The EBMT Registry and CAR-T Cells

Jurgen Kuball

(Executive Committee Member and member of the legal & regulatory affairs committee on behalf of the EBMT)

www.ebmt.org

The European Society for Blood and Marrow Transplantation (EBMT) is a non-for profit organisation

The EBMT Registry

The Registry database has data that goes back to the early **1970's** and is the **single biggest data source of its kind in Europe.**

The registry collects data in more than **>500** centres and from more than **>50** countries.

It receives nowadays **>30,000** new HSCT registrations per year.

It currently contains data on more than **> 500,000** HSCT procedures.

Algeria
Australia
Austria
Belarus
Belgium
Bulgaria
Canada
Colombia
Croatia
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hungary
Iran
Ireland
Israel
Italy
Jordan
Latvia
Lebanon
Lithuania
Malasya
Netherlands, The
New Zealand
Nigeria
Norway
Poland
Portugal
Romania
Russia
Saudi Arabia
Serbia and Montenegro
Slovakia
Slovenia
South Africa
Spain
Sweden
Switzerland
Tunisia
Turkey
United Kingdom

1.) EBMT Registry: Data completeness and quality

2.) The cellular therapy registry and usefulness for follow-up of CAR-T cell treatments

Data completeness and quality
within EBMT registry
depends on purpose of data collection

Data completeness and quality

1. Historical approach to the registry
2. Benchmarking (upcoming)
3. Retrospective EBMT studies
4. NIS and PASS
5. Clinical studies

Liabilities and Informed consent

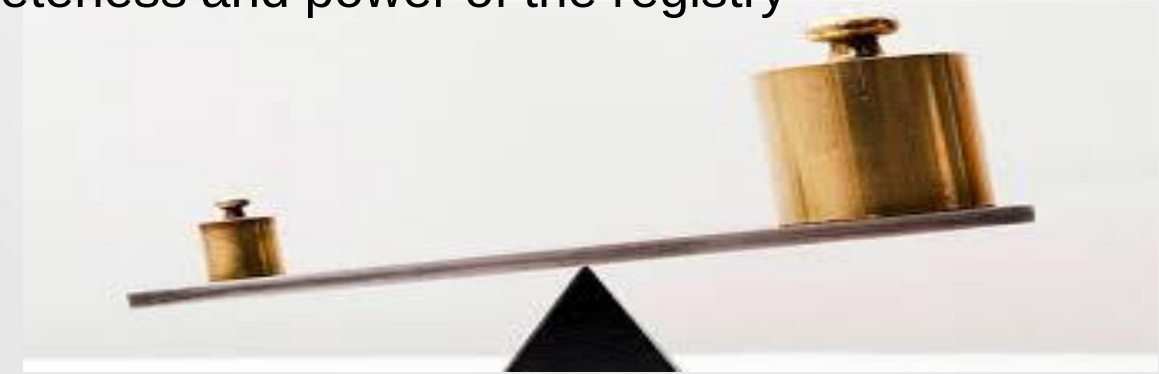
- **Liabilities**
  - It is the **responsibility of the individual centres** or donor registries submitting data to the EBMT to make certain that they comply with their respective national laws
  - It is the **responsibility of the EBMT** to ensure that centres and donor registries are aware of this.

- **Informed consent**
  - **All centres** inside and outside the EU **must obtain informed consents** from their patients and donors before the data can be submitted to the EBMT.
  - This informed consent **must explicitly state** that **the data** is to be kept in an “international” database and **can be exported to a non-EU/EEA country.**

Voluntary data collection: Less is more

Med A forms

- Less than 4% of missing centers in voluntary reporting
- Less than 1% of missing data from all transplantation activities
- Despite this excellent coverage we work on a **continuous simplification of minimal datasets** in order to further improve completeness and power of the registry



Data quality is maintained by

Exact Definitions (harmonization with US in progress)

- All items are completely defined before being placed in the data collection forms
- Same items in different collection forms must mean the same
- A Definitions group made up of representatives of Working Parties and Study offices are always at hand to answer queries

