# Autologous and allogeneic hematopoietic stem cell transplantations: introduction, contemporary indications and trends

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# Hematopoiesis, hematopoietic cells of bone marrow, peripheral blood stem cells – I

- ✓ **Hematopoiesis** – very complicated process, it arises from small group of **pluripotent stem cells of bone marrow.**

  These immature cells are able to **reproduce** and to **differentiate** to various blood lines with production of mature blood cells - leukocytes, erythrocytes and thrombocytes.

- ✓ **Immature hematopoietic stem cells** have got on their surface **antigen structure CD34**, this is very important and typical sign for these cells.

- ✓ **Special flowcytometric examination of bone marrow or peripheral blood –** easy identification of these immature hematopoietic cells according to the surface antigen CD34

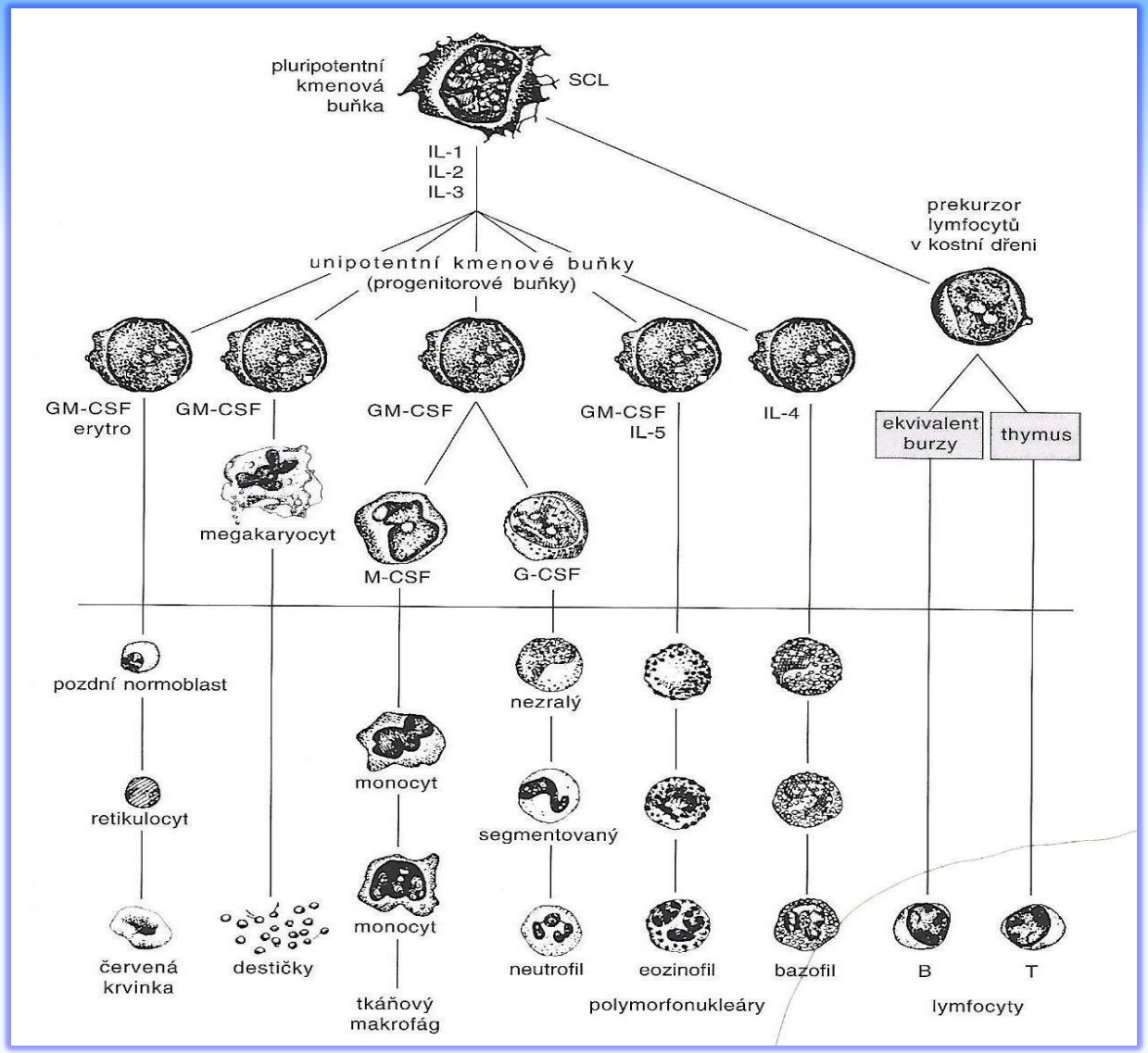
*Adam Z et al. Special Oncology. Galen 2010, 417 pages.*

# Hematopoiesis, hematopoietic cells of bone marrow, peripheral blood stem cells – I

- ✓ **Open communication** between **bone marrow (BM)** and **peripheral blood (PB);** in bone marrow are mostly immature or partially mature cells, in peripheral blood mostly mature cells.
- ✓ **Peripheral blood stem cells (PBSC) – hematopoietic cells –** can be present in peripheral blood in some specific cases, such as **regeneration of BM after administration of chemotherapy or application of leukocyte growth factor (filgrastim, G-CSF)**
- ✓ **Mobilization and harvest of PBSC** – using for transplantation of hematopoietic cells

*Adam Z et al. Special Oncology. Galen 2010, 417 pages.*

# Scheme of Hematopoiesis




*Ganong WF. Overview of Medical Physiology. Galen 2005, 890 pages.*

# Definition of transplantation ( HSCT)

**Hematopoietic stem cell transplantation (HSCT)**

- ✓ refers to any procedure where haematopoietic stem cells of any donor type and any source are given to recipient with the intention of repopulating and replacing the haematopoietic system in total or in part.
- ✓ Sources of hematopoietic cells – bone marrow, peripheral blood, cord blood
- ✓ **Two main types of HSCT:**
  - ❖ **autologous** (donor = recipient)
  - ❖ **allogeneic** (donor = HLA identical sibling or matched unrelated donor)

*(Ljungman P et al., BMT 2010)*

# Hematopoietic stem cell transplantation (HSCT) – history in Europe

- ***1891*** *- Sequard a D'Arsenoval - BM* ***perorally*** *in anemia*
- ***1937*** *- Schretzenmayer - BM* ***subcutaneously*** *in some infectious diseases*
- ***1944*** *- Bernard – application of allogeneic bone marrow to* ***bone marrow cavity***
- **1948-1950** – first experiments about transplantations after radiation and chemotherapy
- **1950-1966** - 417 transplantations of bone marrow were performed, but only three patients alive
- **1969** – the first "modern" allogeneic HSCT from HLA identical sibling, in Leiden, Netherland
- **1974** – **establishment of European Society for Blood and Marrow Transplantation, EBMT – start of new transplant era**
- **1978** – **the first transplantation of peripheral blood stem cells**
- **1990** – start of HSCT program in Czech Republic
- **2017** – HSCT – still very actuall topic, the increasing of HSCT procedures in Europe

# HSCT – introduction - I

- ✓ **Hematopoietic stem cell transplantation –intravenous application of PBSC or BM graft to recipient,** application to central vein catheter ( *mostly in vena subclavia*)
- ✓ **Administration of conditioning – preparative regimen before HSCT** –usually combination of cytostatic drugs or combination of cytostatics and total body irradiation (TBI)
- ✓ **Main indications for HSCT**: hematological malignancies (90%), *but HSCT are performed in many other diseases, such as aplastic anemia, solid tumors and others*

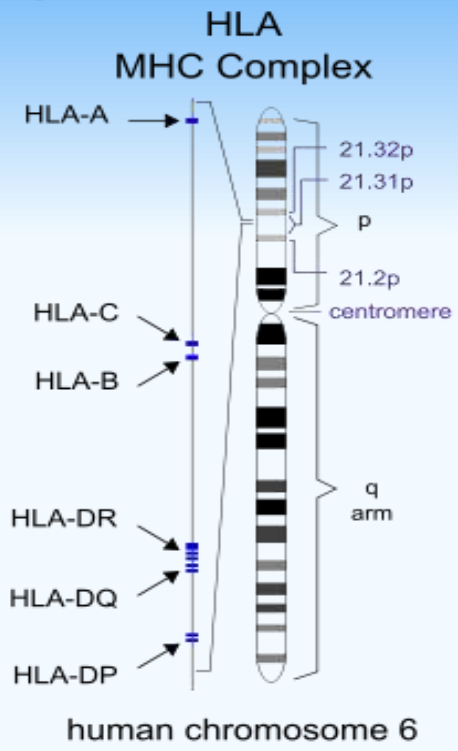
# HSCT – introduction - II

- ✓ Application of high-dose chemotherapy is toxic, there are two main types of treatment **toxicity: hematologic and non-hematologic** (*main toxicity examples: bleeding, infections, mucositis – involvement of oral cavity and GIT tract, organ failure).*
- ✓ We can eliminate serious hematologic toxicity with application of PBSC or BM graft.
- ✓ **Engraftment after HSCT and sequential recovery of hematopoiesis –** usually in **interval 2-3 weeks after PBSC graft.** In HSCT with BM graft is recovery interval longer.

# HSCT – introduction - III

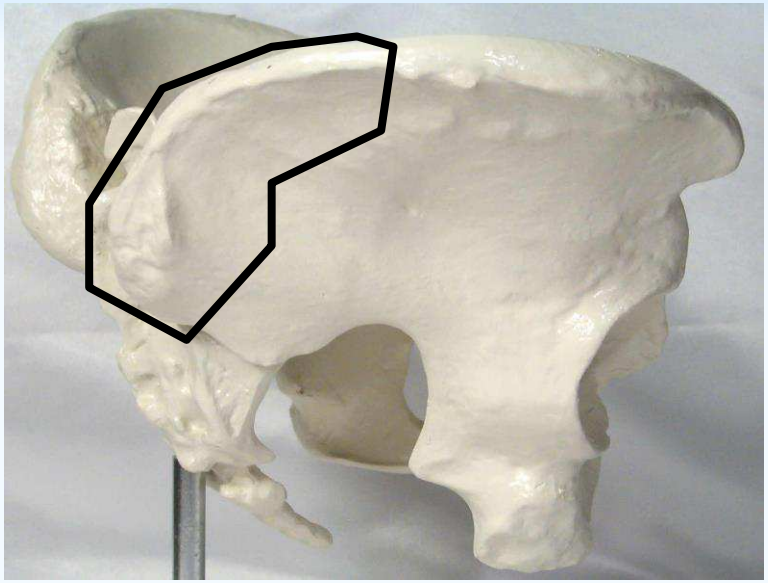
- ✓ **Autologous transplantation** - hematopoietic stem cells of patient (*donor =recipient*) are used. We collect PBSCs usually in remission of disease (*phase without clinical and laboratory signs of disease*).
- ✓ **Allogeneic transplantation** – hematopoietic stem cells of optimal health donor are used from sibling donor or unrelated donor, *donor and recipient are different persons.*
- ✓ **Optimal allogeneic donor – HLA identical sibling or well-matched unrelated donor from donor bone marrow registers (national or international registers)**
- ✓ **A well-matched urelated donor (MUD**) is defined as a 10/10 or 8/8 identical donor based in HLA high-resolution typing for class I (HLA-A,-B,C) and II (HLA-DRB1, DQ-B1).
- ✓ ***Alternative allogeneic donor****: mis-matched unrelated donor (MMUD) - 9/10, 8/10), haploidentical donor (family donor with only one HLA haplotype), blood core donor*

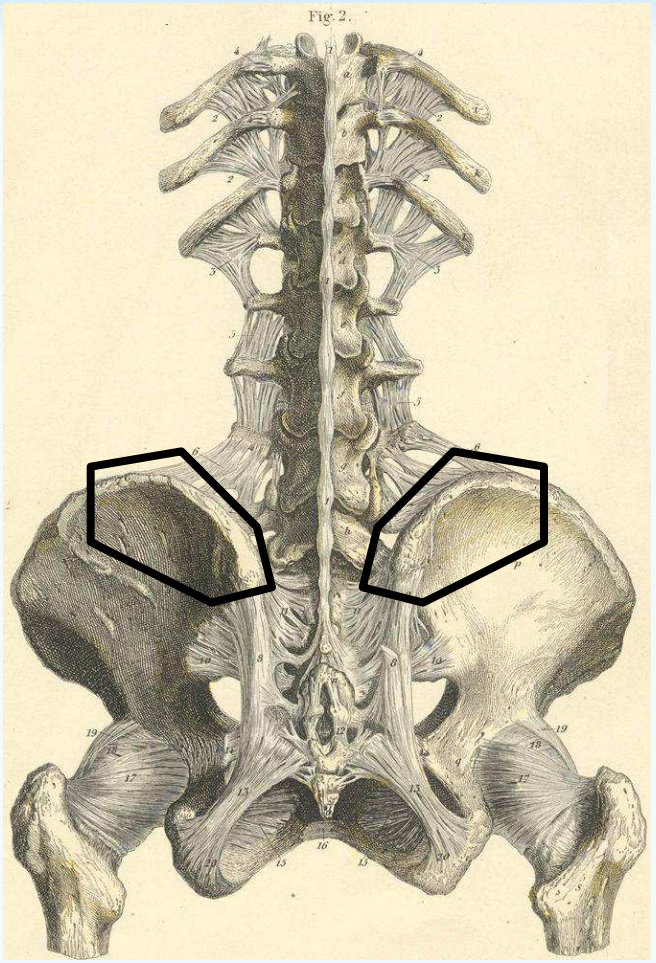
# HSCT – introduction - IV

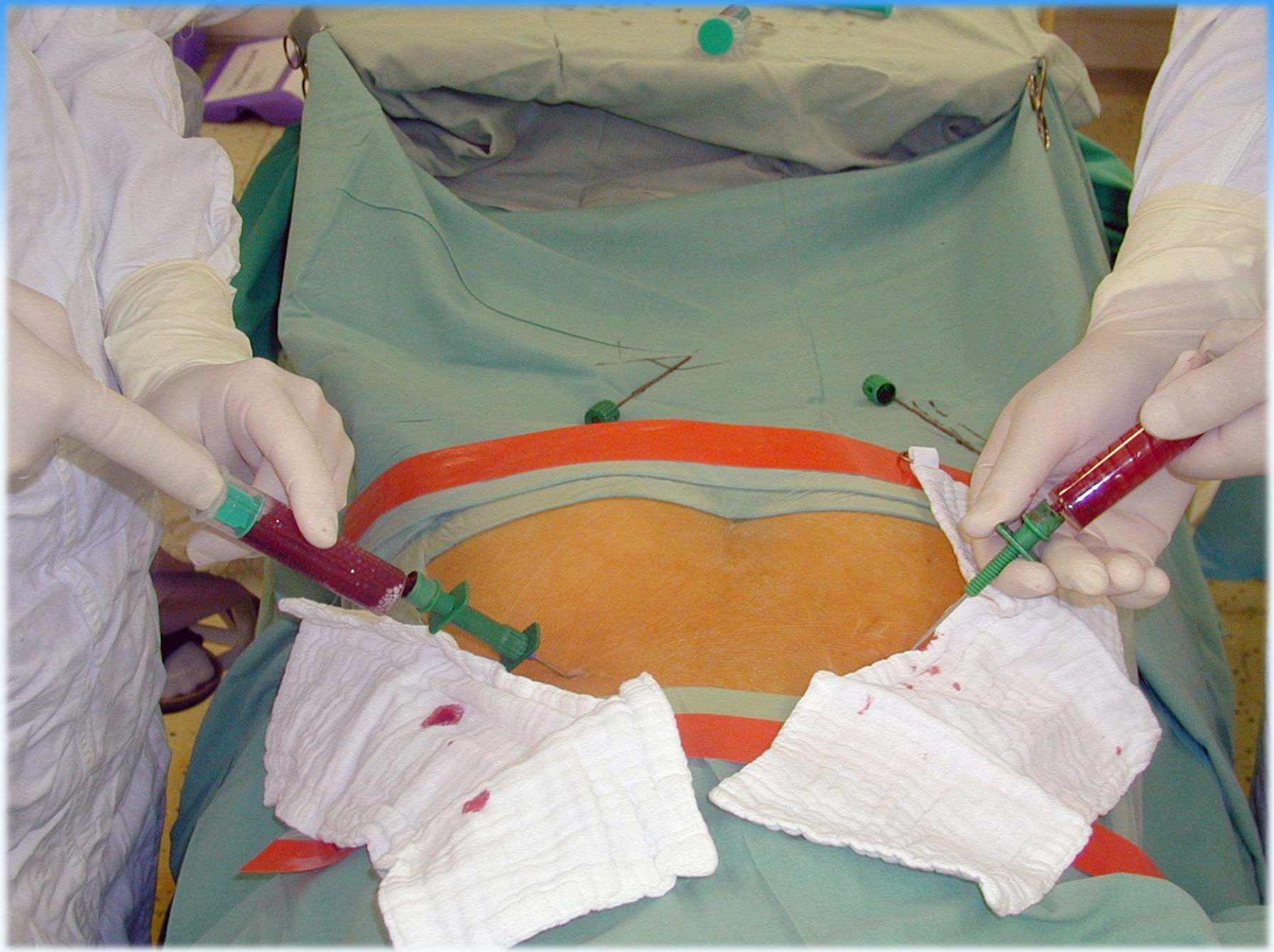



- ✓ **Main post-transplant complications:**
  - toxicity of conditioning (preparative regimen)
  - failure and rejection of graft
  - infections
  - graft-versus host disease (GvHD)
    - *in allogeneic transplantation*
  - relaps/progression of basic disease (*acute leukemia*)
- ✓ **Allogeneic HSCT and conditionings**
  for the first time only **myeablative regimens (MAC),**
  later (from 1990) non-myeoblative conditionings or **reduced-intensity conditionings (RIC)**
- ✓ **RIC regimens**
  immunossupresive effect, lower toxicity, lower anti-tumor effect

