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

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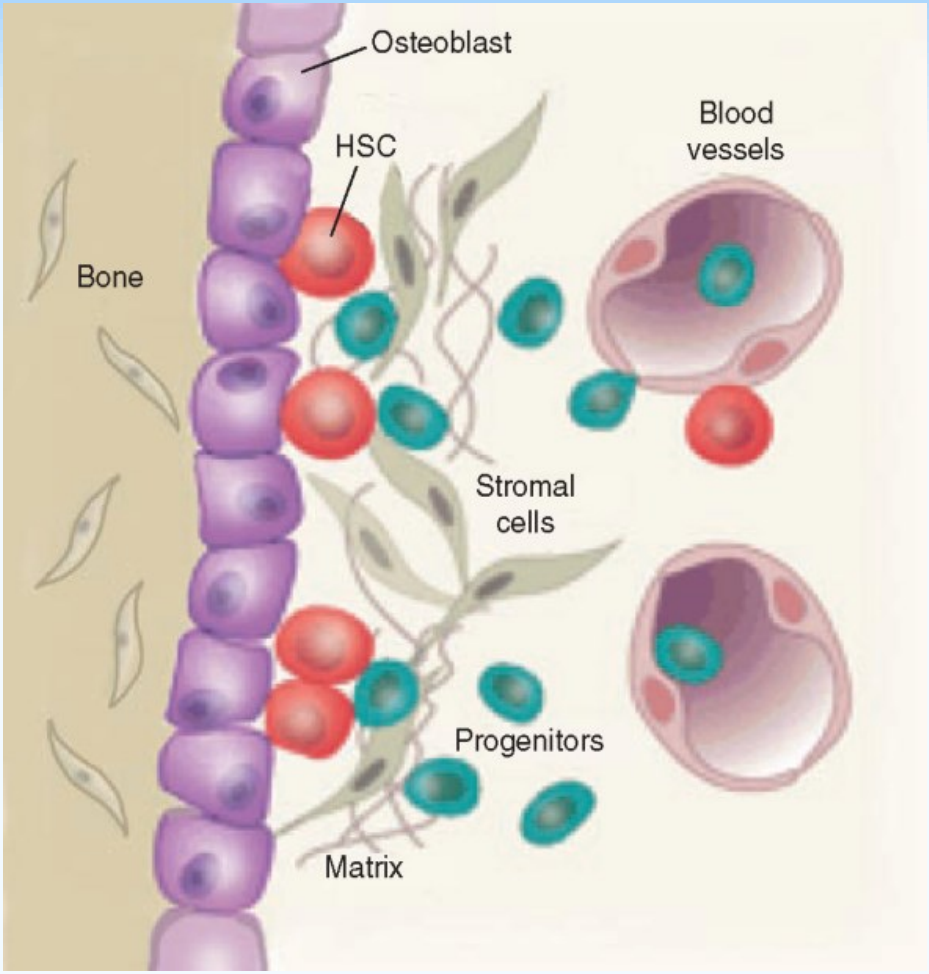
HEMATOPOIESIS

- Complicated and highly regulated **process of production of all blood elements** (erythrocytes, leukocytes, platelets)
- All peripheral blood elements arise from **hematopoietic stem cells (HSCs),** these immature cells are situated in microenvironment of bone marrow
- HSC = 1 : 10 000 – 100 000 mononuclear cells of bone marrow; HSC - ability of continuous restoration
- HSC – ability to **reproduce** and to **differentiate** to various blood lines
-



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 – II

- ✓ **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.

Definition of transplantation (HCT)

Hematopoietic stem cell transplantation (HCT)

- ✓ 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 HCT:**
  - ❖ **autologous** (donor = recipient)
  - ❖ **allogeneic** (donor = HLA identical sibling or matched unrelated donor)

(Ljungman P et al., BMT 2010)

Hematopoietic stem cell transplantation (HCT) – 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 were 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 HCT program in Czech Republic
- **2019** – HCT – still very actuall topic, the increasing of HCT procedures in Europe and in Czech Republic

HCT – 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 HCT** –usually combination of cytostatic drugs or combination of cytostatics and total body irradiation (TBI)
- ✓ **Main indications for HCTs**: hematological malignancies (90%), *but HCTs are performed in many other diseases, such as aplastic anemia, solid tumors and others*

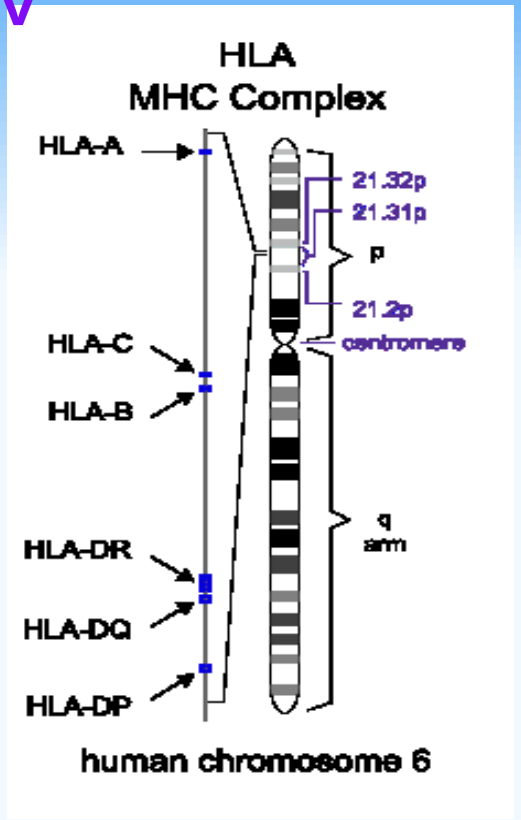
HCT – introduction - II

- ✓ 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 HCT and sequential recovery of hematopoiesis –** usually in **interval 2-3 weeks after PBSC graft.** In HCT with BM graft is recovery interval longer.