Education & Training

- Training sessions for data managers on the use of ProMISe,
- Educational sessions on clinical knowledge specifically aimed at data managers

Database with internal quality controls

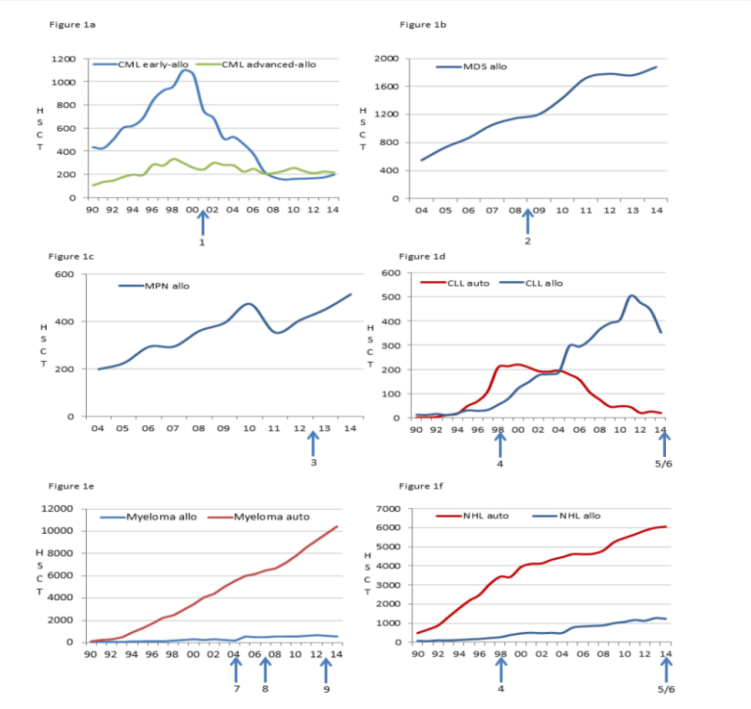
- Over 4,000 triggers control the accuracy and internal consistency of what is entered in the database at the point of entry
- Data quality reports can be run by users at any point to check for missing or unusual data
- Periodic queries on missing / incorrect data and follow up requests

Novel state of the art data base structure

- Promise => MACRO (Elsivier)

Example 1: Activity Survey

Megafile Data Base Studies allow as **neutral ecosystem** monitoring of the impact of novel drugs on treatment choices



Drugs:
1 imatinib,
2 azacitidine,
3 ruxolitinib,
4 rituximab,
5 ibrutinib,
6 idelalisib,
7 bortezomib,
8 lenalidomide,
9 pomalidomide

Passweg et al, BMT 2017

Example 2: Sample Size

Calculating patient numbers eligible to CAR-T cell therapies

(example DLCBL)

Relapse after auto SCT

Year	n
2006	553
2007	558
2008	593
2009	612
2010	600
2011	626
2012	563
2013	550
2014	470
2015	411
2016	333
Total	**5869**

ALLO SCT

Year	n
2006	74
2007	68
2008	79
2009	75
2010	77
2011	74
2012	91
2013	94
2014	103
2015	86
2016	64
Total	**885**