# Sources of hematopoietic cells – bone marrow – region of aspiration of bone marrow from pelvis (*spina iliaca posterior superior*)

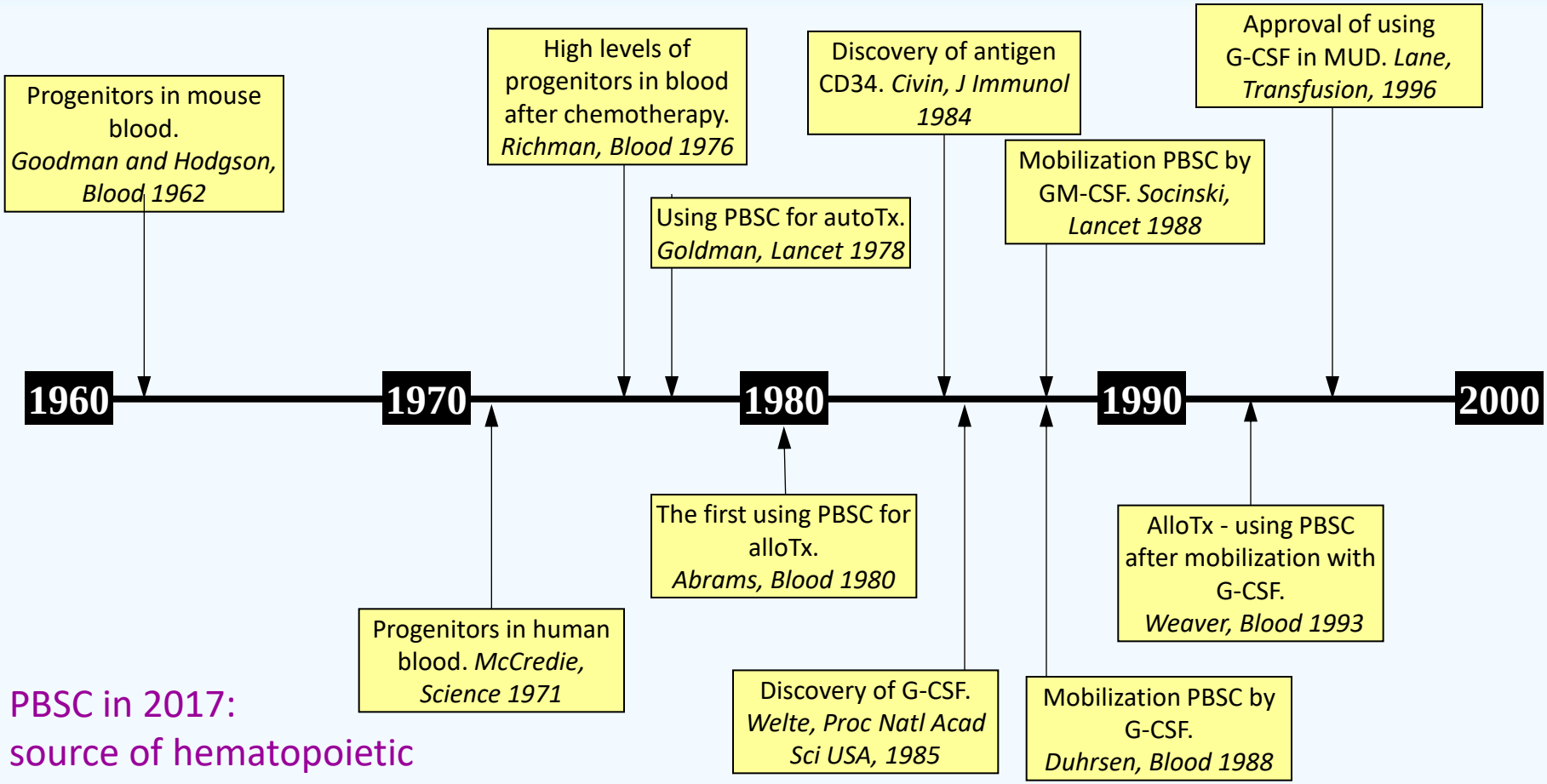




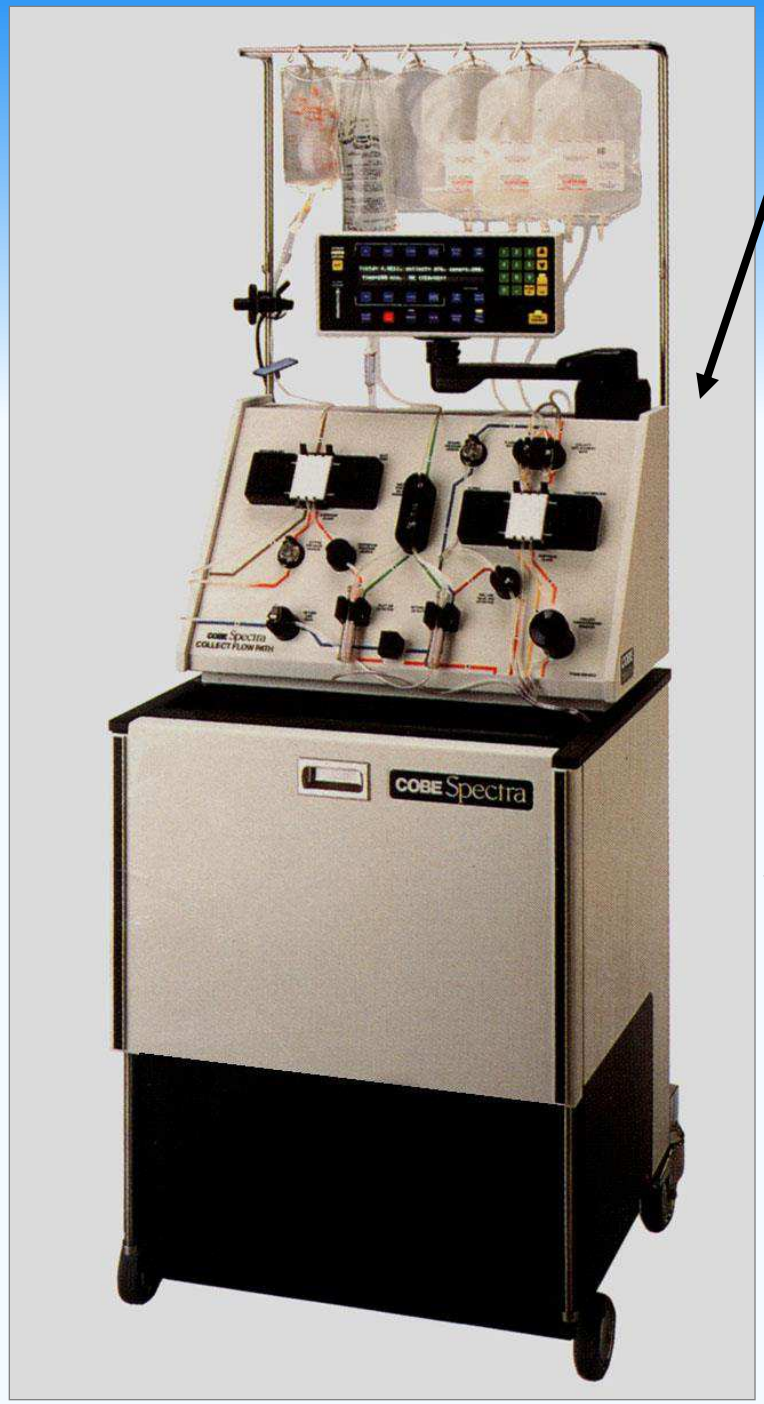


# Peripheral blood stem cells (PBSC)

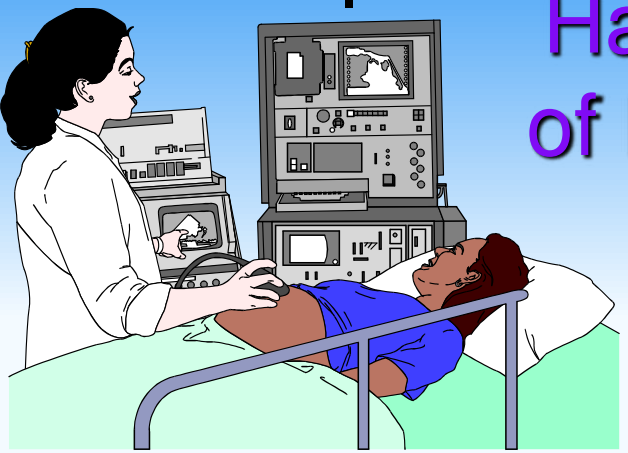
## - *time evolution of knowledges* -

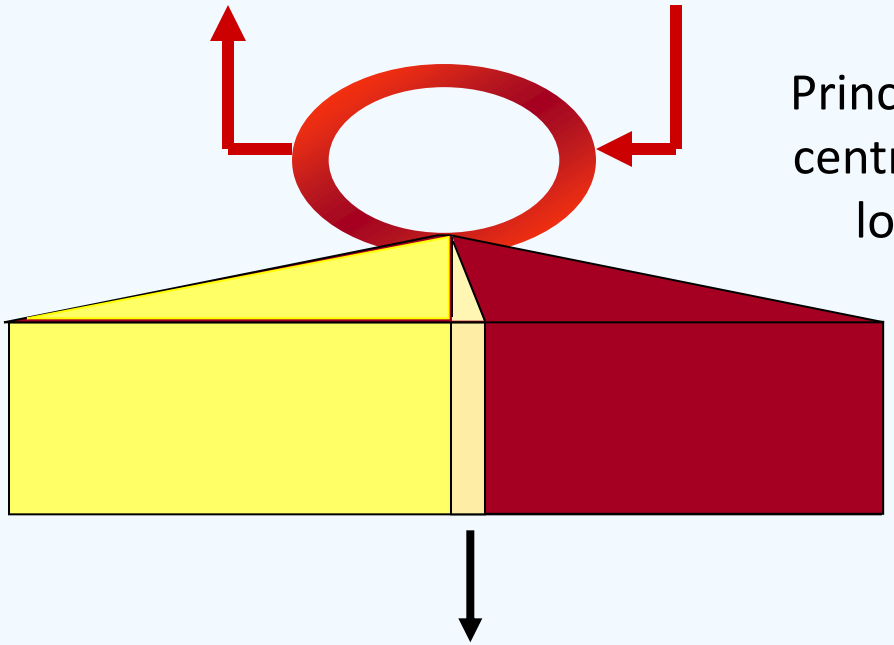



PBSC in 2017:
source of hematopoietic cells in 90% of all transplants




# Harvest of PBSC





Principle – centrifuge loop

**Buffy coat** (layer of white blood cells – leukocytes, in this coat the PBSC are presented after PBSC mobilization)


Bag of PBSC – storing in liquid nitrogen (temperature -196 °C) in tissue bank

# Autologous and allogeneic transplantations - main differences

## Autologous

High anti-tumor intensity

Without immunosuppression

Short risk of infections

TRM < 5%

*(mortality associated with transplantation)*

Relapses of disease

## Allogeneic

Predominantly immunosuppressive efect

Long-term immunosuppressive therapy

Higher risk of infections

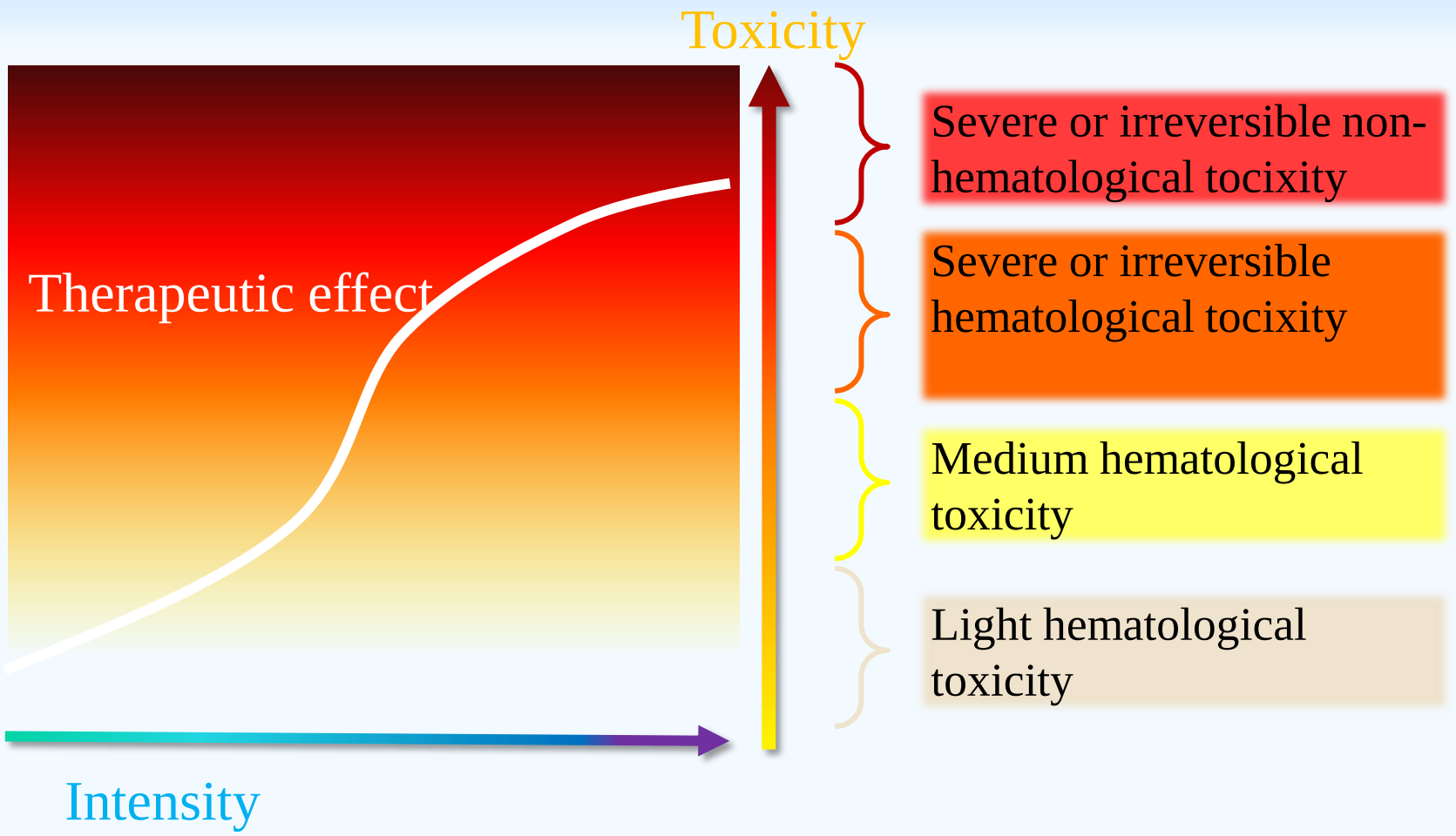
TRM 20-30%

Graft-versus host disease (GvHD)

# Conditioning – preparative regimen – application before HSCT

- ✓ Composition according to main diagnosis
- ✓ Aim – maximal anti-tumor effect
- ✓ Usually it contains some alkylating drug
  - busulfan, melphalan, carmustin (BCNU), cisplatin, carboplatin, cyclophosphamide
  - Why? Efect of alkylating drug is independent to phase of cell cycle.
- ✓ Combination with total body irradiation (TBI)
  - usually in lymphatic malignancies