HSCT – introduction - III

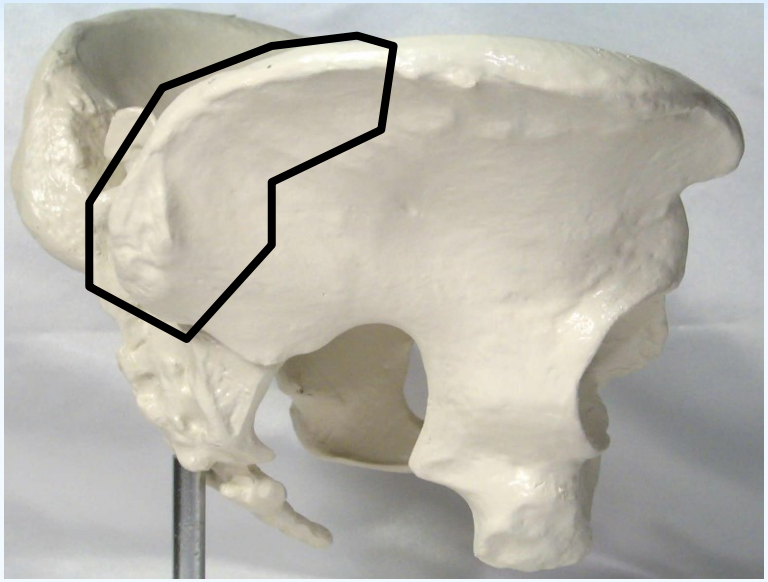
- **Autologous transplantation** - hematopoietic stem cells of patient (*donor =recipient*) are used.
- **Allogeneic transplantation** – hematopoietic stem cells of optimal health donor are used from sibling donor or unrelated donor, *donor and recipient are different persons.*
- **Optimal allogeneic donor – HLA identical sibling or well-matched unrelated donor from donor bone marrow registers (national or international registers)**
- **A well-matched unrelated 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*

