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ARTICLE

Recommendations from the European Society for Blood and Marrow Transplantation (EBMT) for a curriculum in hematopoietic cell transplantation

Mohamad Mohty[1] · Rafael F. Duarte[2] · Jurgen Kuball[3] · Peter Bader[4] · Grzegorz W. Basak[5] · Chiara Bonini[6] · Enric Carreras[7] · Christian Chabannon[8] · Carlo Dufour[9] · Andrew Gennery[10] · Arjan Lankester[11] · Francesco Lanza[12] · Per Ljungman[13,14] · Silvia Montoto[15] · Arnon Nagler[16] · John A. Snowden[17] · Jan Styczynski[18] · Anna Sureda[19] · Nicolaus Kröger[20]

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Abstract

Hematopoietic cell transplantation (HCT) is increasingly used worldwide. This treatment approach is complex and requires specific knowledge and training. The European Society for Blood and Marrow Transplantation (EBMT) identified the need for a set of international recommendations for the clinical training of physicians to qualify them as being competent in performing HCT procedures as well as novel cellular immune therapies and taking care of such patients. The goal is to implement an EBMT HCT-focused global curriculum (EBMT-GC) that can serve as a tool for the development of the HCT sub-specialty worldwide. Despite the diversity and heterogeneity of health and educational systems around the globe, this set of recommendations can be fairly adopted by any national educational and health authorities and can be adjusted to specific conditions and resources of a given country, if needed. The ultimate goal of the EBMT-GC is to define standards for personal knowledge in allogeneic stem cell transplantation for physicians worldwide in order to ensure that all patients will receive treatment by well-trained physicians.

All the authors contributed equally to this work.

✉ Mohamad Mohty
Mohamad.mohty@inserm.fr

[1] INSERM, UMR_S 938, and Hôpital Saint-Antoine, Service d'Hématologie Clinique et de Thérapie Cellulaire, Sorbonne University, Paris, France

[2] Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain

[3] Department of Hematology, University Medical Centre, Utrecht, The Netherlands

[4] Klinik für Kinder- und Jugendmedizin, Universitätsklinikum Frankfurt, Goethe-Universität, Frankfurt am Main, Germany

[5] Department of Hematology, Oncology and Internal Medicine, The Medical University of Warsaw, Warsaw, Poland

[6] Università Vita-Salute San Raffaele, Milan, Italy

[7] Hematology Department, Hospital Clínic, Josep Carreras Foundation & Leukemia Research Institute, Barcelona, Spain

[8] Institut Paoli-Calmettes, Marseille, France

[9] Hematology Unit, G.Gaslini Children's Institute, Genova, Italy

[10] The Institute of Cellular Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle University, Newcastle upon Tyne, UK

[11] Department of Pediatrics, Leiden University Medical Centre, Leiden, The Netherlands

[12] Hematology and BMT Unit, Ravenna, Italy

[13] Department of Cellular Therapy and Allogeneic Stem Cell Transplantation, Karolinska University Hospital, Stockholm, Sweden

[14] Division of Hematology, Department of Medicine Huddinge, Karolinska Institutet Stockholm, Sweden

[15] St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK

[16] Chaim Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel

[17] Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

[18] Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

[19] Institut Català d'Oncologia, Hospital Duran i Reynals, Barcelona, Spain

[20] Department of Stem Cell Transplantation, University Hospital Eppendorf, Hamburg, Germany

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Introduction

The incidence and prevalence of hematologic malignancies continue to increase, mainly due to the aging population. Hematopoietic cell transplantation (HCT; whether autologous or allogeneic) is a well-established treatment for a large range of diseases affecting the hematopoietic systems leading to hematological immunological or metabolic diseases [1].

Well over a million HCTs have been globally performed thus far [2]. Presently, >50,000 HCTs are performed worldwide annually, with a linear progression expected for the foreseeable future [3]. For many hematological diseases, allogeneic stem cell transplantation offers the highest chance for long-term survival and cure. In addition, cellular immune therapies enter clinical standards of care. Despite these encouraging developments, it should be recognized that HCT is a complex therapeutic approach, requiring highly trained health-care providers and a concerted action between highly trained physicians and allied health-care professionals embedded in complex logistics. While the practice of HCT is usually linked to that of clinical hematology and oncology, being a trained hematologist or oncologist or nurse is not sufficient to provide state-of-the-art care and management for HCT patients.