Data completeness and quality

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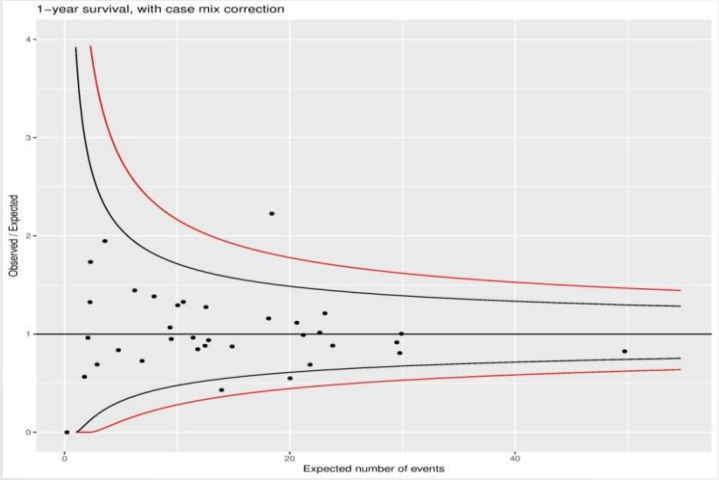
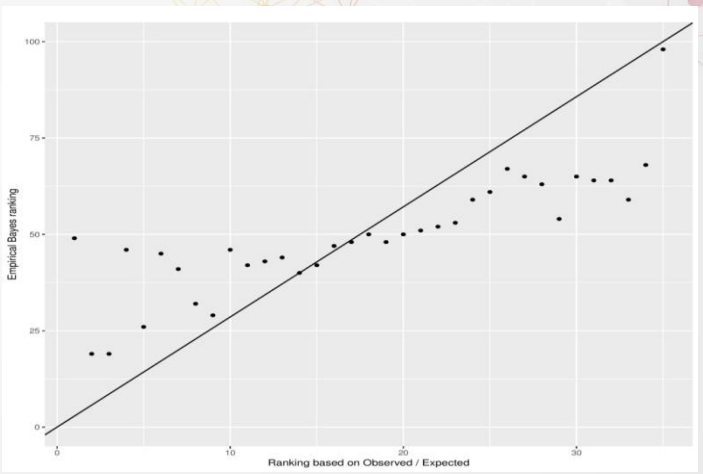
Benchmarking starting 2019 in selected centers





- Funnel plot (left) and Empirical Bayes ranking (right)
- Both can be based on either outcome (survival) or data quality (completeness)

Data completeness and quality

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Next level of data completeness and quality

Med B forms

- Voluntary data collection from selected centers (approximately 20%)

Additional data retrieval and analyses

- Data retrieval and appropriate statistical analysis and interpretation can reduce the possibility of biased conclusions

Example where such studies are useful for approval
ZALMOXIS: case control study resulted in conditional approval

Retrospective EBMT studies

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EBMT Study

Selection of patients meeting study criteria

Management and Outcome of Patients with Diffuse Large B-Cell Lymphoma Relapsed after Autologous Hemopoietic Stem Cell Transplantation (auto-HSCT): A Retrospective Analysis of the Lymphoma Working Party (LWP) of the European Society for Blood and Marrow Transplantation (EBMT)

Eva Gonzalez-Barca, MD, PhD[1*], et al ASH 2017

Total 379

Data completeness and quality

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NIS and PASS Definitions

- **NIS: Non-Interventional prospective Study**
  - Mild patient selection
  - Does not interfere with standard of care and the wide commercial use of the drug
  - Collection of future events: for fixed time and an additional follow up time

- **PASS: Post Authorization Safety Study**
  - carried out after a medicinal product or medical device has been authorized to obtain further information on a medicine's safety , or to measure the effectiveness of risk management measures.

- **Adding a control group**
  - e.g. to calculate the incidence and compare different interventions

We feel that Post Authorization Safety Studies would fall into the category of

The EBMT Non Interventional Study Model

NIS and PASS Requirements

- **Med B and C forms**
  - More data are collected from selected centers

- **Investigator initiated**
  - EC approval needed in certain countries ! (Academia initiated)
  - **EC approval needed in ALL countries ! (Pharma initiated)**

Examples of NIS and PASS within EBMT

- **Based on scientific / pharma interest**
  - TKI second generation: 440 pts treated with dasatinib or nilotinib
  - Iron toxicity: 200 pts with treatment for iron overload

- **Based on requests by EMA**
  - CALM study: 7,800 auto tx for MM or Lymphoma (660 with plerixafor)
  - Defibrotide for VOD: ongoing recruitment (new legal requirements)