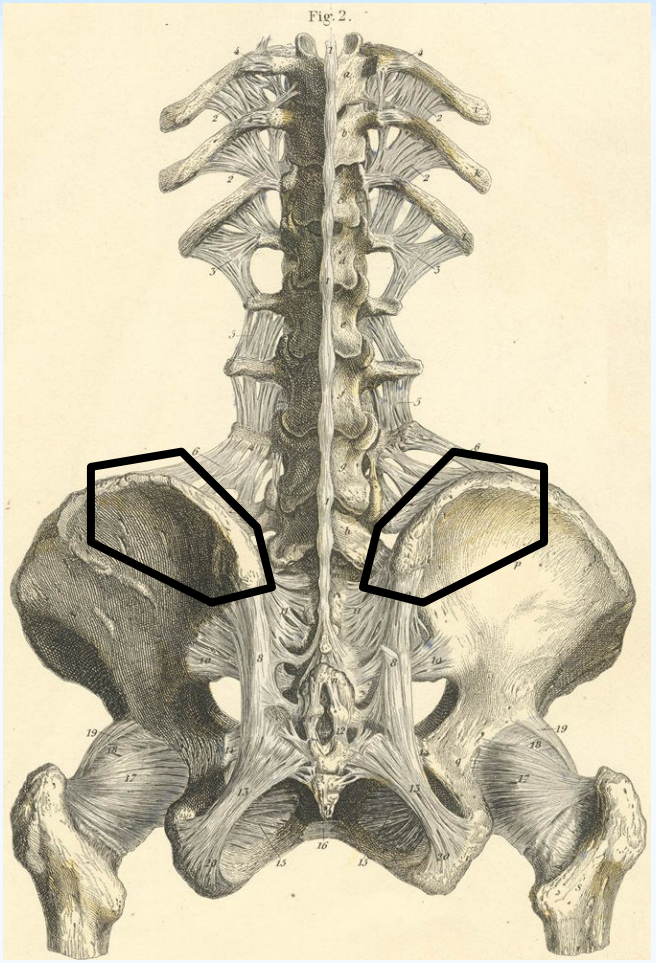
HCT – introduction - IV

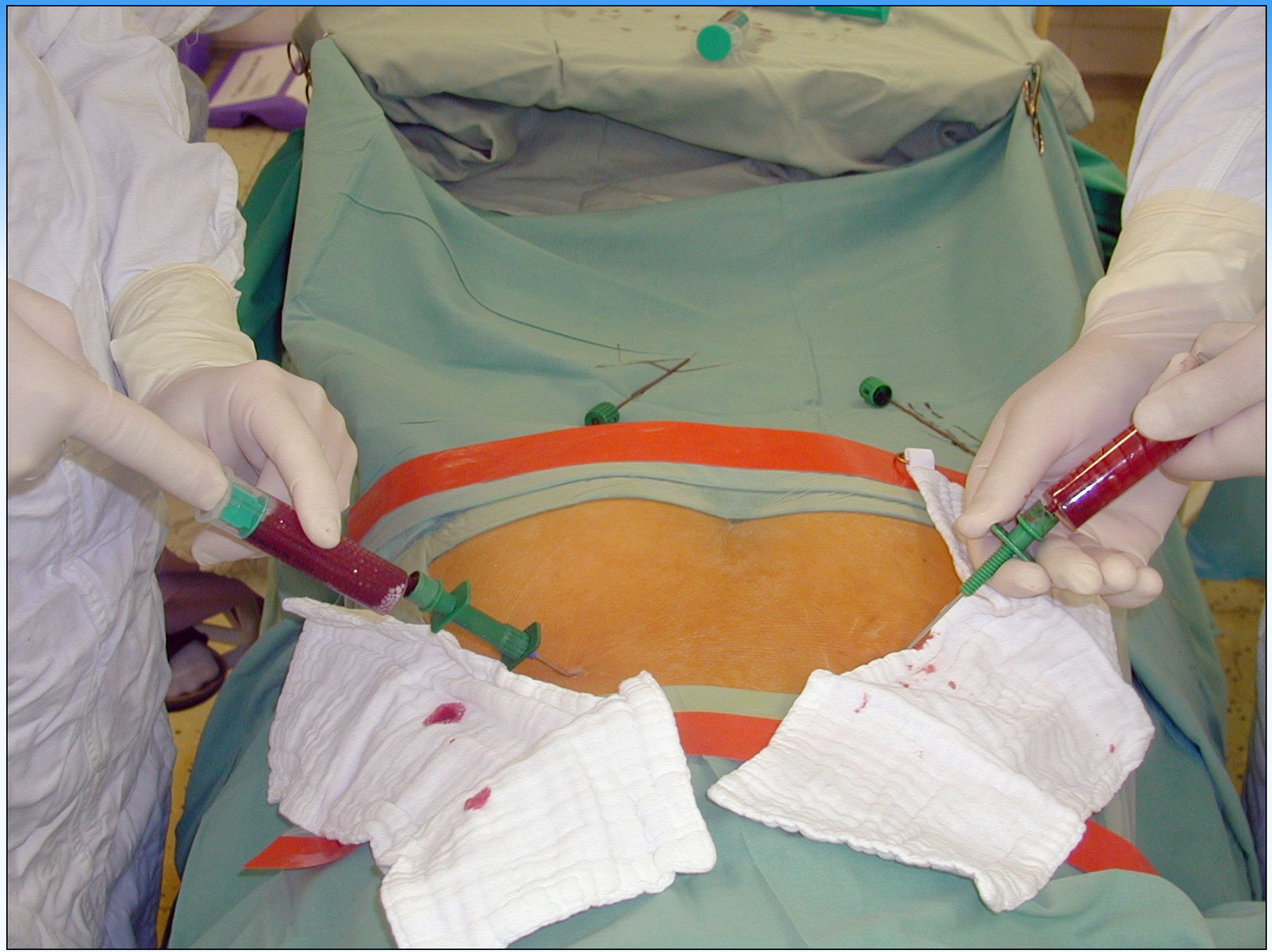


- ✓ **Main post-transplant complications:**
  - toxicity of conditioning (preparative regimen)
  - failure and rejection of graft
  - infections
  - graft-versus host disease (GvHD)
    - *in allogeneic transplantation*
  - relaps/progression of basic disease (*acute leukemia*)
- ✓ **Allogeneic HCT and conditionings**
  for the first time only **myeloablative regimens (MAC),**
  later (from 1990) non-myeloblative 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 illiaca posterior superior*)