With this background, the European Society for Blood and Marrow Transplantation (EBMT) identified the need for a set of international recommendations for the clinical training of physicians and allied health-care professionals to qualify them as being competent to perform HCT and cellular immune therapy procedures and take care of such patients. EBMT board members, committee leaders, and external experts were consulted with the goal of developing an EBMT HCT-focused global curriculum (EBMT-GC) that can serve as a tool for the development of the HCT subspecialty worldwide. This EBMT-GC aims to cover a broad range of recommendations of major importance to the practice of HCT and cellular immune therapies. Despite the diversity and heterogeneity of health and educational systems worldwide, this set of recommendations can be fairly adopted by national educational and health authorities and adjusted to specific conditions and resources of a given country, if needed. The ultimate goal of the EBMT curriculum is to define standards for personal knowledge in allogeneic stem cell transplantation for physicians worldwide in order to ensure that all patients will receive treatment by well-trained physicians. The content of the EBMT-GC has been designed as a dynamic process to take into account the important therapeutic and biologic advances to allow for the selection of the most appropriate therapeutic strategy and/or procedure for a given patient. In addition, less acknowledged areas such as palliative care in HCT, psychosocial aspects, quality standards, bioethical, and legal issues were integrated. While some transplant centers have developed educational training programs, a structured, harmonized curriculum is lacking in Europe.

While it is difficult to propose an exact duration for a specific HCT training period, the task force arbitrarily judged that a 12-month period is the minimum requirement after completing full training (usually 4–5 years in most countries) in specialties, such as clinical hematology, medical oncology, pediatric oncology, clinical immunology, or internal medicine. The program based on the EBMT-GC must include full-time clinical training in a well-established HCT unit, preferentially JACIE accredited or with an equivalent accreditation program with access to a wide variety of general and specialty support, including (but not limited to) pathology and laboratory medicine. Full-time clinical training means that the trainee's professional time and effort during a standard working week is dedicated to specific activities related to the care of HCT patients (inpatient unit care and rounds, ambulatory and day unit care, external consultations, multidisciplinary meetings, performance of procedures on HCT patients, review of diagnostic tests, educational activities such as attending national and international meetings focused on HCT, and reading relevant literature). Exclusive laboratory and biology research activities should not be counted as part of the total 12-month training period. However, research experience in dedicated and reputable facilities with a special interest in the HCT field is strongly recommended, especially for those physicians who want to pursue an academic career. Thus at least 1 month laboratory training is needed to get a "passport" of expert "transplanter" in the field of HCT.

EBMT-GC objectives

The aim of the EBMT-GC is to provide the training content defined by recognized international experts to acquire the necessary background for the overall management of HCT patients with a special focus on practical considerations after which each candidate should be able to:

Understand principles of autologous and allogeneic stem cell transplantation including hematopoiesis and immunology;
Evaluate patients for autologous and allogeneic procedures (including evaluation of potential donors) and be familiar with the techniques to identify potential human leukocyte antigen (HLA)-compatible stem cell or bone marrow donors (siblings and unrelated donors);
Understand and discuss indications of HCT for the different candidate diseases and recognize the importance of a multimodality approach to manage such patients;
Know the eligibility criteria for different types of transplantation and be aware of the biology tools for the assessment of prognosis and the selection of

appropriate treatments in patients with hematopoietic stem cell-derived diseases;
Know the risks and benefits associated with the procedure, as well as ethical and regulatory aspects, and appreciate the relevant disease and transplant-related risk factors;
Define the pretransplant assessment procedures, understand the risks and manage the peritransplant and posttransplant complications for the different types of grafts;
Be able to perform the follow-up of patients early posttransplant and establish immune modulation strategies;
Understand and perform the follow-up of transplant patients on the medium and long term, notably diagnosis and management of acute and chronic graft versus host disease (GVHD);
Know the indications for drug-based therapies and monoclonal antibodies, their side effects, and their therapeutic results for prevention or treatment of post-HCT relapse;
Know the principles of transfusion medicine, apheresis procedures, and collection of hematopoietic cells from patients and donors;
Know the principles of cellular immune therapies of unmanipulated and manipulated products within and outside the context of HCT;
Know how to diagnose, prevent, and treat main early complications after HCT including those of endothelial, infectious, and immunological origin (graft failure and acute GVHD);
Know how to diagnose, prevent, and treat complications appearing late after HCT including late infections, management of long-term chronic GVHD, and secondary cancers;
Be familiar with the problems that derive from disease progression after HCT including the need for supportive and palliative care strategies;
Interpret diagnostic test results properly;
Use appropriately medication and diagnostic procedures;
Develop interpersonal and communication skills for a proper communication with patients, their families, and team members, such as nurses, transplant coordinators, and data manager;
Be familiar with quality management system; and
Know the principles of clinical trials and basics in medical statistics

EBMT-GC training program content

In order to achieve the above objectives, the following training program is recommended (obviously, some items are not relevant for pediatric HCT practice and vice versa):

- To be able to perform specialist assessment, define indications, and undertake counseling for allogeneic and autologous HCT in specific diseases, e.g.,:

  Aplastic anemia and paroxysmal nocturnal hemoglobinuria
  Myelodysplastic syndromes
  Acute myeloblastic leukemia
  Philadelphia negative myeloproliferative neoplasms and chronic myeloid leukemia
  Acute lymphoblastic leukemia
  Chronic lymphocytic leukemia
  Non-Hodgkin lymphoma
  Hodgkin lymphoma
  Plasma cell disorders such as multiple myeloma and amyloidosis
  Non-malignant hematologic, immunologic/autoimmune and metabolic diseases
  Solid tumors

