationships with a patient (that is, being a relative or having had close contact during many years, which could also include a common exposure to carcinogenic agents) and it is obvious that motivation patterns might differ between different countries depending on different recruitment strategies of individual registries. Another issue that complicates the interpretation of long-term donor follow-up data is the effect of medical clearance before donation: Donors may be healthier than a non-donating age- and gender-adjusted control group as they have passed the medical clearance on confirmatory typing and work-up level. Furthermore, very little is known about the 'lifestyle' or socioeconomic status of individuals who register as potential stem cell donors compared with the general population. Thus every comparison of donor malignancies with age- and gender-adjusted incidence ratios of the general population has to consider this potential bias. Currently, a prospective study is under way at the German Bone Marrow Donor Center (DKMS) that addresses this question by analyzing the incidence of potential late SAE in donors who donated compared with registered donors who were not asked yet to donate but underwent the same health checks simultaneously (AH Schmidt, DKMS, personal communication).

Short-term application of G-CSF changes lymphocyte subset populations and might lead to long-term immunological effects. New onset autoimmune disorders have been reported rarely,[39, 40] but a causal relationship with previous G-CSF exposure has not been confirmed.

Recommendations for a minimal donor follow-up

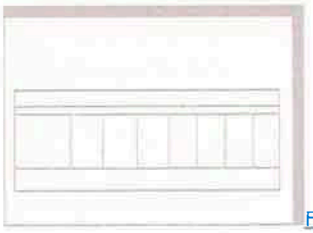
Practical aspects for donor outcome follow-up are addressed below (Tables 2 and 3).

Table 2 - Minimal data set to be reported after the end of the donation procedure.



Full table

Table 3 - Minimal data set to be reported for long-term follow-up.



Full table

Types of donors to be registered and length of follow-up

All consenting donors who start the donation procedure for allogeneic HSC or other therapeutic cells from peripheral blood or BM shall be registered and followed for 10 years after the last donation procedure. Cord blood donors will not be followed except if they donate additional stem cells later, for example, by BM collection to increase the cell count for transplantation. Donors who do not consent will not be followed, either.

Definition of donation procedure

The donation procedure is defined as a procedure with the intent to collect an adequate number of therapeutic cells, that is, HSC, MSC, lymphocytes, natural killer cells or other cells. The donation procedure starts with the first injection of a mobilizing agent, the start of anesthesia or the start of apheresis (in cases of non-stimulated leukapheresis, for example, for DLI) and usually ends with one or multiple collections. However, the accomplishment of a collection is not required. Even if the preparative actions (that is, start of injections, apheresis or anesthesia)

are stopped prematurely (because of donor or recipient reasons) the activity fulfils the definition of a donation procedure and the donor shall be registered and followed-up.

Data registries

It is proposed that recording of donor outcome data should become a part of the already well-established registries of member societies of WBMT (that is, Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), Asia Pacific Blood and Marrow Transplantation Group (APBMT), Center for International Blood and Marrow Research (CIBMTR), European Group for Blood and Marrow Transplantation (EBMT), Eastern Mediterranean Blood and Marrow Transplantation Group (EMBMT), World Marrow Donor Association (WMDA)). Identical data sets will allow combining data for analysis from registries of different societies of WBMT. Societies and national registries are encouraged to reach agreements on how to organize data collection so that double reporting will be avoided.

Data collection

Data from the donation procedure and from long-term follow-up will be collected. Questions have been designed to be as simple and as few as possible, and are based on WHO toxicity criteria and International Classification of Diseases (ICD) code where appropriate, as these items are already implemented in routine use in many countries, well established and standardized.

For reporting, the current International Classification of Diseases (ICD)10 code should be used. The most recent version for coding including the possibility for online search can be accessed at www.who.int/classifications/icd/en/.

Time of data reporting for procedure-related data including donor and collection procedure characteristics (Table 2)

These data should be reported between day 30 and day 100 after the procedure is completed. The time interval covered is the period from the beginning of the donation procedure until day 30 after the completion of the procedure. It is important to note that more rapid initial reporting for SAR might be required by authorities or individual societies.

Every new attempt to collect cells is regarded as a separate donation procedure with the focus on the donation procedure, not the type of cells collected, that is, a BM donor undergoing a donation procedure for BM-derived HSC or MSC should be registered and followed irrespective of the collected cell type. Many cells might be collected without a mobilization procedure. For example DLI donation may occur several times, either by whole blood donation or after repeated apheresis. Other examples may be natural killer cell or DC donations. Whatever the cell type is, the donation will be characterized as unstimulated leukapheresis donation. The time schedule for follow-up is always determined by the last donation procedure. Contrary to voluntary unrelated donors, an upper limit for the frequency and the total number of therapeutic cell donations is frequently missing in related donors. Prolonged persistent lymphopenia has been described in donors after repeated collections,[41] but information on the long-term follow-up are very scarce.