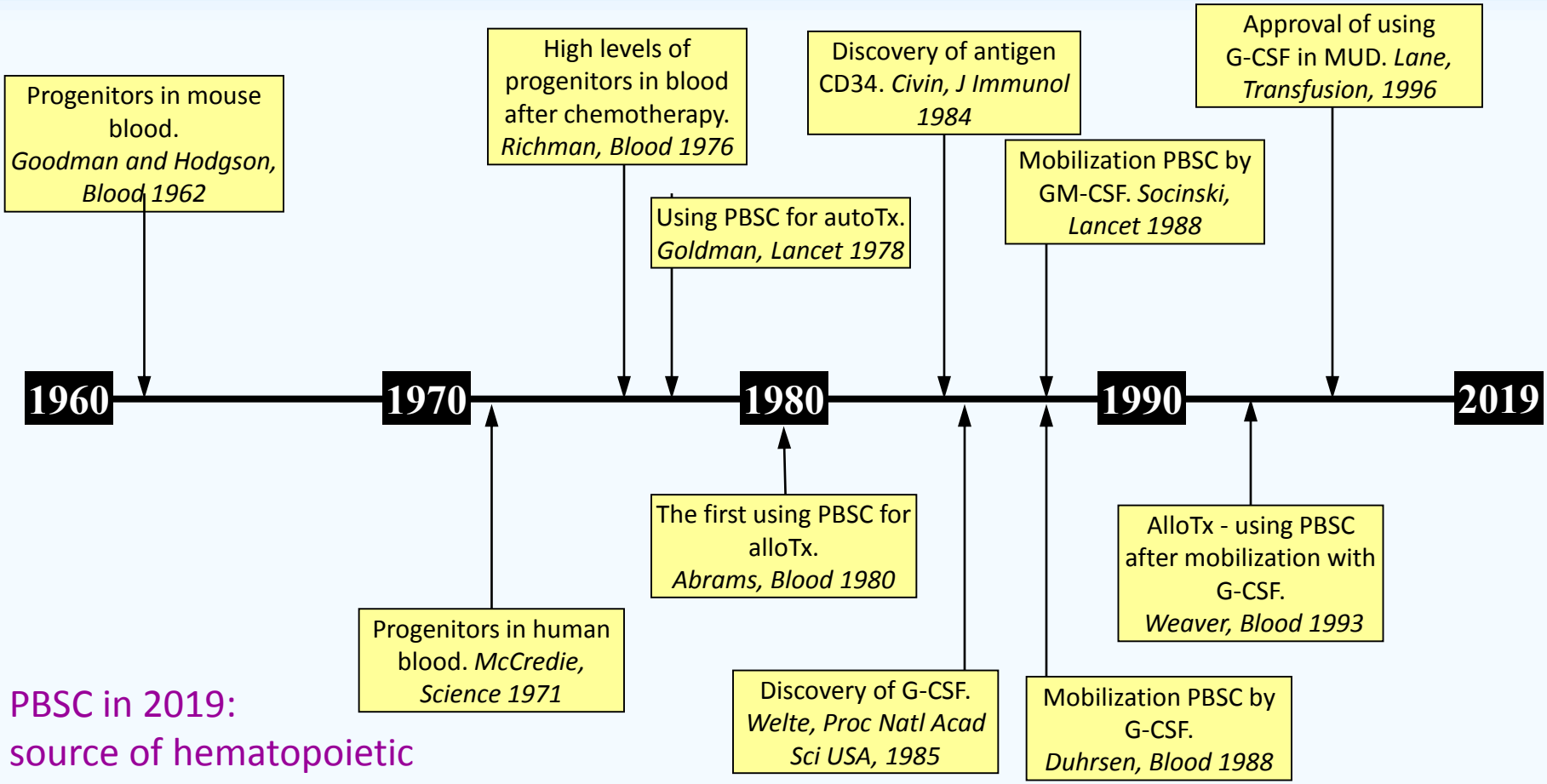




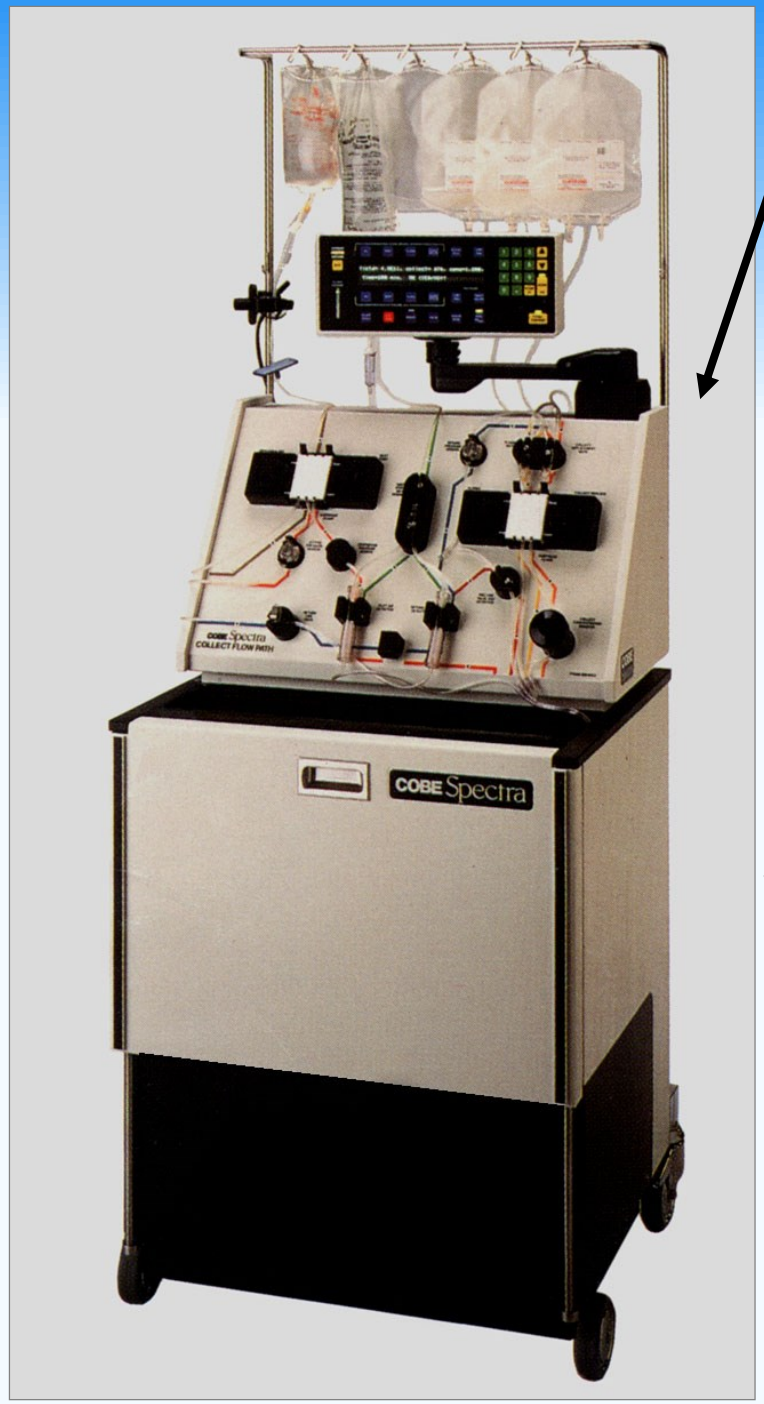


Peripheral blood stem cells (PBSC)