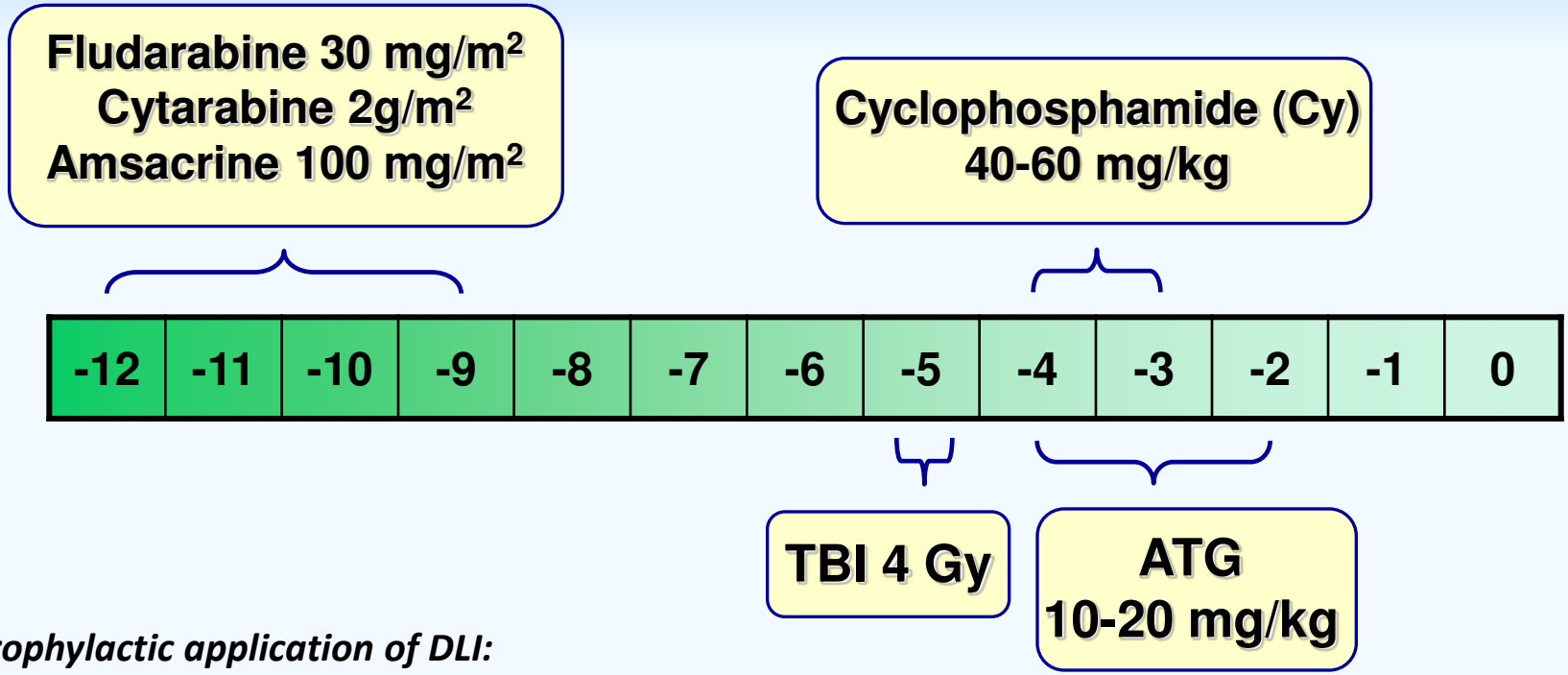
# Intensity and toxicity of conditioning



# Various types of conditionings

- ✓ Total body irradiation+cyclophosphamide (**TBI/CY**) – **myeloablative**
- ✓ Busulfan + cyclophosphamide (**Bu/Cy**) -**myeloablative**
- ✓ **Reduced intensity conditionings (RIC)**
  - *Non-myeablative regimens, high immunosupressive effect, lower toxicity (mostly containing of fludarabine, anti-thymocyte globulin). RIC examples: FLAMSA/RIC Cy+TBI, BuFlu+ATG*
- ✓ **BEAM - myeloablative**
  - *Autologous transplantation in lymphomas*
- ✓ **High-dose melphalan 200mg/m$^2$ - myeloablative**
  - *Autologous transplantation in multiple myeloma*

# Example of sequential administration of chemotherapy and RIC regimen - FLAMSA/RIC protocol




***Prophylactic application of DLI:***

*In patients with AML remission from day +120 after transplant*

*(Schmid et al., JCO 2005; 23:5675-5687)*

***GvHD profylaxis:***

*CsA, mycophenolate mofetil, ATG*

# Complications of allo-HSCT - GvHD

**GvHD** (*graft-versus host disease*)

- ✓ one of main complications of allo-HSCT
- ✓ Compatibility between donor and recipient – main role in etiopathogenesis of GvHD
- ✓ Antigens of recipient are recognized with donor T-lymphocytes. *Donor T-lymphocytes are presented in PBSC graft. These cells form GvHD reaction, but also reaction graft versus tumor (GvT reaction), which is positive for recipient.*
- ✓ GvHD – proliferation and diferentiation of donor T-lymphocytes, tissue damage of recipient, development of GvHD symptomatology.

# Acute GvHD

- ✓ Clinical symptoms are very variable, the first signs of acute GvHD are usually appeared from day+30 after allo-HSCT, acute GvHD to day +100 after allo-HSCT
- ✓ Usually involvement of skin, liver, or gastrointestinal involvement *(GIT symptomatology – nausea, loss of weight, vomitus, diarrhorea, abdominal pains)*
- ✓ GvHD- mostly combination of involvement more organs or systems, but it would be involvement only of the one organ or system (*skin or mucosa of oral cavity*), intensity is also very variable.

# Etiopathogenesis of acute GvHD

- Three phases: - afferent phase
  - induction and expansion phase
  - effector phase

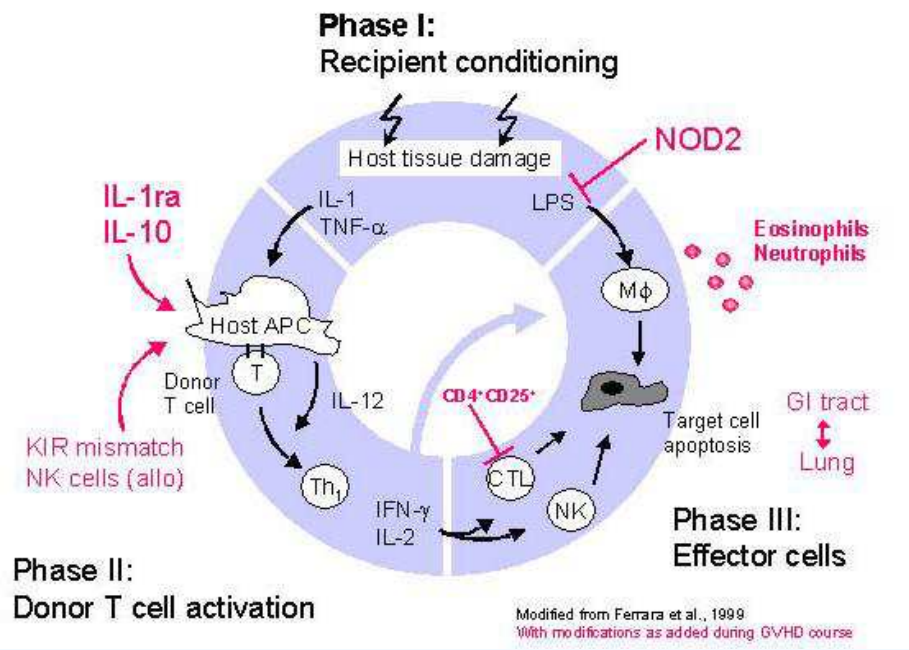
- ***Phase I –*** host tissue damage, induction of increasing of inflammatory cytokines-IL2, TNF, IL6; increasing expression of HLA antigens on the surface antigen-presented cells of recipient

- ***Phase II –*** activation of donor T-lymphocytes

- ***Phase III –*** cytotoxic damage recipient cells with clinical

manifestation of GvHD – skin,

GIT tract, liver, lung and others



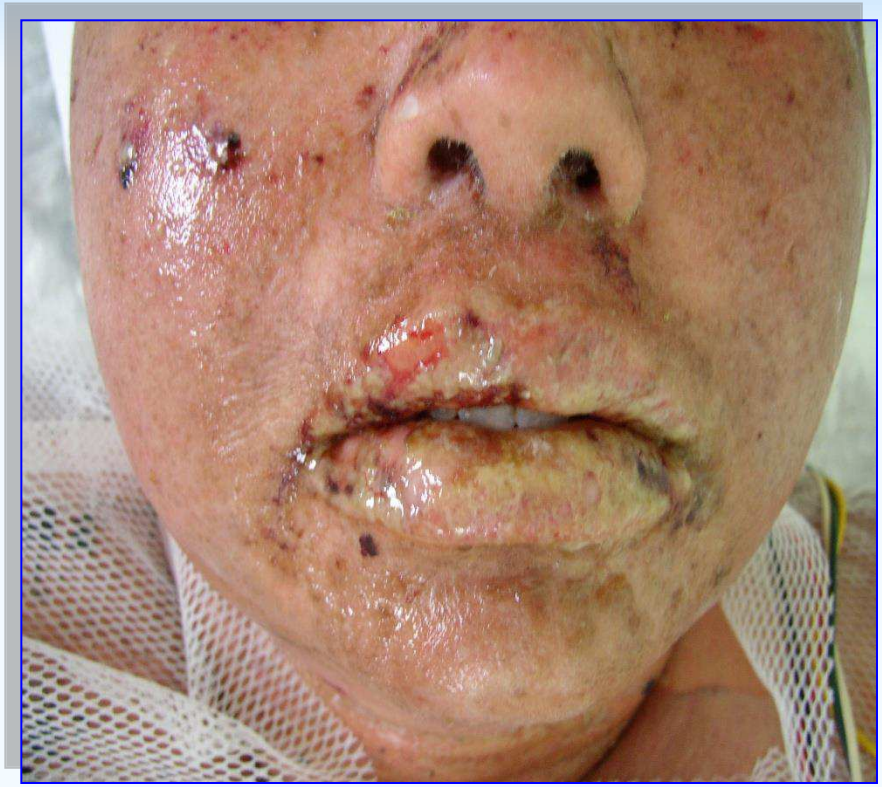
# Prophylaxis of acute GvHD - possibilities

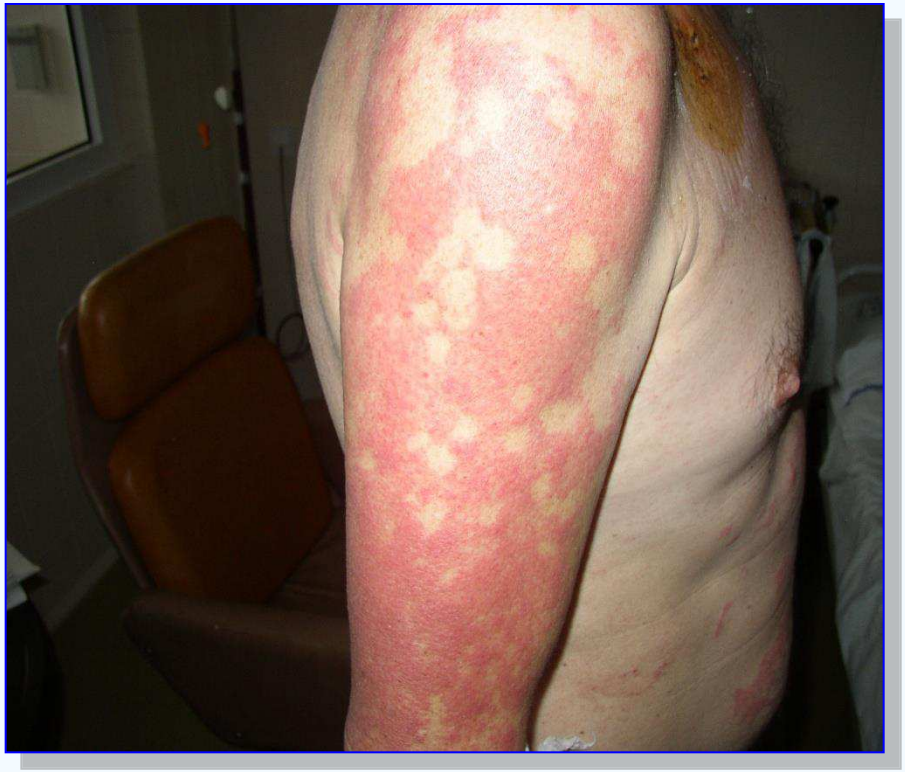
- ✓ Standard combination of cyclosporine A (CsA) and methotrexate (MTX)
- ✓ Other possibilities – combination of CsA and mycophenolate mofetil, combination tacrolimus+sirolimus
- ✓ Anti-thymocyte globulin – important part of conditioning, GvhD prophylaxis in allogeneic HSCT from unrelated donors
- ✓ CsA: calcineurin inhibitor with strong immunosuppressive effect - blockade of transcription IL-2 and other cytokines in activated T-lymphocytes
- ✓ Adverse events of CsA: hypertension, nephrotoxicity, tremor, hirsutism, hyperkalemia, hypomagnesemia

# Therapy of acute GvHD

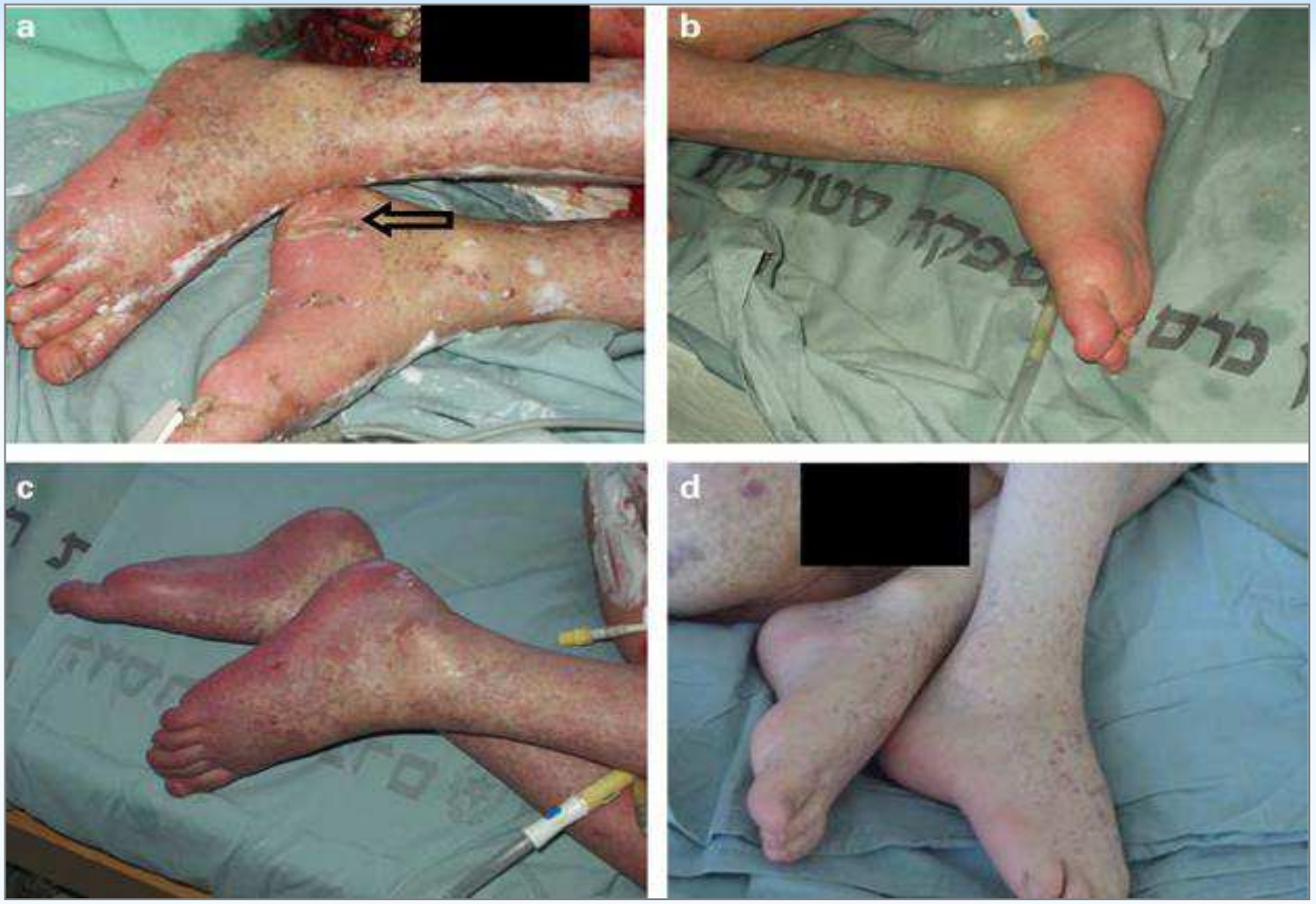
- ✓ Standard first-line treatment aGvHD: corticosteroids in dose 2mg/kg for 7-14 days, after this period decreasing of corticosteroids, this therapy is effective in 50-60% pts
- ✓ Categories of treatment responses: complete response (CR), partial response (PR), stable disease (SD), progression (PD)
- ✓ Steroid-refractory GvHD - no response to cortisteroids, this is very complicated treatment situation, treatment possibilities for steroid-refractory GvHD are effective only partially
- ✓ Steroid-refractory GvHD - associated with high morbidity and mortality

# Acute GvHD after allo-HSCT: involvement of skin and oral mucosa





# Steroid-refractory skin GvHD after allogeneic HSCT




*Shapira MY et al. BMT 2005; 36:1097–1101.*

# Chronic GvHD

- ✓ Very different and various clinical course, from mild involvement of one organ to multiorgan involvement with high morbidity and mortality; mostly from day +100
- ✓ Symptoms cGvHD – can be similar as symptoms of autoimmune diseases – such as systemic lupus erythematosus, Sjögren syndrome, skleroderma or rheumatoid arthritis
- ✓ Serious cGvHD – treatment by systemic immunosupression- incidence at 30-70% pts after allo-HSCT, mostly long-time GvHD treatment

# Risc factors for development of cGvHD

- ✓ 1-2 mismatches in I or II class of HLA system
- ✓ Previous aGvHD grade II and higher
- ✓ Peripheral blood stem cells versus bone marrow
- ✓ Higher age of recipient
- ✓ Female donor  for male recipient
- ✓ Female donor after more pregnancies
- ✓ Unrelated donor versus sibling donor

# Diagnosis of chronic GvHD – NIH consensus *(Filipovich 2005)*

1. **The presence of at least 1 diagnostic clinical sign of chronic GvHD** (e.g. poikiloderma, oral lichen planus=oral mucosal specificic lesions and many others)
2. **The presence of at least 1 distinctive manifestation** (e.g. keratoconjuctivis sicca and others) confirmed by pertinent biopsy or other relevant tests (e.g. Schirmer test) in the same or another organ

*Filipovich AH et al., BBMT, 2005*

# Therapy of cGvHD

- ✓ Course of cGvHD - typically long-term process, with repeating exacerbations of GvHD. It takes for several months or years.
- ✓ Aim of treatment - to interrupt of destructive immunologic process, to reduce of clinical symptoms and to stop progression cGCHD to stage of irreversible damage of organs.
- ✓ Systemic IS treatment - in medium or severe forms of cGvHD (extensive previously)
- ✓ In mild form cGvHD (limited previously) - *mostly sufficient local IS therapy*

# Why we can still try to improve the results of HSCT?

## Success versus failure of HSCT

- **Economic point of view** – cost of autologous HSCT - aproximatelly $10^5$ Czech crowns or 3333 Euro;

  cost of allogeneic HSCT- approximatelly $10^6$ Czech crowns or 33 333 Euro.