Practice of data reporting may be essentially the same as for patient data. Precise rules might be defined by the individual member societies of WBMT or legal authorities from individual countries.

Definition and reporting of SAR

Common adverse events are well known and will not be collected in this dataset (modifications of the current proposal might become necessary in the future for selected donor groups if new mobilizing agents become regularly used in healthy donors). Reports shall include adverse events defined by WHO toxicity grades 3 and 4[42] or SAR using essentially the same definition as WMDA: (1) death, (2) life-threatening events, (3) events requiring in-patient hospitalization or prolongation of existing hospitalization owing to WHO grade 3 or 4 toxicity and (4) events that result in significant disability/incapacity.[43]

In many countries, these events are also required to be reported to the regulatory authorities. It is evident that a causal relationship with the donation procedure will often be difficult to establish; therefore, all events occurring in temporal relationship to the donation procedure and fulfilling either of these definitions shall be reported.

Long-term outcome data—time of data reporting and items: Until otherwise required by national regulatory authorities minimal follow-up should be reported after 1, 5 and 10 years but annual or biannual follow-up reports are encouraged.

Reporting will be limited to three items: survival, onset of malignancies and onset of autoimmune diseases. These are simple questions that can be asked by written or electronic mail, by internet-based survey or by phone.

In the case of a positive reply, the level of evidence should be indicated, that is if the diagnosis was confirmed by medical data (that is, a diagnostic procedure as a pathology report, serological confirmation in certain autoimmune diseases, diagnostic criteria, for example, American Rheumatism Association (ARA) criteria fulfilled in rheumatoid arthritis and so on). The exact diagnosis should again be coded according to the International Classification of Diseases (ICD) classification.

Use of newsletters, short message services, new media and social network facilities may help to maintain contact with donors, decrease numbers of donors lost to follow-up and ensure adequate data capturing. Many initiatives are already in place in different countries. Hence, one aim will be to connect and combine the already ongoing efforts. Analysis of donor outcome data may follow the same rules as, for example, analysis for late effects in transplant recipients.

Conclusions

Thanks to ongoing progress in transplant techniques and supportive care, allogeneic HSCT can be offered as a curative treatment to a steadily increasing number of patients. Securing the willingness of donors to donate in the future is crucial for further development of treatments with allogeneic therapeutic cells. It is obvious that this willingness will heavily depend on the safety of current and future donation procedures. Many issues on donor safety have been addressed in the recent years by different groups. Side effects during HSC donation are frequent but only transient in the overwhelming majority of related and unrelated donors. However, serious adverse events do occur rarely in the context of BM and PBSC donation. A causal relationship is not always evident and the true incidence of these events remains unknown because of different definitions and observation intervals for SAE/R. Most data on donor safety are from unrelated donors who represent a positive selection among healthy individuals. Data on related donors are scarce[12, 13, 14, 15, 44, 45, 46, 47] and only a few prospective trials or registration studies are underway (RDSafe study in the US (cf.: www.cibmtr.org), registries for related donors in Japan, Spain, Poland, Nordic donor registry and Switzerland). Certain donor populations may represent special risk groups, like children, elderly donors, haploidentical donors (when higher doses of

mobilizing agents and/or larger volumes for cell collection by apheresis might be used in these donors), donors with multiple donations for HSC and/or other therapeutic cells and need to be studied in more detail.

Theoretical concerns about long-term effects after donation have not been verified yet. However, reliable data based on prospective registration and follow-up of all kinds of donors are still lacking. Current data sets are too small, follow-up is too short and numbers of donors lost to follow-up remain a problem, approaching 50% even in well-conducted registry studies[11] and thus impair the robustness of the conclusions drawn.

Data collection and analysis of donor outcome have to become an integral part of HSCT, to define incidence and risk factors for SAE/R in short and long term to protect donors' health. The aim of a global standardized data collection is to allow us to define risks by large international combined registries.

Donor safety must be included in overall HSCT risk assessment. These issues also need to become part of accreditation standards. Reimbursement for donor outcome data registration must become part of the transplant coverage by insurance companies or national healthcare systems. Joint efforts led by WBMT in collaboration with its member societies are needed to achieve this goal. Additional private funding might become valuable, depending on national properties.