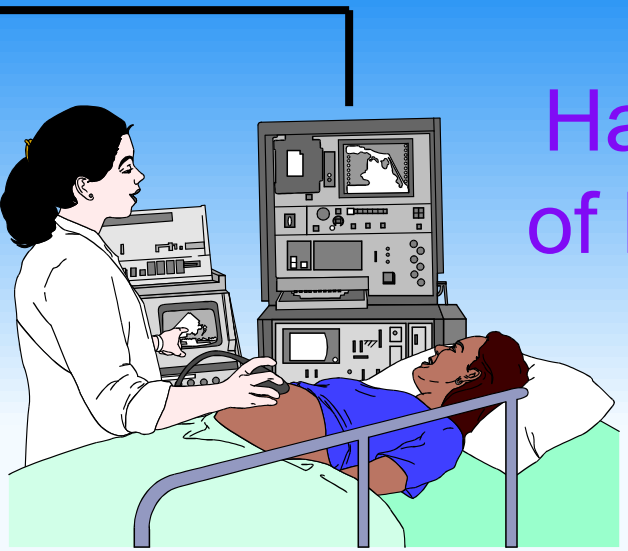
- *time evolution of knowledges* -

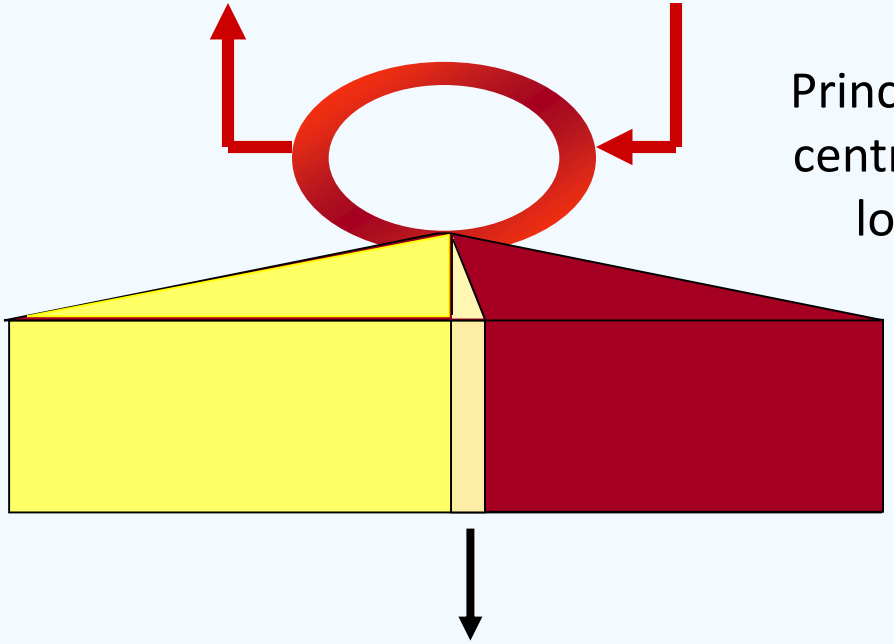


PBSC in 2019:
source of hematopoietic cells in 90% of all transplants



Harvest of PBSC





Principle – centrifuge loop

Buffy coat (layer of white blood cells – leukocytes, in this coat the PBSC are situated 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

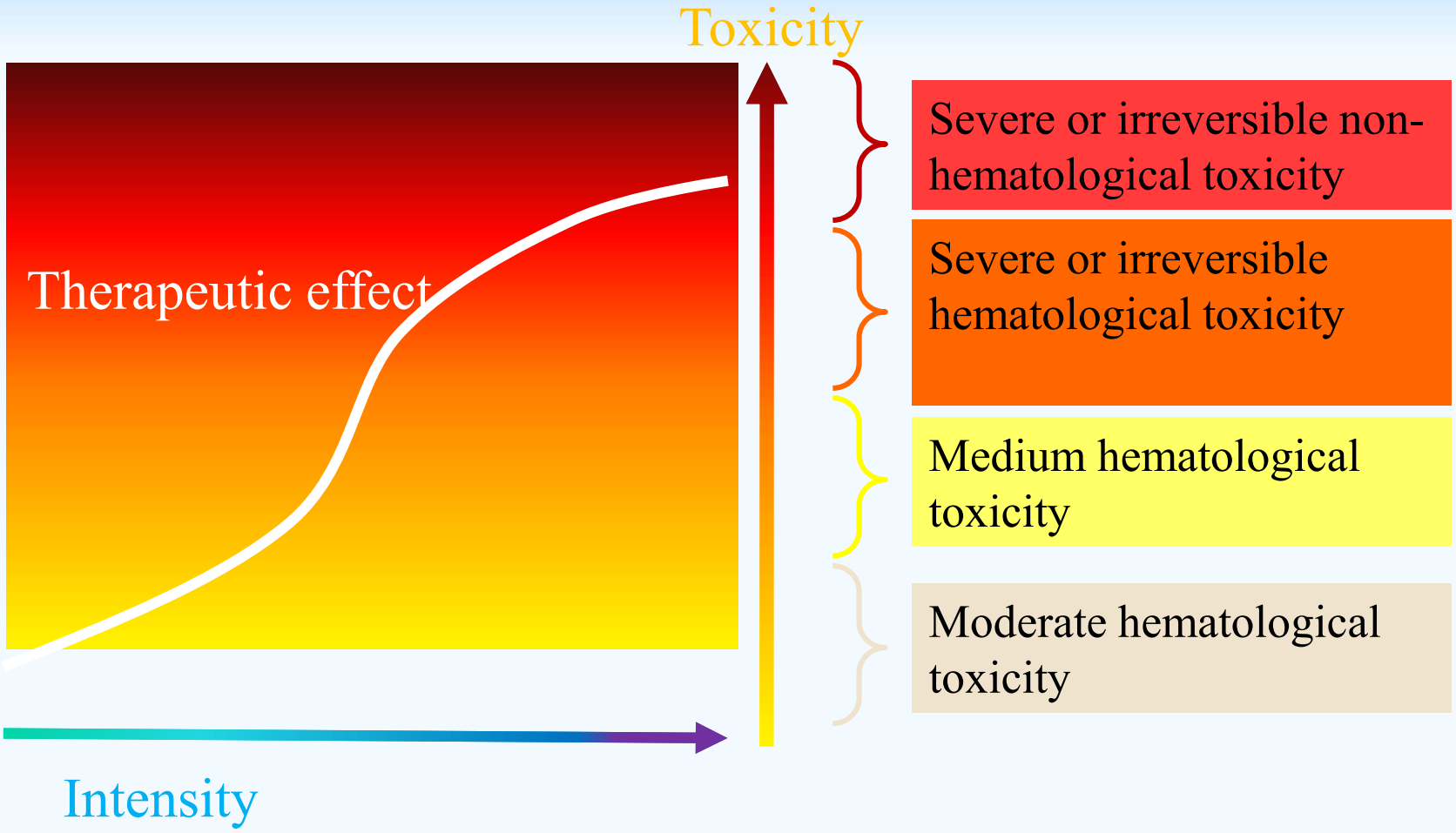
TRM 20-30%

Graft-versus host disease (GvHD)