  *(example from real life: patient after allo-HSCT: sum for one year financial cost according to health insurance company: 4.5 million of Czech crowns = 150 000 Euro)*

- **Medical point of view** – achievement of curing or prolongation of remission of disease

- **Ethical point** - emphasis on quality of life, comeback to common life

# How to improve of HSCT results?

- ✓ Correct indication of HSCT – using of prognostic factors for various diseases and transplant risk score
- ✓ Optimal timing of HSCT
- ✓ Optimal choice of conditioting
  – decreasing of post-transplant toxicity → RIC regimens

  *(reduced-intensity conditionings)*
- ✓ Influencing of GvHD **(graft-versus host disease)** in allo-HSCT
  – accent to GvHD prophylaxis - using of anti-thymocyte globulin (ATG); effort to improving of steroid-refractory GvHD therapy
- ✓ Modification of GvL effect **(graft-versus leukemia effect)**
  – prophylactic application of donor lymphocyte infusions (DLI) in high-risk patients with aim to prevent relaps of disease

# Reduced intensity regimens in allo-HSCT

**Positive factors:**

- Lower toxicity, it is possible to transplant older patients with presence of comorbidities

**Negative factors:**

- Higher risk of relapses, low effectivity for patients with acute leukemia

**How to improve results of HSCT after RIC regimen?**

- Sequential application of chemotherapy and RIC regimen –higher anti-tumor effectivity
- Prophylactic application of ATG – with aim to impact GvHD
- Prophylactic application of DLI (*infusion of donor lymphocytes*) with aim to induce GvL effect

# Hematopoietic stem cell transplantation (HSCT) in Europe

- HSCT is an established procedure for many acquired and congenital disorders of the hematopoietic system, including disorders if the immune system, and as enzyme replacement in metabolic disorders.

**A record number of 40 829 HSCT in 36 469 patients were reported by 656 centers in 47 countries to the 2014 survey of the *European Society of Blood and Marrow Transplantation* (EBMT).**

- ✓ 40 829 HSCT in 36 469 patients per year in Europe,
  - 15 765 allogeneic HSCT (43%)
  - 20 704 autologous HSCT (57%)
- ✓ HSCT in children – 4400 procedures, 11% of all HSCT, 3279 allogeneic and 1121 autologous

*Passweg JR et al., BMT 2016*

# Indications for allo- and auto-HSCT

- ✓ International recommendations – are updated repeatedly
  - ❖ EBMT recommendations: *the last 6th special report: Sureda A et al. Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe 2015. Bone Marrow Transpl 2015: 1037-1056*
- ✓ National Czech recommendations – according to the EBMT guidelines
  - ❖ Transplant section of Czech Haematology Association *(the last version of recommendations from year 2016)*

# Categorization of transplant procedures

1. **Standard of care (S):** results compare favourably to those of non-transplant treatment approaches.
2. **Clinical option (CO):** HSCT as a valuable option for individual patients after careful discussions of risks and benefits with the patient
3. **Developmental (D):** limited experience with this indication, additional research is needed to define role of HSCT
4. **Generally not recommended (GNR):** disease in a phase or status in which pts are conventionally not treated by HSCT

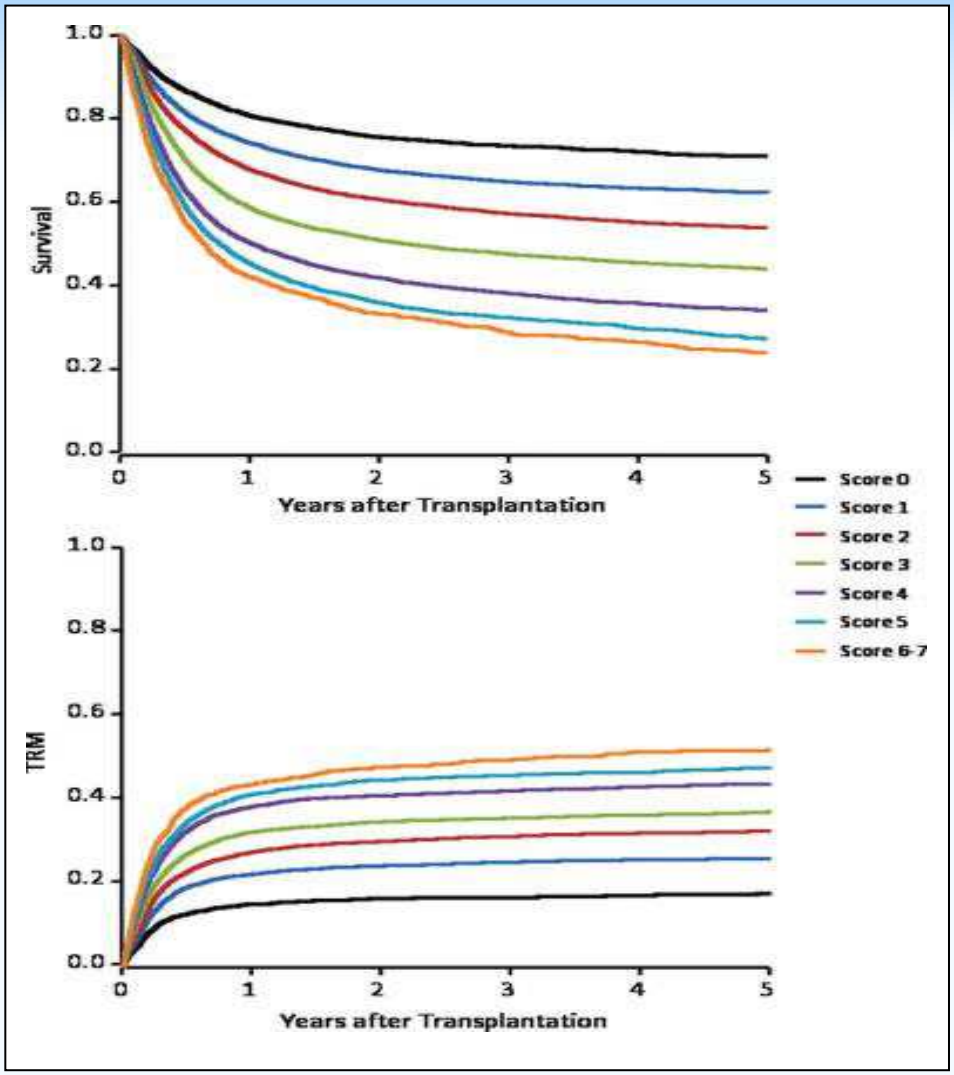
***Evidence grading**: evidence from randomized trial (I), evidence from well-designed clinical trial (II), other possibilities (III)*

*Sureda A et al., BMT 2015*

# HSCT – complications

1. Performance of HSCT – this procedure has got a lot of risk for pts, the major problems – infections, toxicity, GvHD.
   Transplants may be performed in a specialist centre with experience with HSCT procedures and an appropriate infrastructure – in Czech Republic 10 hemato-oncology transplant centres – in University Hospital Brno, Prague, Pilsen, Hradec Kralove, Olomouc, Ostrava
2. Indications for HSCT- influence of many factors – whole clinical status, presence of comorbidities, age, status of main disease, prognostic factors, availibility of donor and others
3. Allogeneic HSCT - EBMT risk score (*Gratwohl et al., Cancer, 2009*) and comorbidity index (*HCT-CI skore, Sorror et al., Blood 2005*) – carefull balancing of the risk of allo-HSCT against the risk factors and course of disease in each individual patient

# EBMT transplant risk score

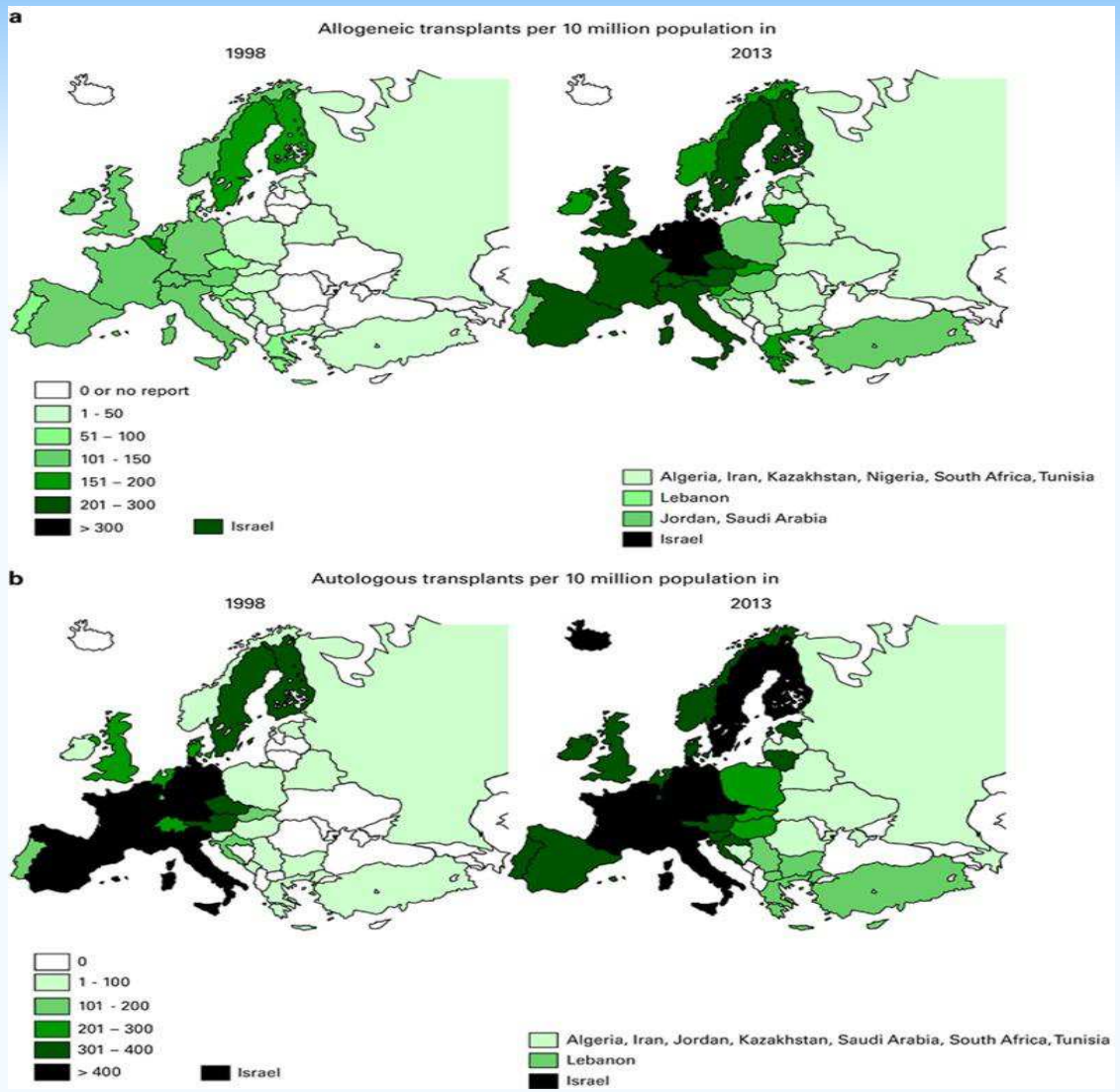



Survival and TRM of 56,605 patients with an allogeneic hematopoietic stem cell transplantation for an acquired hematological disorder is shown by risk score.

Graphs reflect probability of survival (Top) and transplant-related mortality (Bottom) over the first 5 years after HSCT.

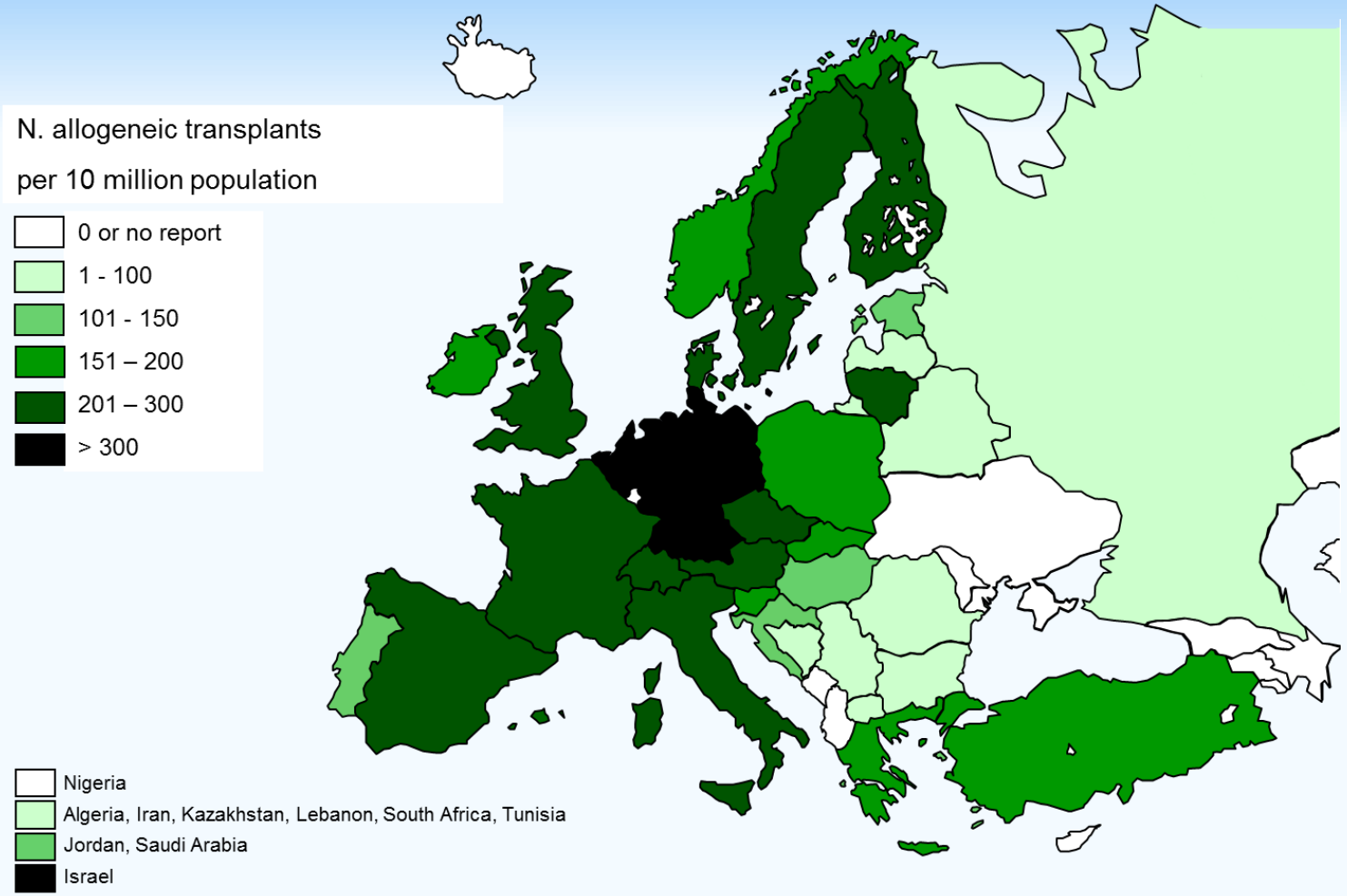
*Gratwohl A et al, Cancer, 2009*

# Transplant rates in Europe (= total number of auto- and allo-HSCT per 10 million inhabitants): comparison of 1998 and 2013