Conflict of interest

The authors declare that they have no conflict of interest.

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TABLE 1

FROM:

Allogeneic hematopoietic stem cell donation—standardized assessment of donor outcome data: A consensus statement from the Worldwide Network for Blood and Marrow Transplantation (WBMT)

J P Halter, S M van Walraven, N Worel, M Bengtsson, H Hägglund, G Nicoloso de Faveri, B E Shaw, A H Schmidt, M Fechter, A Madrigal, J Szer, M D Aljurf, D Weisdorf, M M Horowitz, H Greinix, D Niederwieser, A Gratwohl, Y Kodera and D Confer

Table 1. Differences between related and unrelated donor characteristics

	Unrelated donors[a]	*Related donors*
Age limit	Limited to adult donors 18–60 years	Unlimited 0–>70 years
Number of donations allowed for same donor	Variable, but limited by registries PBSC: 1–2 BM: 1–2 Maximal: 1–4 donations, median 2 donations[48]	Unlimited, except for center-specific guidelines
Maximal dose of G-CSF per day	Usually 10–12 μg/kg/d	Usually 10–12 μg/kg/d, doses up to 20 μg/kg/d possible
Maximum volume per donation (volume for apheresis or volume for BM collection)	Often limited depending on donor's body weight/blood volume	Unlimited
DLI	Number of donations variable from one to multiple (no limit)[48]	Unlimited, except for center-specific guidelines
New mobilizing agents	Used very conservatively, usually not recommended before first experiences have been collected in related donors	Used conservatively but may be used more liberally than in unrelated donors
Donor eligibility criteria	'Healthy donor',[21] most often very similar to the eligibility criteria for blood donors	Multiple co-morbidities might be accepted
Donor motivation	Altruistic/volunteer	Emotional relationship with the recipient or family. Mostly very willing, but some may donate because of familial obligation alone
Donor advocacy	Yes	Might be the same team as for the patient[49]

[a] Limits might differ depending on individual donor registry's guidelines.

TABLE 2

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Table 2. Minimal data set to be reported after the end of the donation procedure

Time interval covered: start of donation procedure until day 30 after completion of the procedure
Time of report: between day 30 and day 100 after the donation procedure
Donor data
Donor ID[a]
Age at donation
Sex
Relationship to the recipient:
Twin
Sibling
Other family member
Unrelated donor
Collection data
Start date of the procedure
Was the product collection completed?
Yes/no
Number of collections/subsequent donations
Were hematopoietic growth factors used (for example, G-CSF)?[b]
Yes/no
Were cell binding inhibitors used (for example, plerixafor)?[b]
Yes/no
Was EPO used?[b]
Yes/no
Were other drugs used for mobilization?
Yes/no (without further specification)
Product
BM (including collection of MSC)
PBSC
Both (BM and PBSC)
Unstimulated leukapheresis (for example, DLI)
Others
Complications in temporal association with the donation procedure
Report only serious adverse reactions (SAE/R) with International Classification of Diseases (ICD)10 coding (a list with a selection of the anticipated most frequent events is available in Supplementary Information)
Report every SAE/R occurring within the interval between start of the donation procedure and day 30 after end of the donation procedure

[a] There is no global unique donor identifier yet. Each center/registry defines the unique donor ID by its own identifier (in the future, the ongoing WBMT activity towards a unique transplant center and patient identifier may also include a unique donor identifier).

[b] Mobilizing agents may be used before either PBSC or BM collection and should be reported in any circumstances. Neither generic names nor information on dosage will be collected in this data set.

TABLE 3

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Table 3. Minimal data set to be reported for long-term follow-up

Time interval covered: up to 10 years after completion of the last donation procedure
Time of report: minimal reporting after 1year, 5 years and 10 years but annual or biannual reporting is recommended
Donor survival status
Date of last follow-up or death
Donor alive?
Yes/no
If no, cause of death: ICD code
Malignancy
Hematologic malignancy?
Yes/no/unknown
If yes, certainty of the diagnosis: confirmed/unconfirmed by medical data
ICD code
Non-hematologic malignancy?
Yes/no/unknown
If yes: certainty of the diagnosis: confirmed/unconfirmed by medical data
ICD code
Autoimmune disease
Autoimmune disease? (a list with a selection of the anticipated most frequent events is available in Supplementary Information)
Yes/no/unknown
If yes, certainty of the diagnosis: confirmed/unconfirmed by medical data
ICD code