Conditioning – preparative regimen – application before HCT

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

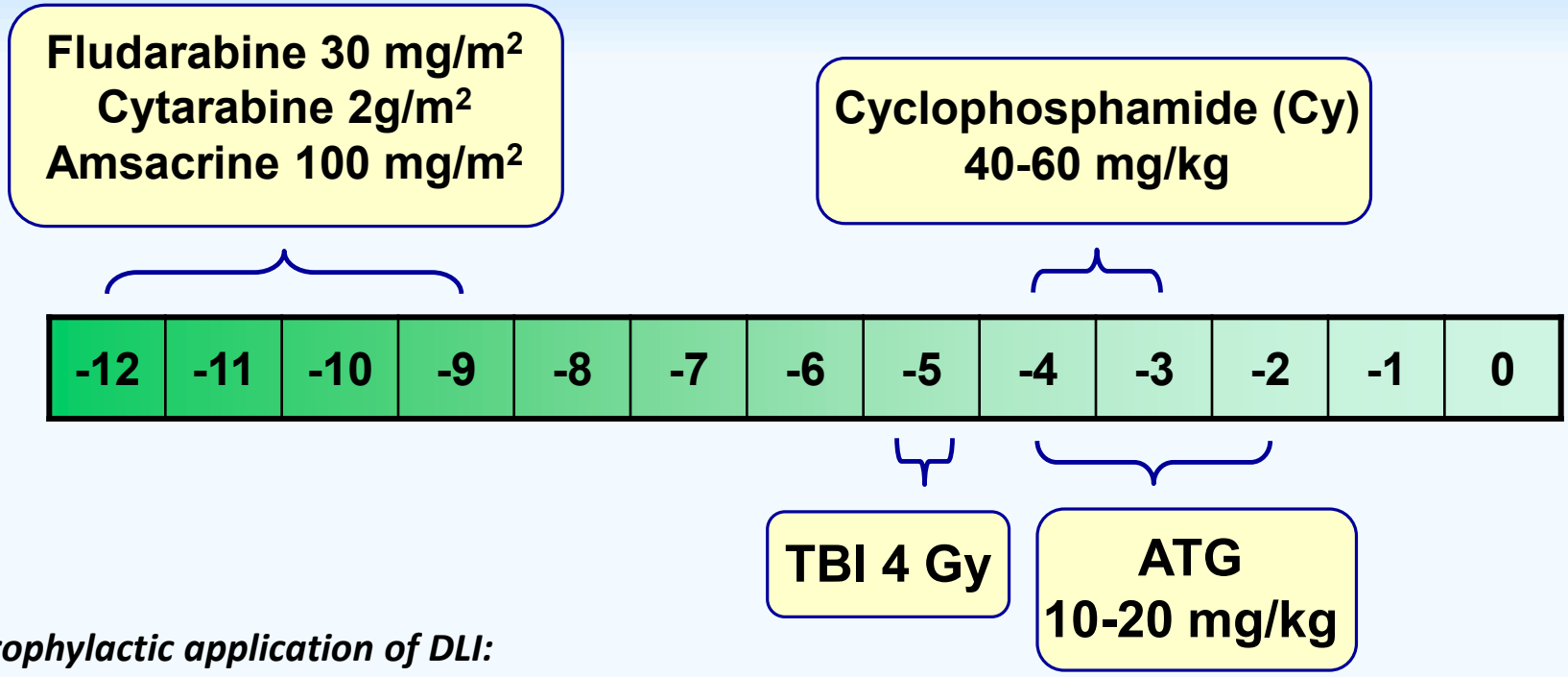
Intensity and toxicity of conditioning



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-HCT - GvHD

GvHD (*graft-versus host disease*)

- ✓ one of main complications of allo-HCT
- ✓ 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 graft versus tumor reaction (GvT reaction), which is positive for recipient.*
- ✓ GvHD – proliferation and differentiation 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-HCT, acute GvHD to day +100 after allo-HCT
- ✓ 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 only one organ or system involvement (*skin or oral cavity mucosa*) is possible too.
- ✓ GvHD intensity is also very variable.