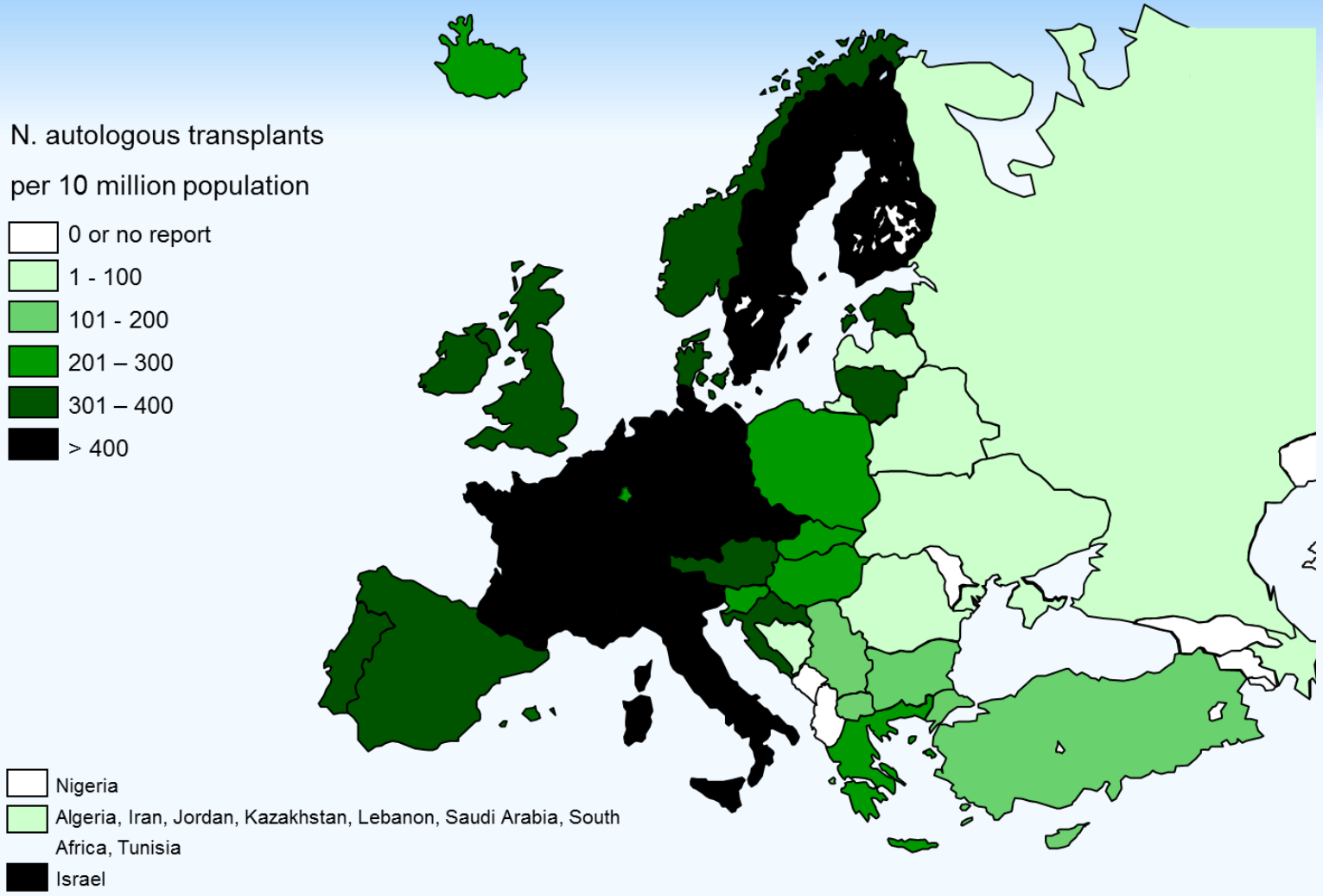

*Passweg JR et al., BMT 2016*

# Allogeneic HSCT – rates in Europe 2014




*Passweg JR et al., BMT 2016*

# Autologous HSCT – rates in Europe 2014




*Passweg JR et al., BMT 2016*

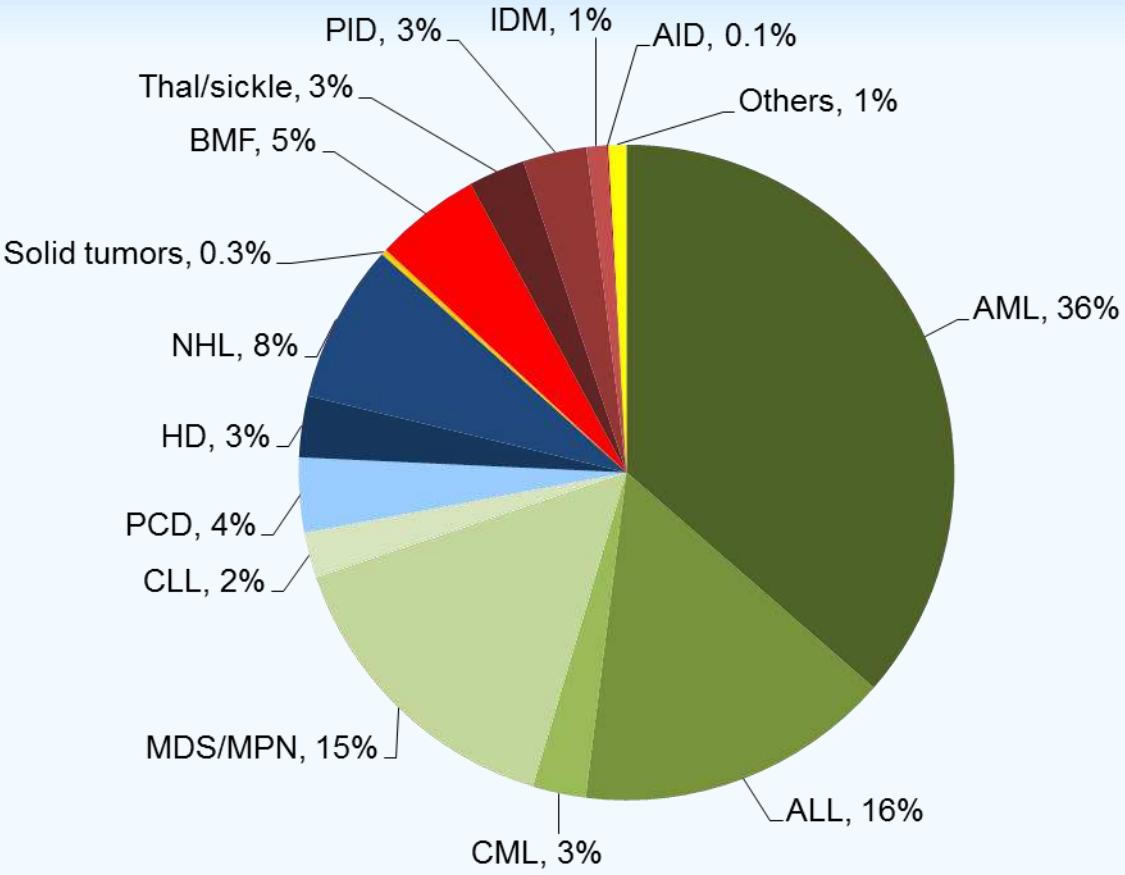
# EBMT Activity Survey in 2014:

## Main indications

| Indication | Allogeneic 1st HSCT | Autologous 1st HSCT | Total |
|---|---|---|---|
| Leukemia | 11348 | 505 | 11853 |
| Lymphoma | 1712 | 8089 | 9801 |
| Plasma Cell disorder | 580 | 10421 | 11001 |
| Solid tumor | 44 | 1414 | 1458 |
| Non-malignant disorders | 1942 | 261 | 2203 |
| *Bone marrow failure* | *833* | *4* | *837* |
| Other | 139 | 14 | 153 |
| Total 1st Transplants | 15765 | 20704 | 36469 |

*Passweg JR et al., BMT 2016*

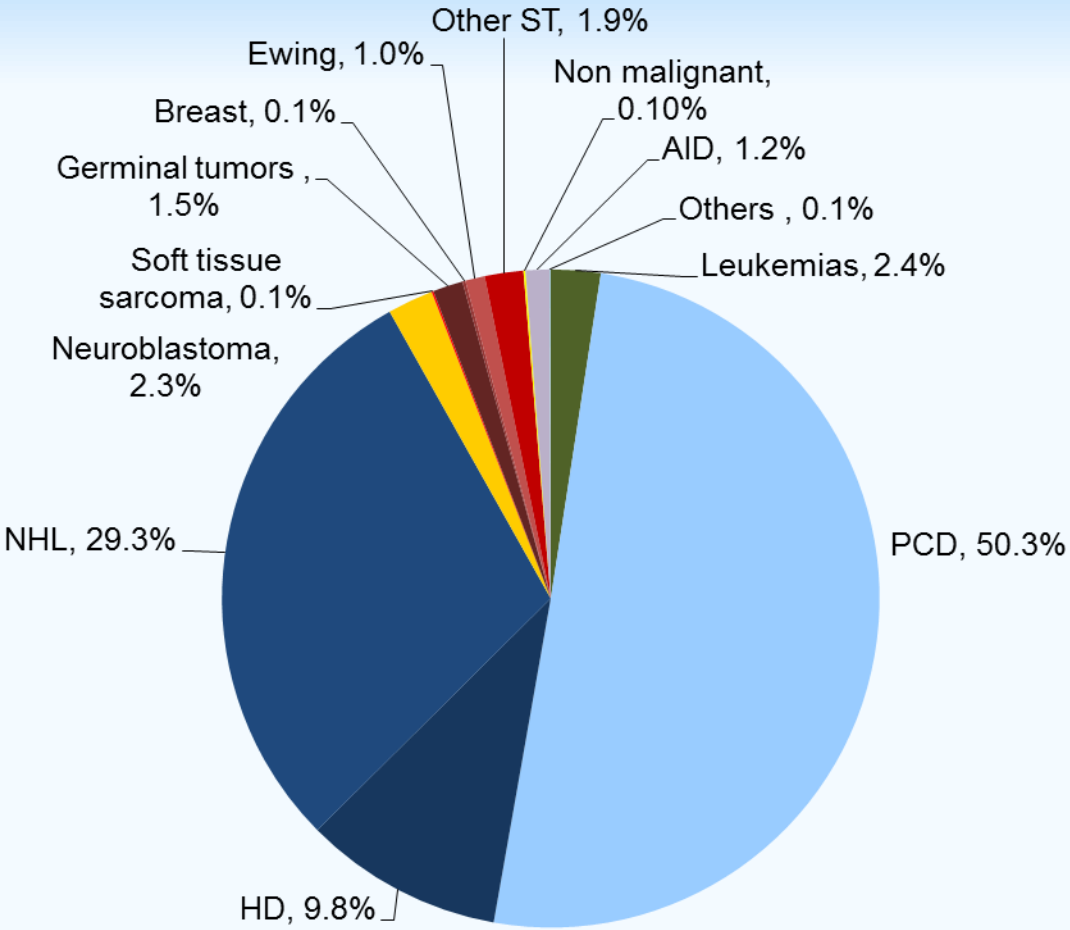
# Allogeneic HSCT in Europe 2014
## 1st HSCT




*Passweg JR et al., BMT 2016*

Baldomero: Transplant Activity Survey Dec 2015

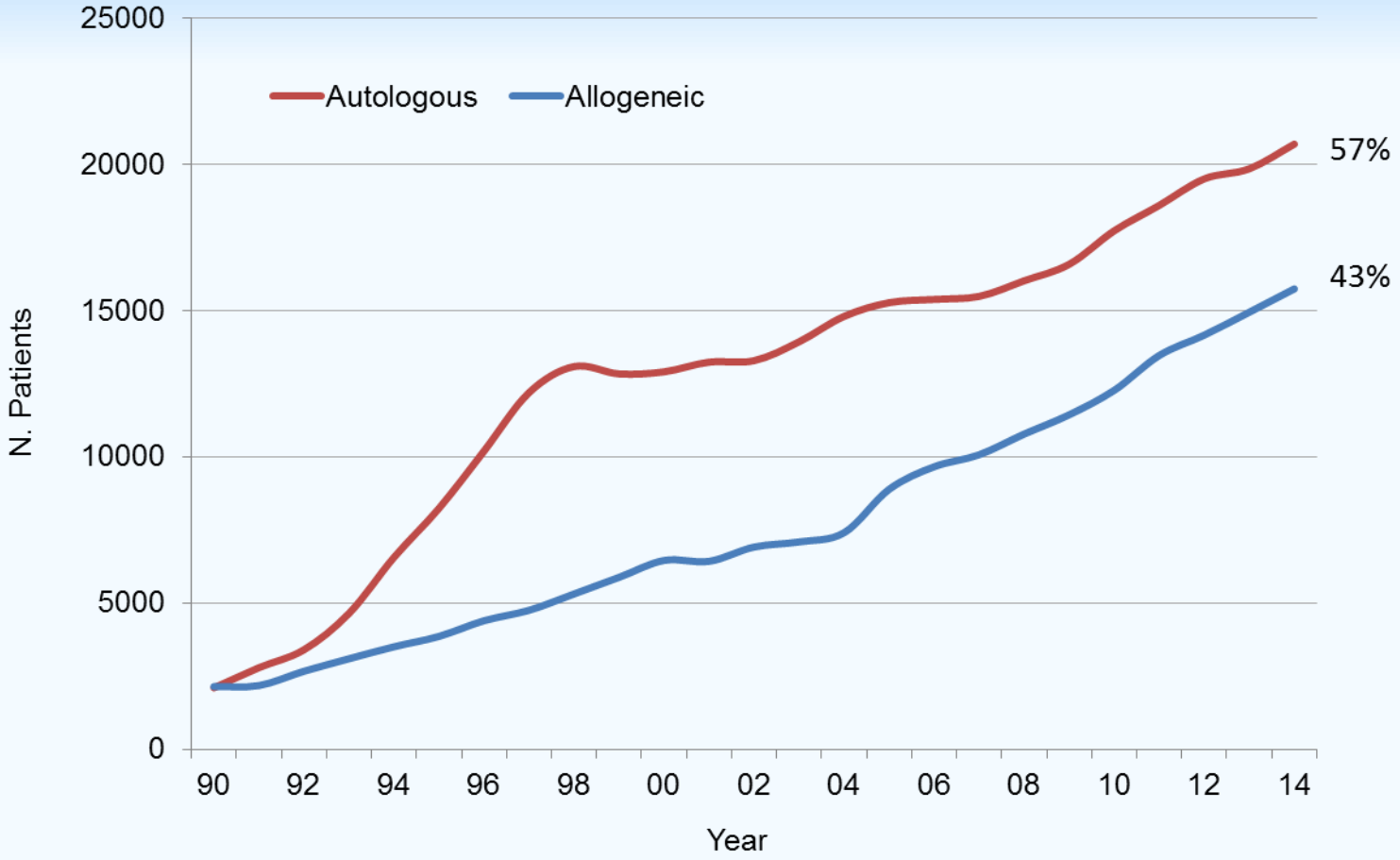
# Autologous HSCT in Europe 2014
## 1st HSCT