Data completeness and quality

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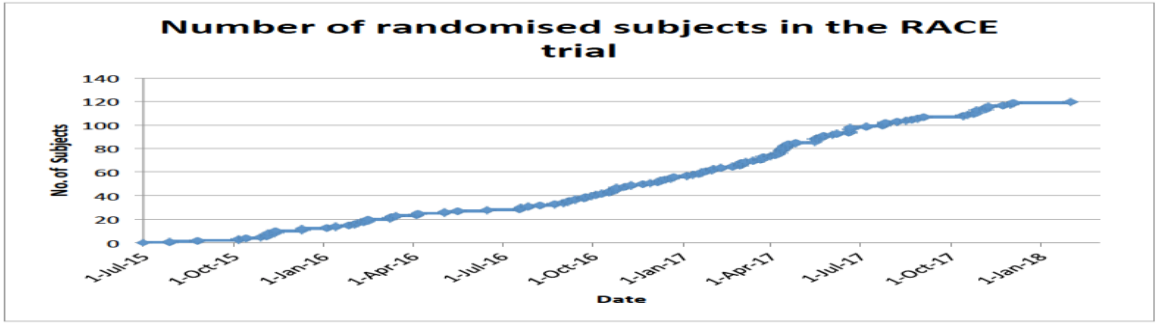
Example: the RACE study

Title of clinical trial	A prospective Randomized multicenter study comparing horse Antithymocyte globuline (hATG) + Cyclosporine A (CsA) with or without Eltrombopag as front-line therapy for severe aplastic anemia patients.



residual hematopoiesis.

Incentive driven data collection is more complete than voluntary data collection, once more information is needed than provided by Med-A

Further considerations

- **Bias in data completeness** of control cohorts is compensated by retrospective matched cohort analyses with appropriate statistical tools and does mainly affect power of the study but not the evaluation of the general outcome (example: Zalmoxis)

- EBMT registry has the **capacity to accommodate regulatory requests** for amendments or for collection of additional variables based on emerging information during post-authorisation surveillance.

- **EBMT is keeping track with all proofs of evidence for legal requirements:** patient consents, data ownership, and level of data sharing with the regulator or an independent third party in sponsored studies undertaken for regulatory purposes.

Frequency of reporting

- In **technical** terms, the frequency of data collection is entirely open to discussion.
  - Frequency can be increased or decreased as need.

- In **practical** terms, frequency must take into account the real capacity of centres to timely report – high frequency may be very challenging to centres unless they had very strong support.
  - Increased frequency of reporting should be clearly justified and **resourced as necessary**

Data ownership, consent, control, and use

- The **owner** is the PATIENT. The focus has to be on CONSENT, CONTROL and USE.

- Definitions taken from the General Data Protection Regulation (**GDPR**) show **EBMT as the controller**, and the **LUMC in The Netherlands as the data processor** (because they host the database). EBMT as the controller is currently taking all the necessary steps to comply with the GDPR in time for May 2018.

- **Privileges of a controller:** For a centralized data collection of newly approved drugs it could be reasonable to discuss timely embargos (1 year)

General Conclusion Part I

- The **quantity, quality, and frequency of data collection is mainly determined by the goals and nature of the study**

- **Adequate allocation of resources allows an improvement of the quality** of the data collected

1.) EBMT Registry: Data completeness and quality

2.) The cellular therapy registry and usefulness for follow-up of CAR-T cell treatments

General considerations

- EBMT assumes that transplantation units will be the main context of administration of CAR-T cells in Europe, at least in the short-term

- Thus the EBMT registry should provide a satisfactory coverage of the target population.

Why should we register patients receiving cell and gene therapies?

- Capture **“Real life” data**
- Collect even **rare and long-term AE**
- **Compare clinical results** of cell and gene therapy products with alternative or gold standard therapeutic approaches
- **Increase collaborative interactions** between Cell and Gene Therapy stakeholders, in order to optimize conditions for safe manufacturing and delivery of this new category of medicinal products