Etiopathogenesis of acute GvHD

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

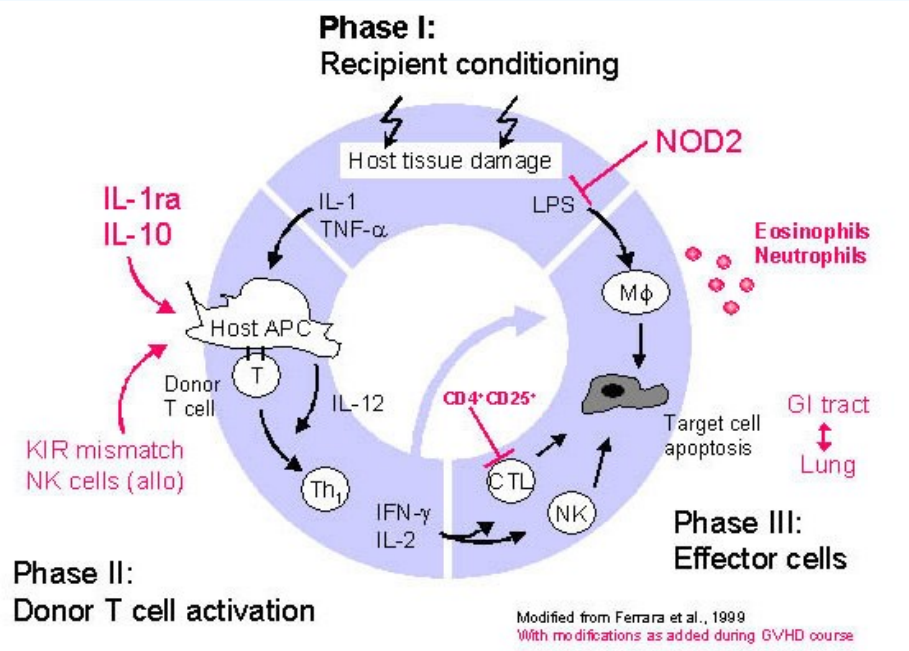
- *Phase I –* host tissue damage, induction of increasing of inflammatory cytokines-IL2, TNF, IL6; increasing expression of HLA antigens on the surface antigen-presented cells of recipient

- *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



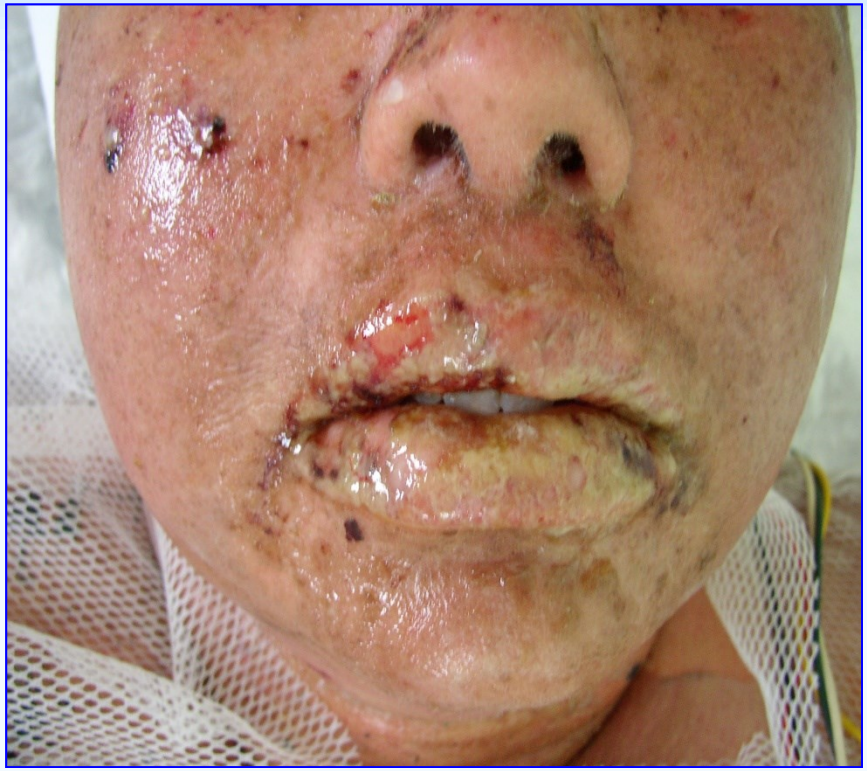
Prophylaxis of acute GvHD - possibilities

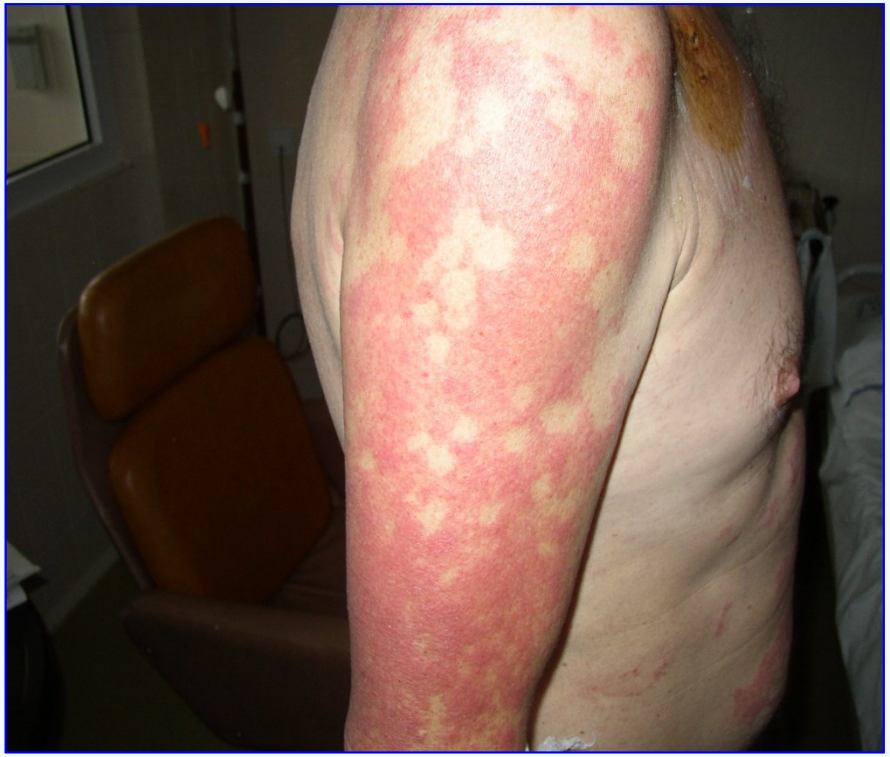
- ✓ Standard combination of cyclosporine A (CsA) and methotrexate (MTX)
- ✓ Other possibilities – combination of CsA and mycophenolate mofetil, combination tacrolimus+sirolimus
- ✓ Anti-thymocyte globulin – important part of conditioning, GvhD prophylaxis in allogeneic HCT from unrelated donors
- ✓ CsA: 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