*Passweg JR et al., BMT 2016*

# HSCT Activity in Europe 1990 - 2014:

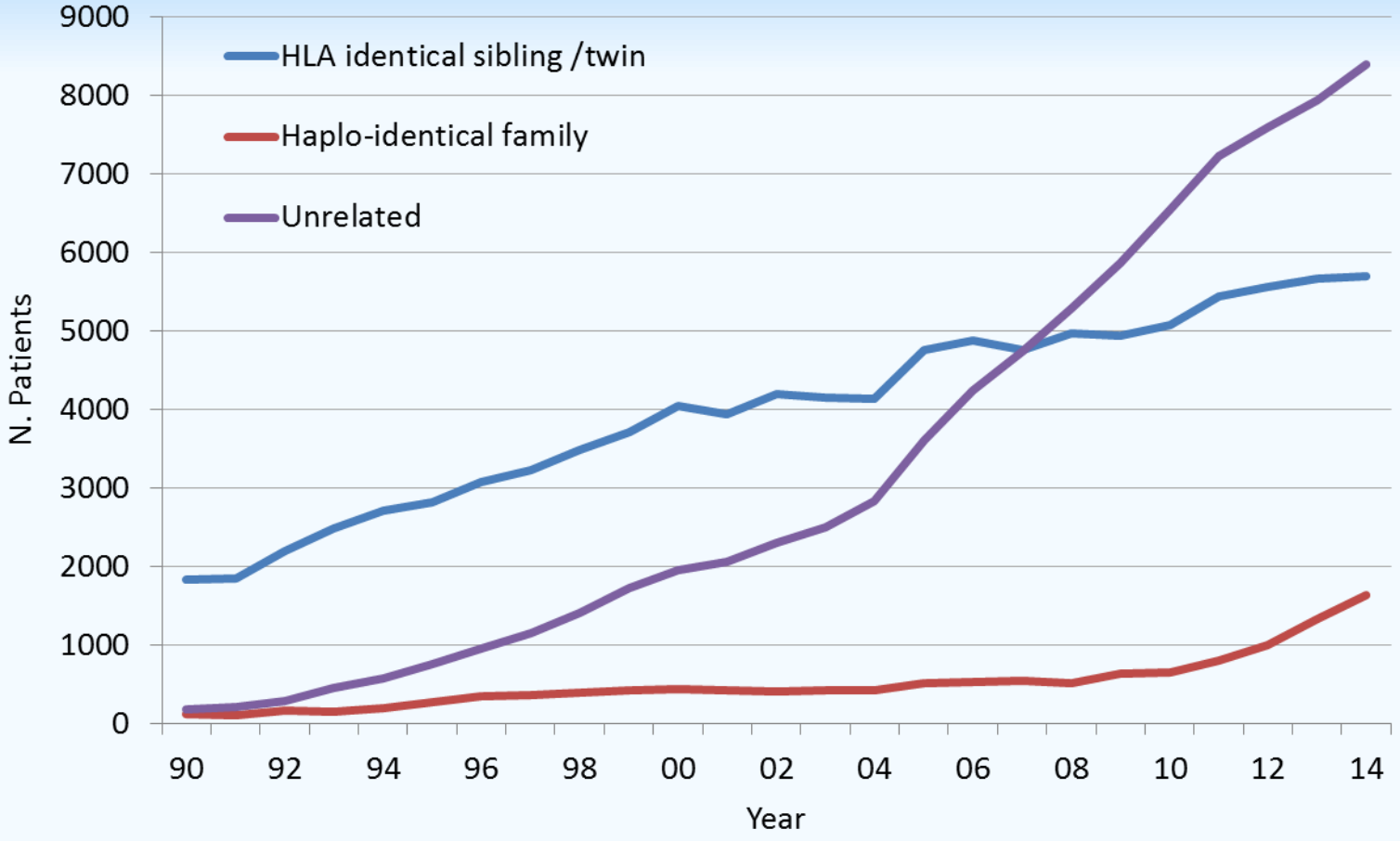
## Transplant type 1st HSCT




*Passweg JR et al., BMT 2016*

# HSCT Activity in Europe 1990 - 2014:

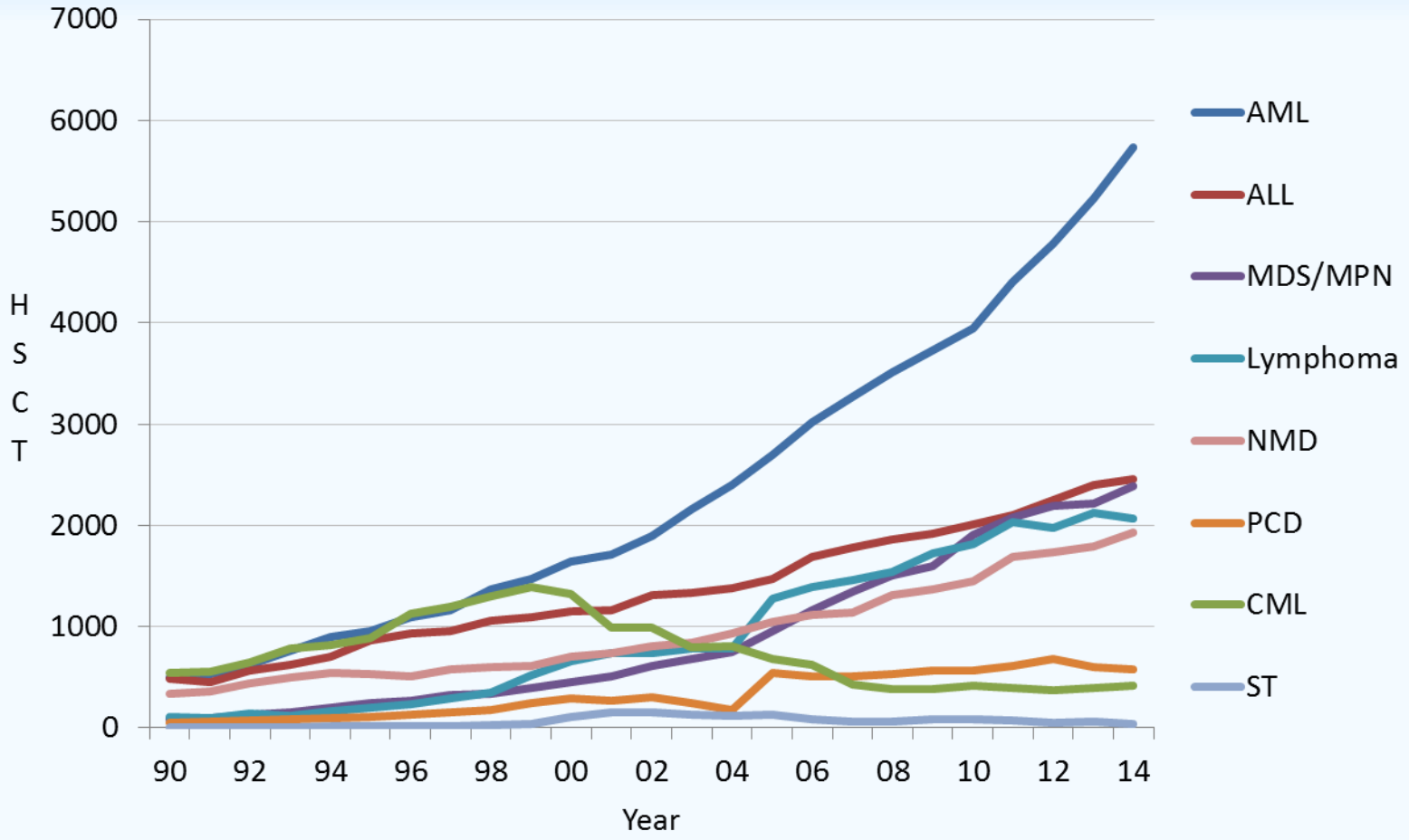
## Donor origin: 1st HSCT




*Passweg JR et al., BMT 2016*

# HSCT Activity in Europe 1990 - 2014:

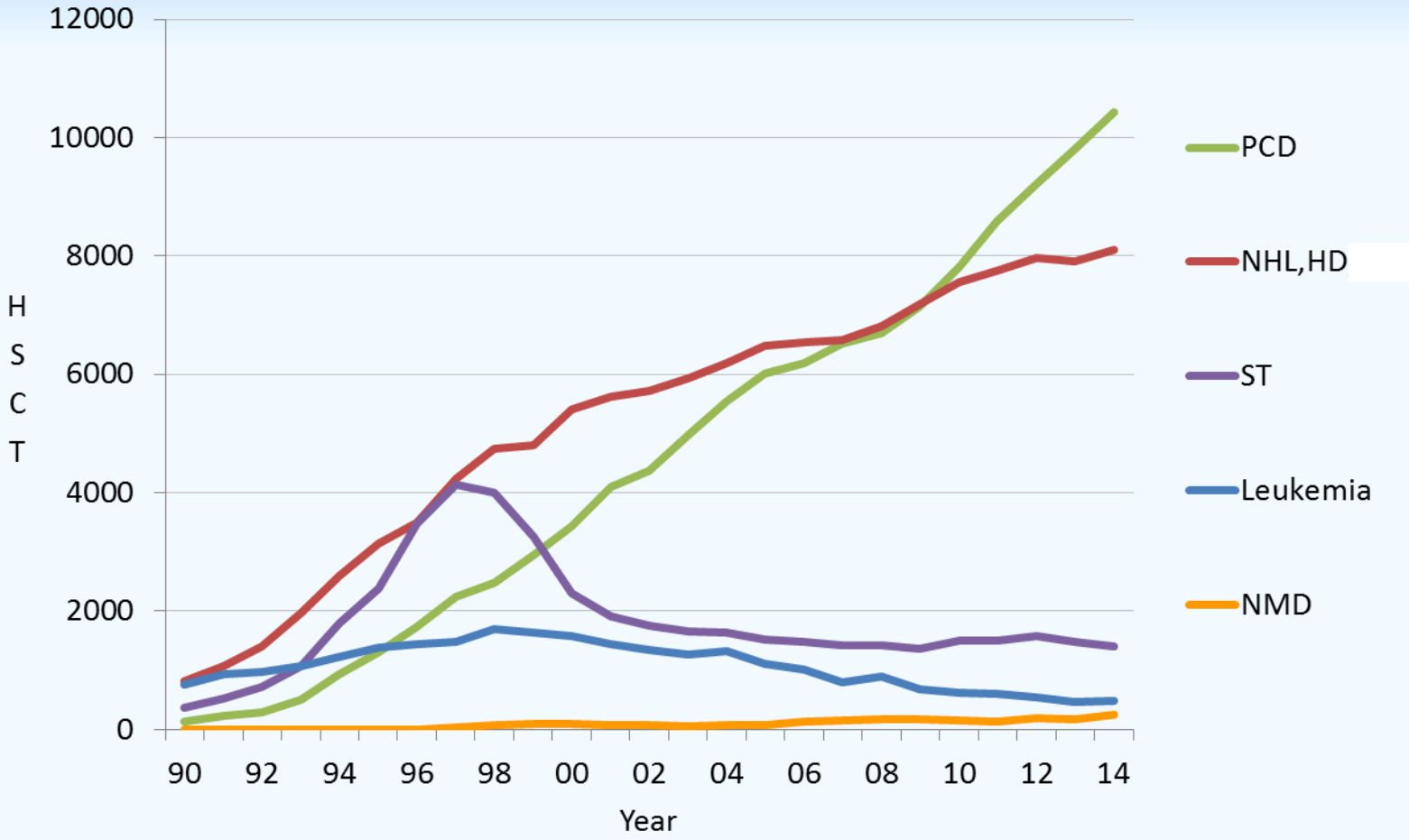
## Main Indications: allogeneic




Baldomero: Transplant Activity Survey Dec 2015

# HSCT Activity in Europe 1990 - 2014:

## Main Indications: autologous



# Main indications of HSCT in Europe - year 2014 -

- ✓ Leukemia: 11 853 (33% of all HSCT; 96% allogeneic), mostly AML+ALL
- ✓ Lymhoid neoplasias: 20 802 (57% of all HSCT; 89% autologous), mostly PCD (multiple myeloma) and NHL
- ✓ Solid tumors: 1458 (4%; 3% allogeneic)
  mostly children neuroblastoma, germ cell tumours, Ewing´s sarcoma
- ✓ Non-malignant disorders: 2203 (6%, 88% allogeneic)
  mostly BMF- SAA and other types, hemoglobinopathies, primary immune deficiences, inherited diseases –metabolic diseases, autoimmune diseases

*Passweg JR et al., BMT 2016*

# HSCT - trends in Europe
# - year 2014 -

- ✓ **Increasing numbers of both auto- and allo-HSCTs**
- ✓ **Increasing numbers of sibling and unrelated donors**
- ✓ In patients without a matched sibling or unrelated donor, alternative donors are used, the **number of transplants performed from haploidentical relatives is increased** (802 in 2010, 1571 in 2013)
- ✓ The number of unrelated cord blood transplants has sligthly decreased (789 procedures in 2010, 666 in 2013, 632 in 2014).

*Passweg JR et al., BMT 2015 and 2016*

# Impact of new drug development on the use of HSCT: a report by the EBMT – I

- ✓ Hematopoietic stem cell transplantation (HSCT) is used with increasing frequency in Europe with 40 000 transplants reported in 2014.
- ✓ **Transplant-related mortality remains high in allogeneic HSCT (10–20%);** high-dose chemotherapy is toxic and demanding for patients.
- ✓ **Drug development** is accelerating and with limited toxicity of some targeted drugs may replace HSCT, whereas others may function as a 'bridge to transplant'.

*Passweg JR et al., BMT 2017*

# Impact of new drug development on the use of HSCT: a report by the EBMT – II

- ✓ We analyzed HSCT reported to the activity survey for selected diseases in which major advances in drug development have been made.
- ✓ Tyrosine kinase inhibitors markedly changed the number of allogeneic HSCT in early **CML.**
- ✓ In **myelodysplastic syndromes**, hypomethylating agents show no effect on HSCT activity and Janus kinase inhibitors for **myeloproliferative neoplasm** appear to have only a temporary effect.

*Passweg JR et al., BMT 2017*

# Impact of new drug development on the use of HSCT: a report by the EBMT – III

- ✓ For **CLL** autologous HSCT decreased after publication of trials showing improved PFS but no overall survival advantage and allogeneic rates are dropping after the introduction of Bruton kinase and PI3K Inhibitors. Whether these are 'game changers' as was imatinib for CML requires additional follow-up.
- ✓ For **myeloma**, proteasome inhibitors and new immunomodulatory drugs do not appear to impact transplant rates.
- ✓ **Drug development data show different effects on HSCT use; highly effective drugs may replace HSCT, whereas other drugs may improve the patient's condition to allow for HSCT**.

*Passweg JR et al., BMT 2017*

# Indications for allo- and auto- HSCT for haematological diseases, solide tumours and immune disorders: current practice in Czech republic in 2016

*(in accordance with European guidelines)*



## Indikace k alogenním a autologním transplantacím krvetvorných buněk v ČR v roce 2016: doporučení Transplantační sekce České hematologické společnosti ČLS JEP a České onkologické společnosti ČLS JEP

**Krejčí M.[1], Sedláček P.[2], Jindra P.[3,12], Šťastná-Marková M.[4], Faber E.[5], Žák P.[6], Trněný M.[7], Kozák T.[8], Štěrba J.[9], Hájek R.[10], Büchler T.[11], Kuříková M.[13], Mayer J.[1], Starý J.[2], Karas M.[3], Vítek A.[4], Raida L.[5], Pohlreich D.[7], Kořístek Z.[10], Cetkovský P.[4]**

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*Transfuze Hematol. dnes, 22, 2016, No. 2, p. 127–150*

# Indications for HSCT in adults in 2016: leukemias, myeloproliferative disorders, MDS, CLL

**Tab. 1** Indikace k transplantacím krvetvorných buněk u dospělých – leukemie, myeloproliferativní onemocnění a myelodysplastický syndrom

| | | Alogenní | | | Autologní |
|---|---|---|---|---|---|
| Diagnóza | Stav nemoci | dárce sourozenec | nepříbuzný dobře shodný dárce | alternativní dárce | |
| AML | CR1 (nízké riziko) | CO | D | GNR | CO |
| | CR1 (střední riziko) | S | S | CO | CO |
| | CR1 (vysoké riziko) | S | S | CO | CO |
| | CR2 | S | S | CO | CO |
| | CR3, incipientní relaps | S | CO | D | GNR |
| | M3 molekulární perzistence | S | CO | GNR | GNR |
| | M3 druhá molekulární remise | S | CO | GNR | S |
| | relabující/refrakterní AML | CO | CO | D | GNR |
| ALL | Ph-negativní, CR1 (standardní riziko) | D | D | GNR | CO |
| | Ph-negativní, CR1 (vysoké riziko) | S | S | CO | GNR |
| | Ph-pozitivní, CR1 | S | S | CO | CO |
| | CR2, počínající relaps | S | S | CO | GNR |
| | relabující/refrakterní ALL | S | D | D | GNR |
| CML | 1. chronická fáze –bez reakce na TKI | S | S | CO | GNR |
| | akcelerovaná fáze nebo > 1. CP | S | S | CO | D |
| | blastická krize | S | S | CO | GNR |
| Myelofibróza | primární nebo sekundární se středním nebo vysokým DIPSS skóre | S | S | S | GNR |
| MDS | RA, RCMD, RAEB I a II | S | S | S | GNR |
| | sekundární AML v CR1, CR2 | S | S | S | CO |
| CLL | vysoké riziko | S | S | D | GNR |

*Krejci M et al., Transfuze Hematol dnes, 22, 2016, p.127-150; Sureda A et al., BMT 2015.*

# Indications for HSCT in adults in 2016: lymphoid neoplasia, plasmocelular neoplasia – multiple myeloma

**Tab. 2** Indikace k transplantacím krvetvorných buněk u dospělých – lymfoidní malignity a mnohočetný myelom

| | | Alogenní | | | Autologní |
|---|---|---|---|---|---|
| **Diagnóza** | **Stav nemoci** | **dárce sourozenec** | **nepříbuzný dobře shodný dárce** | **alternativní dárce** | |
| DLBCL | CR1 (střední/vysoký IPI při diagnostice) | GNR | GNR | GNR | CO |
| | chemosenzitivní relaps, ≥ CR2 | CO | CO | D | S |
| | chemosenzitivní relaps, po selhání auto-HCT | S | S | CO | GNR |
| | refrakterní onemocnění | CO | CO | D | CO |
| MCL | CR1 | D | D | GNR | S |
| | CR/PR > 1, předchozí auto-HCT ne | CO | CO | D | S |
| | CR/PR > 1, předchozí auto-HCT ano | S | S | CO | GNR |
| | refrakterní onemocnění | CO | CO | D | GNR |
| Folikulární lymfom | CR1 | GNR | GNR | GNR | D |
| | chemosenzitivní relaps, ≥ CR2 | CO | CO | GNR | S |
| | ≥ CR2 po selhání auto-HCT | S | S | D | GNR |
| | refrakterní | CO | CO | CO | GNR |
| WM | CR1 | GNR | GNR | GNR | D |
| | chemosenzitivní relaps, ≥ CR2 | GNR | GNR | GNR | CO |
| | vysoké riziko | CO | CO | D | GNR |
| TCL | CR1 | CO | CO | D | GNR |
| | chemosenzitivní relaps, ≥ CR2 | S | S | CO | CO |
| | refrakterní | CO | CO | CO | GNR |
| HL | CR1 | GNR | GNR | GNR | GNR |
| | chemosenzitivní relaps, bez předchozí auto-HCT | D | D | GNR | S |
| | chemosenzitivní relaps, s předchozí auto-HCT | S | S | CO | CO |
| | refrakterní | D | D | D | CO |
| MM | | CO | CO | D | S |
| AL amyloidóza | | CO | CO | GNR | CO |

*Krejci M et al., Transfuze Hematol dnes, 22, 2016, p.127-150; Sureda A et al., BMT 2015.*

# Indications for HSCT in adults in 2016: other diseases

**Tab. 3** Indikace k transplantacím krvetvorných buněk u dospělých – ostatní onemocnění

| Diagnóza | Stav nemoci | Alogenní | | | Autologní |
|---|---|---|---|---|---|
| | | dárce sourozenec | nepříbuzný dobře shodný dárce | alternativní dárce | |
| Získaná SAA | nová diagnóza | S | CO | GNR | GNR |
| | relabující/refrakterní | S | S | CO | GNR |
| Získaná AA/PNH | nová diagnóza | S | CO | GNR | GNR |
| Získaná AA/PNH | relabující/refrakterní | S | S | CO | GNR |
| Konstituční SAA | Fanconiho anémie<br>kongenitální dyskeratóza | S | S | CO | GNR |
| Hemolytická PNH | | GNR | GNR | GNR | GNR |
| Germinální tumory | druhá linie léčby,<br>vysoké riziko | GNR | GNR | GNR | CO |
| | primární refrakterní on.,<br>druhý a další relaps | GNR | GNR | GNR | S |
| Ewingův sarkom | lokálně pokročilý/metastazující, chemosenzitivní | GNR | GNR | GNR | CO |
| Roztroušená skleróza | forma relabující/remitující, s vysokou zánětlivou aktivitou a rezistentní ke standardní léčbě nebo forma maligní | D | GNR | GNR | CO |
| Systémová sklerodermie | časná (pod 5 let od diagnózy)<br>závažná forma splňující kritéria orgánového postižení | D | GNR | GNR | CO |
| Systémový lupus erythematodes | časné formy rezistentní k alespoň 6měsíční terapii | D | GNR | GNR | CO |
| Crohnova nemoc | | GNR | GNR | GNR | CO |
| Revmatoidní artritida, vaskulitidy | | GNR | GNR | GNR | CO |
| Imunní cytopenie | | CO | CO | GNR | CO |