- To be able to perform specialist assessment for eligibility criteria for HCT and awareness of the principles of donor selection, including specific issues in children:

  Pre-transplant work-up in the recipient (including a focus on fertility preservation whenever applicable)
  Basic knowledge on systematic of international search of unrelated donors
  Evaluation of comorbidities in both donor and recipient
  Assessment of vascular access
  Evaluation of disease status in recipient (including minimal residual disease)
  Choice of related and unrelated donors, cord blood cells, haplo-identical donors
  Clearance of donor and pre-donation work-up
  Follow-up of the donor after hematopoietic cell donation

- Choice and strategies for graft collection

  Unmanipulated bone marrow versus mobilized peripheral blood stem cells
  Graft source: family donors, unrelated donors, cord blood cells, and haplo-identical donors
  Mobilization procedures/techniques and hematopoietic cell collection process
  Quality and release criteria of the graft
  Conditions for preservation of the graft
  Conditions to transport the graft

Procedures for manipulation of the graft (red blood cell depletion, T-cell depletion, CD34+ cell selections, stem cell expansion, etc.)

- Immunological bases, HLA system, and matching principles and blood transfusions

Animal models of HCT
HLA typing: methods, techniques, and quality control
Principles for selection of related and unrelated donors
The HLA system and graft rejection
The HLA system and GVHD
Blood product selection (nature, CMV serostatus, irradiation, etc.)
Major and minor ABO incompatibilities: risks and management

- Conditioning and preparative regimens prior to graft infusion

Myeloablative, reduced intensity and non-myeloablative regimens
Concepts behind reduced-intensity and reduced-toxicity conditioning regimens
Total body irradiation

Advantages and side effects
Short and long-term follow-up

Chemotherapeutic agents and rationale for combinations as part of a conditioning regimen
Advantages and side effects
Short and long-term follow-up

- Immunosuppressive agents: principles of action, dosing and administration, toxicities, choice, monitoring and management
- Follow-up after transplantation

Engraftment
Diagnosis and management of primary and secondary graft failure/rejection
Chimerism analysis and interpretation
Acute GVHD
Definition, clinical presentation, and grading
Strategies for prevention and treatment

Graft versus leukemia or graft versus tumor effect
Diagnosis, prevention, and treatment of relapse post-transplant
Donor lymphocyte infusion (DLI)
Principles of immune modulation and immunosuppressive therapy management posttransplant
Recognition of importance of chimerism (e.g., when full donor is important or lineage-specific mixed donor chimerism is sufficient)
Principles of supportive care: nutritional counseling, pain and nausea management
Immune reconstitution

- Acute complications posttransplant

Infectious complications: bacterial, fungal, viral, and parasitic
Lympho-proliferative syndromes
Drug toxicities and interactions
Cytopenia
Early complications of endothelial origin (veno-occlusive disease, thrombotic microangiopathy, capillary leak syndrome, engraftment syndrome, diffuse alveolar hemorrhage, etc.)
Idiopathic pneumonia syndrome
Hemorrhagic cystitis

- Long-term follow-up and management of long-term complications (including specific issues in children):

Chronic GVHD: diagnosis, grading, and management
Management of side effects of immunosuppressive therapy, especially steroids
Immunodeficiency and vaccinations
Endocrinopathies
Fertility, libido, and sterility
Cardio-vascular and lung complications
Secondary cancers
Quality-of-life issues and recognition of the psycho-social implications of HCT

- Cellular therapies

Regulation of advanced therapy medicinal products and other cellular therapies
Principles of unmanipulated and manipulated cellular products
Adoptive cellular therapies (e.g., antiviral cytotoxic lymphocytes, mesenchymal cells, natural killer cells, DLI, T-cell add-back with suicide gene, chimeric antigen receptor T cells)
Management of side effects, such as neurological toxicities, cytokine release syndrome, tumor lysis, insertional mutagenesis, etc.

- Regulatory and ethical issues and quality management

  Healthy donors registries
  Cord blood banks
  JACIE accreditation
  Clinical research methods and statistics

- HCT-specific pediatric issues (as discussed above)
- HCT-specific nursing and allied health professional care issues (including physiotherapy, nutrition, social support, etc.)
- Communication skills:

  Effective communication to HCT patients and healthcare providers
  Communication of serious news
  Transition from cure to end-of life care

Concluding remarks

Despite the diversity and heterogeneity of health and educational systems around the globe, the EBMT believes that the above set of recommendations can be fairly adopted by any national educational and health authorities and can be adjusted to specific conditions and resources of a given country, if needed. The ultimate goal is to define standards for personal knowledge in allogeneic HCT for physicians worldwide in order to ensure that all patients will receive treatment by well-trained physicians.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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