The Cellular Therapy Registry Committee

- Chiara Bonini (CTIWP)
- Christian Chabannon (CTIWP)
- Carmen Ruiz (EBMT Registry)
- Anja van Biezen, EBMT
- Steffie van der Werf, EBMT
- Fabio Ciceri (CTIWP)
- Alessandro Aiuti (IEWP, ESGCT)
- Maria Pia Cicalese (IEWP)
- Alessandra Magnani (IEWP)
- Maria Ester Bernardo (CTIWP)
- Marina Cavazzana Calvo (IEWP, ESGCT)
- Elisa Magrin (IEWP)
- Fabien Touzot (IEWP)
- Attilio Bondanza (CTIWP)
- Eliane Gluckman (CTIWP, Eurocord)
- Dominque Farge-Bancel (ADWP)
- John Snowden (ADWP)
- Francesco Lanza (STWP)
- Paolo Pedrazzoli (STWP)
- Patrizia Comoli (STWP)
- Francesco Dazzi, (CTIWP)
- Martin Bonhauser (CTIWP)
- Hans-Jochem Kolb (CTIWP)
- Jakob Passweg (CTIWP)
- Helen Baldomero (CTIWP)
- Andrea Velardi (CTIWP)
- Loredana Ruggeri (CTIWP)
- Katarina LeBlanc (ADWP, CTIWP)

Chiara Bonini
Member CTIWP

Christian Chabannon
CTIWP Chair, Legal & regulatory affairs committee

Jurgen Kuball
EBMT, EXCOM, Legal & regulatory affairs committee

Eoin McGrath
EBMT Barcelona, Legal & regulatory affairs committee

Carmen Ruiz
EBMT London

Anja van Biezen
EBMT Leiden

Minimalized core data set for cellular therapies

- **Med-A “2.0” for cellular therapies operational since 2017**
  - Med-A “2.0” for cellular therapies has been created by EBMT
  - Also here “less is more”: avoid extensive medical history or co-medication as well as bio-banking
  - EBMT collaboration with CIBMTR and others: harmonization of content and computational interaction between both systems. This is currently used for joined research projects

Cell therapy Registry: Example ATMPs

2016	2017	Total in database (2004 – now)	
8	69	86	Ex-vivo manipulation
4	2	8	Drugs (any type)
1	2	5	Mitogens
3		5	Growth factor
	5	8	Retroviral vector
	10	10	Lentiviral vector
		4	Transgene suicide gene
	13	14	Transgene other
2	3	5	Viral
1	2	3	Cytomegalovirus
1	1	2	Epstein-Barr virus
3	19	22	Tumor/ cancer antigen

Among the Transgene other, we have:

ADA-GENE	6
ARSA-gene	4
WAS-gene	4
b-globin	2

AE/SAE reporting

- EBMT only assumes responsibility for (S)AE reporting where EBMT is a study sponsor. Where a study is sponsored, the sponsor must assume this responsibility.
  - EBMT has direct experience for its own trials

- **EBMT can collect (S)AE data in the registry** and use it to prepare aggregate data reporting but this does not constitute reporting in a safety sense.
  - Data is collected retrospectively

Limitations that registries can address (1)

- **Creating a strong and comprehensive data set**
  - **Sponsor-specific registries can create ‘silos’** which blocks sharing and comparison.
  - **A single reporting resource will avoid fragmentation** of small data sets
  - **Strongly contribute to standardisation** by establishing and enforcing definitions across countries and diagnoses.
  - This will allow to **achieve a meaningful body of pooled data,** which could be used to generate aggregate reports for third parties such as regulators

Limitations that registries can address (2)

- **Real world testing**
  - Testing whether benefits observed in clinical trials are also seen in unselected patient populations in **real-world settings**
  - **Justify public investment** to ensure availability of tissue and cell therapies

- **Covering the lifetime of a patient**
  - A **single individual** patient can sequentially receive **several types and categories of cellular therapies in combination** with other categories of treatments and so a broader data capture strategy than just a therapy-specific focus is necessary.