*Krejci M et al., Transfuze Hematol dnes, 22, 2016, p.127-150; Sureda A et al., BMT 2015.*

# Indications for HSCT in children 2016: hematological malignancies

**Tab. 4** Indikace k transplantacím krvetvorných buněk u dětí – hematologické malignity

| | | Alogenní | | | Autologní |
|---|---|---|---|---|---|
| **Diagnóza** | **Stav choroby** | **dárce sourozenec** | **nepříbuzný dobře shodný dárce** | **alternativní dárce** | |
| AML | CR1 nízké riziko | GNR | GNR | GNR | GNR |
| | CR1 vysoké riziko | S | S | CO | GNR |
| | CR1 velmi vysoké riziko | S | S | CO | GNR |
| | CR2 | S | S | S | GNR |
| | > CR2 | S | CO | CO | GNR |
| ALL | nízké riziko CR1 | GNR | GNR | GNR | GNR |
| | vysoké riziko CR1 | S | S | CO | GNR |
| | CR2 | S | S | CO | GNR |
| | > CR2 | S | S | CO | GNR |
| CML | chronická fáze | CO | CO | CO | GNR |
| | akcelerovaná fáze | CO | CO | CO | GNR |
| | blastická krize | CO | CO | CO | GNR |
| MDS | | S | S | CO | GNR |
| NHL | CR1 (nízké riziko) | GNR | GNR | GNR | GNR |
| | CR1 (vysoké riziko) | CO | CO | CO | CO |
| | CR2 | S | S | CO | CO |
| HL | CR1 | GNR | GNR | GNR | GNR |
| | první relaps, CR2 | CO | CO | CO | S |

*Krejci M et al., Transfuze Hematol dnes, 22, 2016, p.127-150;*
*Sureda A et al., BMT 2015.*

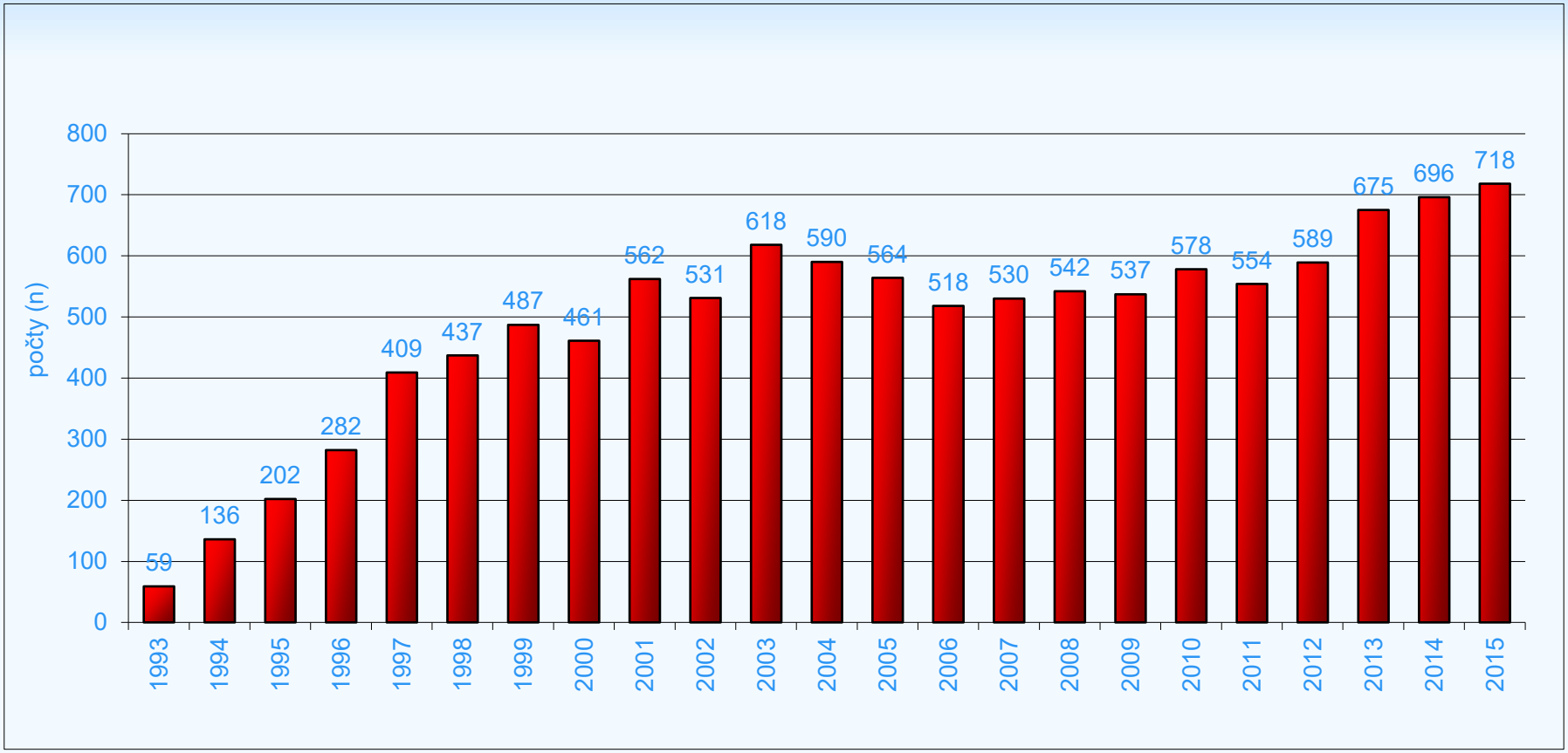
# Indications for HSCT in children 2016: non-malignant diseases and solid tumors

**Tab. 5** Indikace k transplantacím krvetvorných buněk u dětí – vybraná nemaligní onemocnění a solidní tumory

| Diagnóza | Alogenní | | | Autologní |
|---|---|---|---|---|
| | dárce sourozenec | nepříbuzný dobře shodný dárce | alternativní dárce | |
| Primární těžké imunodeficience | S | S | S | GNR |
| Talasemie | S | CO | CO | GNR |
| Aplastická anémie | S | S | CO | GNR |
| Fanconiho anémie | S | S | CO | GNR |
| Blackfan-Diamondova anémie | S | S | CO | GNR |
| Chronická granulomatóza | S | S | CO | GNR |
| Kostmanova nemoc | S | S | CO | GNR |
| Mukopolysacharidóza I. typu (Hurler) | S | S | CO | GNR |
| Mukopolysacharidóza VI. typu (Maroteaux-Lamy) | CO | CO | CO | GNR |
| Maligní osteopetróza | S | S | S | GNR |
| Autoimunitní/autoinflamatorní nemoci | CO | CO | GNR | CO |
| Germinální tumory | CO | CO | CO | CO |
| Ewingův sarkom (vysoké riziko nebo > CR1) | D | D | D | S |
| Sarkom měkkých tkání (vysoké riziko nebo > CR1) | D | D | D | CO |
| Neuroblastom (vysoké riziko) | CO | D | D | S |
| Neuroblastom > CR1 | CO | D | D | S |
| Wilmsův tumor > CR1 | GNR | GNR | GNR | CO |
| Tumory mozku | GNR | GNR | GNR | CO |

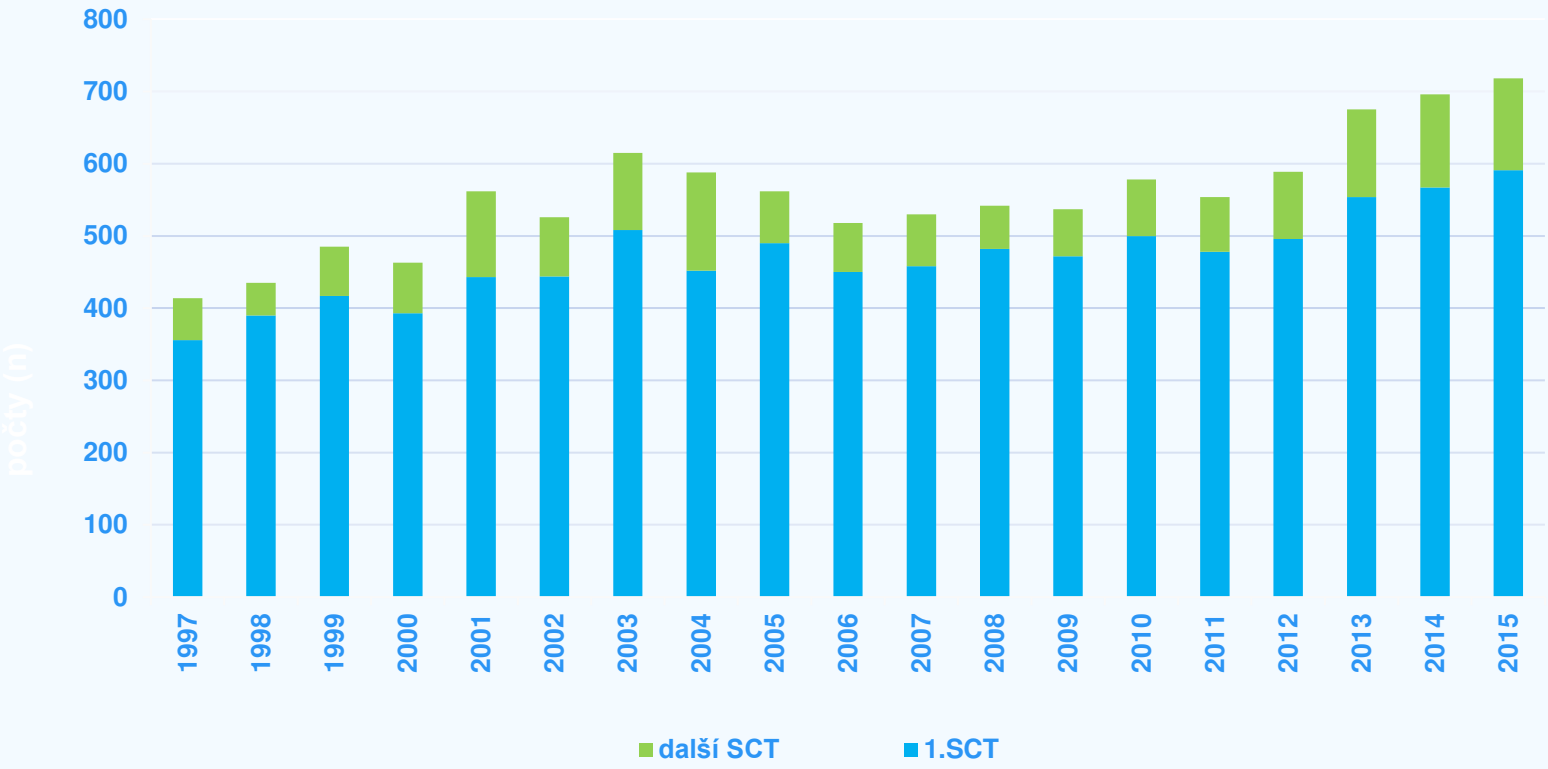
*Krejci M et al., Transfuze Hematol dnes, 22, 2016, p.127-150;*
*Sureda A et al., BMT 2015.*

# Transplant rates - total number of HSCT per 10 million inhabitants in Czech Republic (period 1993 - 2015)




*Survey on Transplant Activity, EBMT*

# Proportion of the first and additional HSCT in Czech Republic (time period 1997-2015)

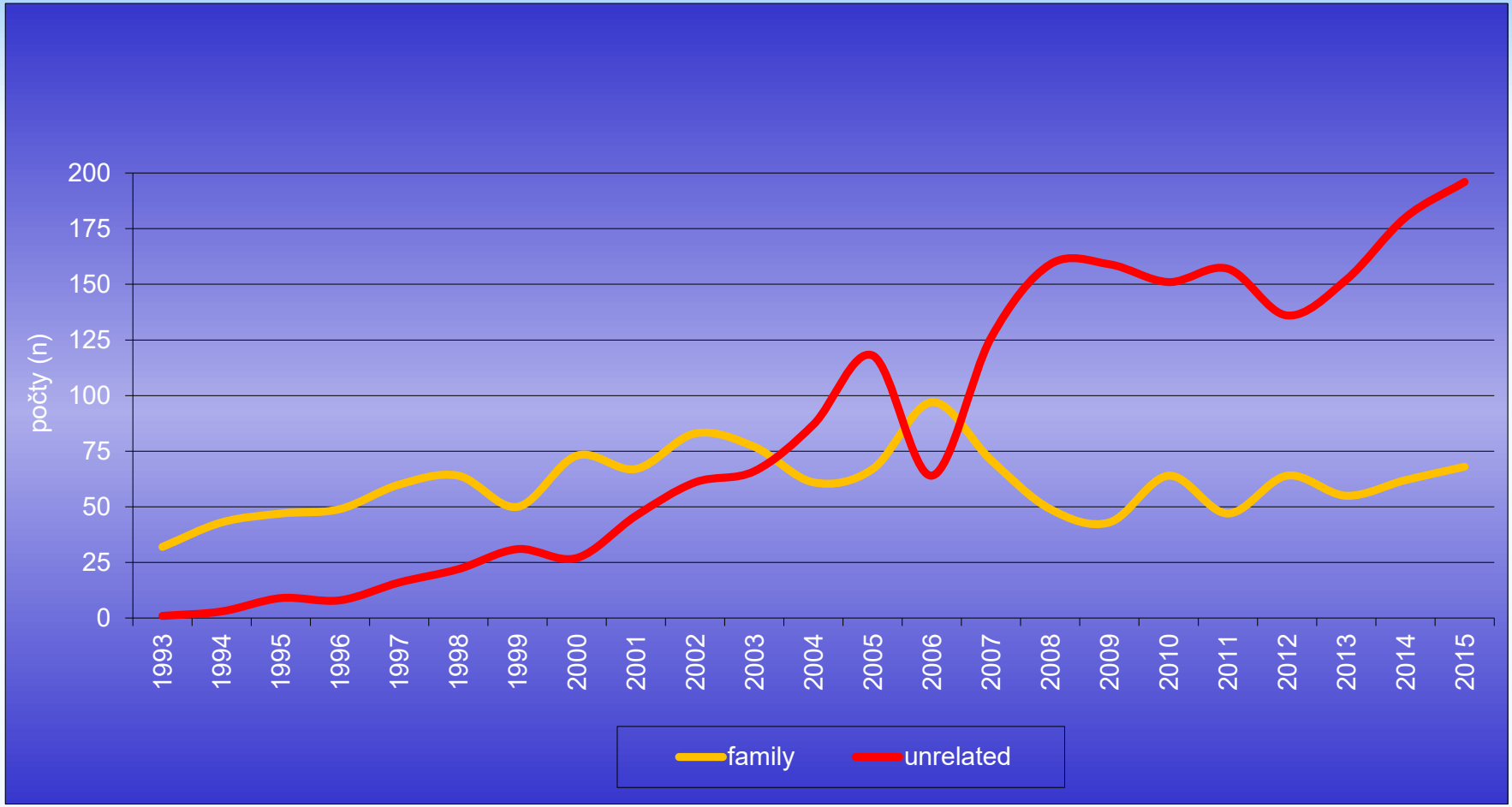



*Survey on Transplant Activity, EBMT*

# HSCT activities in Czech Republic in 2015

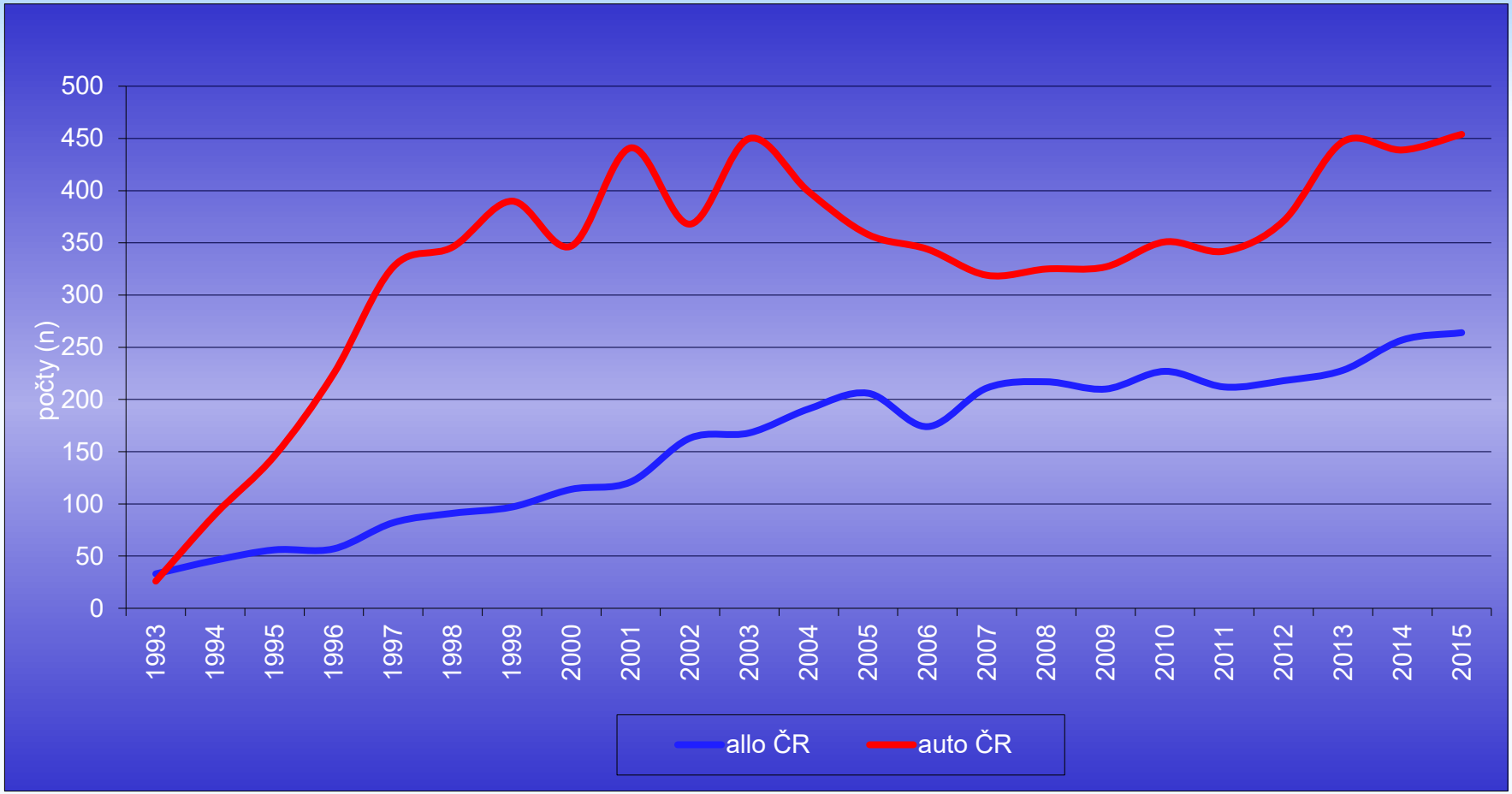
- ✓ 718 HSCT were performed in 2015 in Czech Republic in 10 transplant centres
  - 264 allogeneic HSCT
  - 454 autologous HSCT
- ✓ The first HSCT: 591 (83%)
  - 348 autologous HSCT
  - 243 allogeneic HSCT
  - Number of non-myeloablative HSCT: 143
  - Number of DLI applications (donor lymphocyte infusions): 92

# Grafts from sibling and unrelated donors in the first allogeneic HSCT in Czech Republic



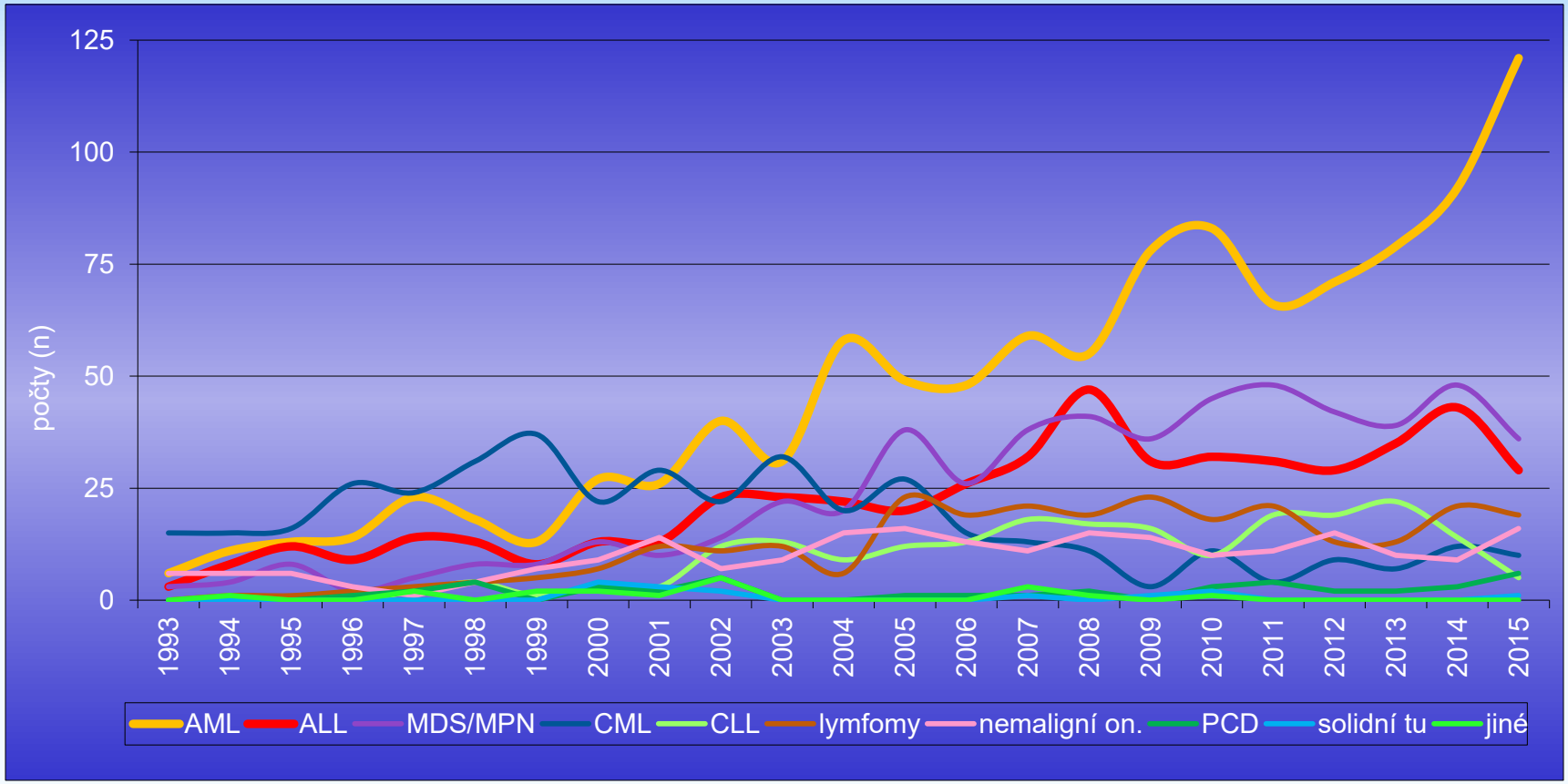

*Survey on Transplant Activity, EBMT*

# Numbers of allogeneic and autologous HSCT in Czech Republic (time period 1993 - 2015)



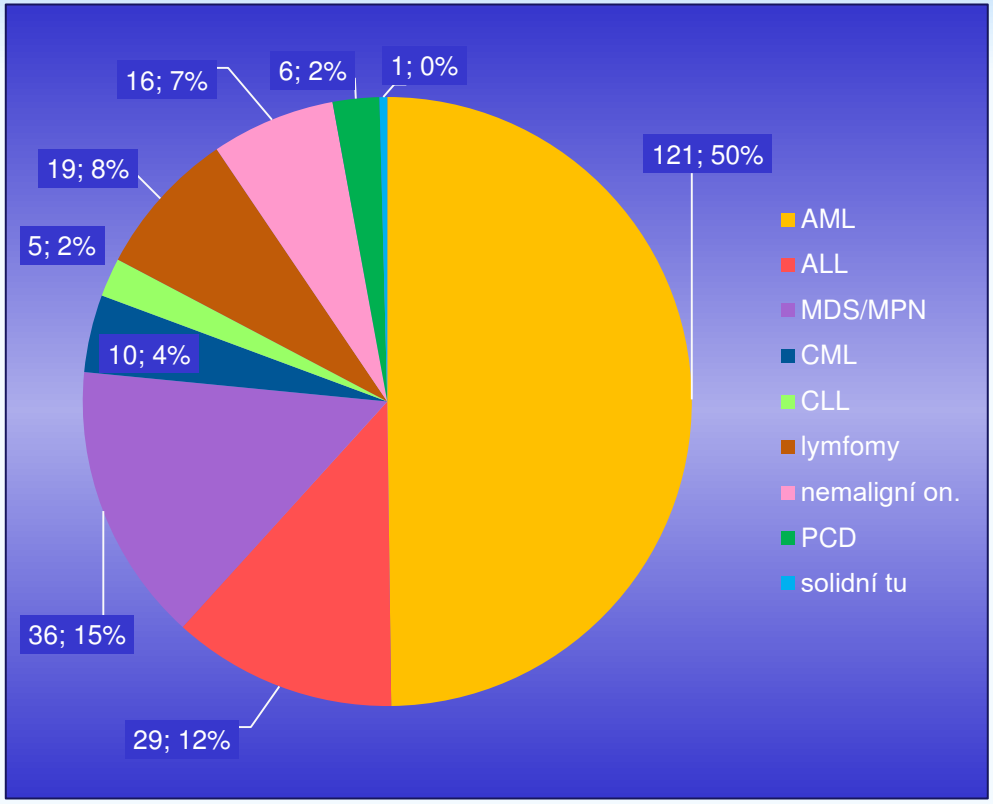

*Survey on Transplant Activity, EBMT*

# Main diagnoses for allo-HSCT in Czech Republic and time evolution (1993 - 2015)



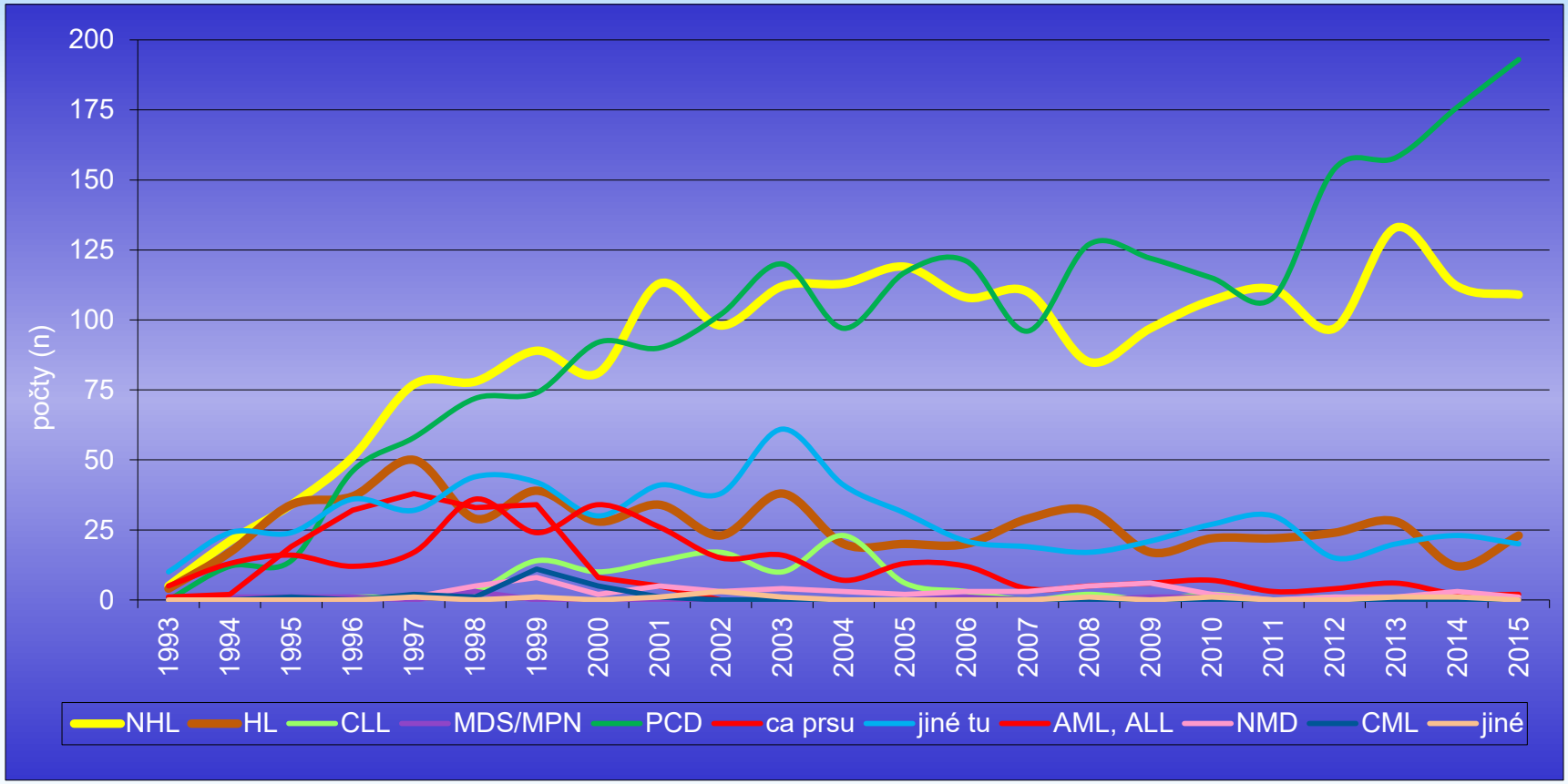

*Survey on Transplant Activity, EBMT*

# Main indications for allogeneic HSCT in Czech Republic in 2015: AML, ALL, MDS/MPD



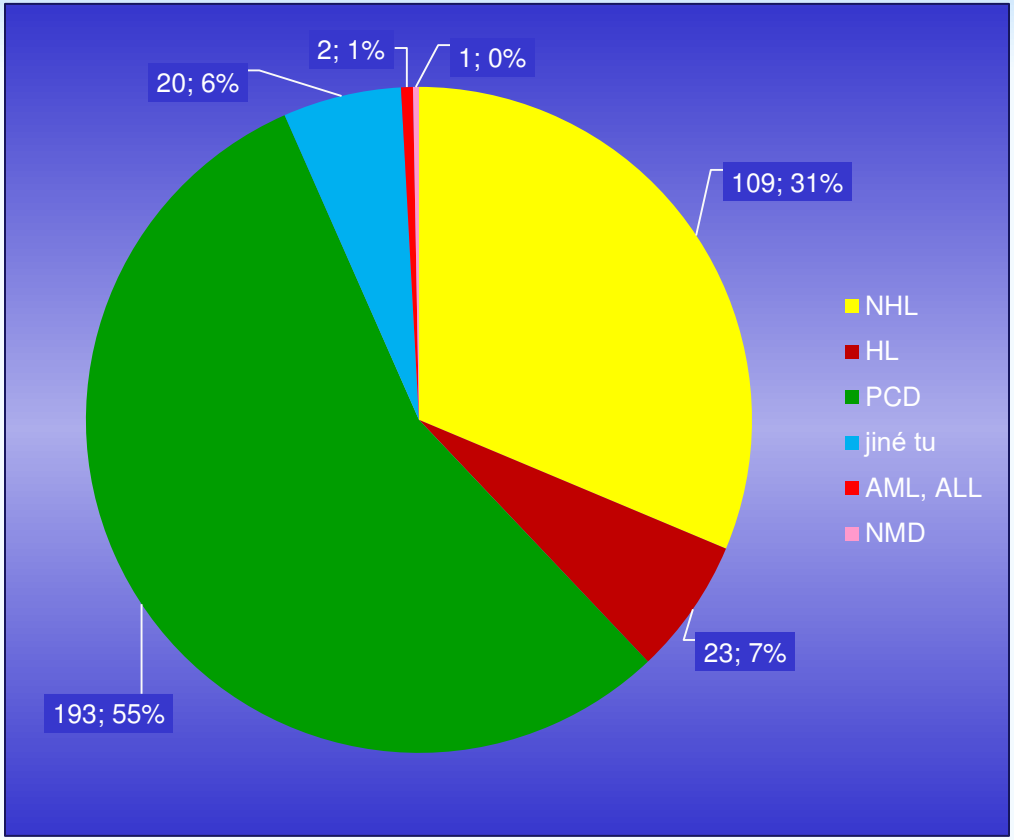

*Survey on Transplant Activity, EBMT*

# Main diagnoses for auto-HSCT in Czech Republic and time evolution (1993 - 2015)




*Survey on Transplant Activity, EBMT*

# Main indications for autologous HSCT in Czech Republic in 2015: PCD, NHL, HL




*Survey on Transplant Activity, EBMT*

# Conclusions - I

- Main indications for HSCTs in Czech Republic are in concordance with EBMT guidelines.
- Hematological malignancies – 93% of all HSCT indications in Czech Republic; rest (7%): non-malignant diseases and solid tumors.
- In Czech Republic 591 first HSCTs were performed in 10 transplant centres (Brno, Prague, Ostrava, Hradec Kralove, Pilsen, Olomouc) in 2015; 243 (41%) allogeneic and 348 (59%) autologous HSCT.

# Conclusions - II

- **Main indications for autologous HSCT**: multiple myeloma and non-hodgkin lymphomas, **86%** of all indications.
- **Main indications for allogeneic HSCT**: acute leukemias (AML+ALL) and myelodysplastic syndrome + myeloprolipherative disease (MDS+MPD) -**77%** of all indications.
- The decision to transplant involves careful balancing of the risks of allo-HSCT against the risk factors and course of disease in each individual patient.
- HSCT still remain in present time (year 2017) treatment method of choice in many hematological and non-hematological disorders at suitable patients.

# Thank you for your attention.