EBMT – EMA - Interaction

- 16-10-2016 Patients Registry Workshop: Challenges and Opportunities for Collaboration **The EBMT Registry**

- 05-05-2017 Report of the meeting: EMA/180341/2017 Inspections, Human Medicines, Pharmacovigilance and Committees Division Patient Registry Initiative- Strategy and Mandate of the Cross-Committee Task Force

- 07-2017 Scientific advice meeting on CAR-T approval: EBMT was asked to join from both parties (pharma and EMA)

- 6-10-2017 Teleco Bonini/Kuball & Tavridou National Expert on Secondment, Scientific Advice, Product Development Scientific Support Department EMA

Outcome TC 06-10-2017

- EMA are suggesting that **EBMT goes through a process of qualification for registration of cellular products like CAR-T** where EMA will be more than happy to guide EBMT through such a process given the high importance for the European health care system.

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000319.jsp&d=WC0b01ac0580022bb0#section1

- In addition EMA wants to know if **EBMT is interested in entering this process: HTA body (health technology access body):**

  http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000476.jsp

- Board EBMT approves this process 07-10-2017

EBMT Registry Qualification Dossier, next steps ….

- 23-11-2017 Submission documents under lead of Eoin McGrath plus whole EBMT team in all offices (Anja van Biezen, Marianne Mol, Carmen Ruiz de Elvira)
  - EBMT Registry Qualification Dossier
    - Specific questions for EMA review and EBMT positions
      - **The Agency is asked if the data quality control mechanisms proposed by EBMT are adequate for PLEG purposes for CAR-T cell products.**
      - **…..**
- 07-02-2018 First feed back EMA on the Registry qualification dossier
- 09-02-2018 EBMT invited to Registry initiative CAR-T (along with CIBMTR) which will create a minimal data set which will be different from the exisiting

Minimal data sets requested by EMA after a stakeholder meeting with registries and pharma

Table 3. Proposed data elements relating to Efficacy, priority for collection, current capture in registries and participant comments

Topics	Data	Priority for collection in Registry	Already captured by the Registries?	Comments from Workshop
Demographics	Age, Gender, Height, Weight, Centre	Crucial	Yes	Collected
Information on the malignancy	Documented diagnosis using a standard terminology (Read, ICD, other)	Crucial	Yes	Variable definition and details across centres and countries; Need agreed common definitions to permit outcome comparisons. EBMT uses WHO definition system for haematological malignancies CIBMTR: WHO system currently undergoing implementation
	Date of Diagnosis	Crucial	Yes	Date of definitive diagnosis using histology, molecular, cyto-genetic methods
	Disease burden / stage at cellular therapy treatment	Crucial	Yes	Recorded at the date of treatment – this is a likely outcome effect modifier
Functional status / Prognostic information	Performance status	Crucial	Yes	Both registries collect Karnofsky performance status and Comorbidities Index information
Prior therapy for the malignancy	Lines of therapies	Crucial	Yes	Captured, but therapies differ between centres & countries & there is no definition of what constitutes a 'line of therapy'. EBMT suggests product name plus start & end dates for all therapies should be sufficient. CIBMTR suggests two-tier determination: up-front v relapsed / progressed disease therapy
CAR T-cell administration	Product and dose	Crucial	Yes	Registries note that details are captured along with the product information – implicit in name of product

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2018/05/WC500249248.pdf

Cellular therapy of the EBMT has been explored by EMA and resulted in a (draft) qualified opinion

Draft qualification opinion on Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry

Agreed by Scientific Advice Working Party	17 May 2018
Adopted by CHMP for release for consultation	31 May 2018*
Start of public consultation	29 June 2018†
End of consultation (deadline for comments)	21 August 2018‡

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2018/06/WC500251193.pdf

Next challenges (1)

- Get all pharma aboard
  - Generate transparent rules of data analyses and potential embargo periods

- Get regulators in different countries aligned
  - Legal differences
  - Do not underestimate language barriers

Next challenges (2)

- Get the physician community aligned
  - Be inclusive and extend the registry to disease registries (ongoing)
  - Create educational tools and quality criteria for centers who use the products

- Get payers aligned
  - Generating a next stakeholder meeting with registry pharma and payers to defined a minimal data set for HTA bodies ?

EBMT European Society for Blood and Marrow Transplantation

Go-CART: The Global EBMT CAR T Strategy

Pre and Post Marketing Registration

CAR T Center Accreditation

CAR T Education