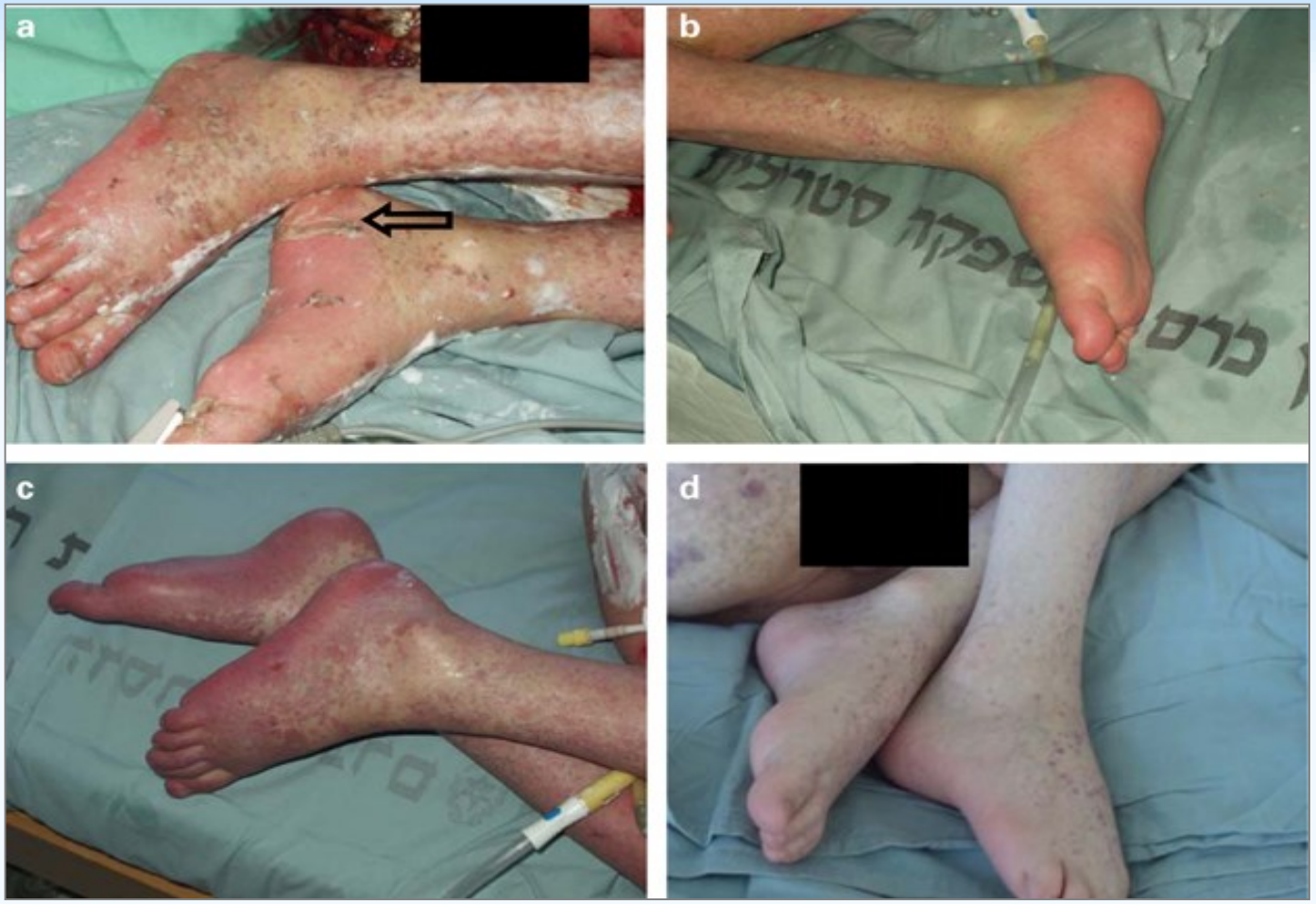
- ✓ Standard first-line treatment aGvHD: corticosteroids in dose 2mg/kg for 7-14 days, after this period decreasing of corticosteroids, this therapy is effective in 50-60% of pts
- ✓ Categories of treatment responses: complete response (CR), partial response (PR), stable disease (SD), progression (PD)
- ✓ 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-HCT: involvement of skin and oral mucosa





Steroid-refractory skin GvHD after allogeneic HCT



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% of pts after allo-HCT, mostly long-time GvHD treatment

Risk 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 immunosupressive (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 HCT?

Success versus failure of HCT

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

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

  (example from real life: patient after allo-HCT: 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 cure or prolongation of remission of disease

- **Ethical point** - emphasis on quality of life, return to common life, return to job and family life

How to improve of HCT results?

- ✓ Correct indication of HCT – using of prognostic factors for various diseases and transplant risk score
- ✓ Optimal timing of HCT
- ✓ Optimal choice of conditioting
  – decreasing of post-transplant toxicity → RIC regimens
  (reduced-intensity conditionings)
- ✓ Influencing of GvHD **(graft-versus host disease)** in allo-HCT
  – 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-HCT

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 HCT 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 (HCT) in Europe

- **HCT** is an **established procedure for many acquired and congenital disorders of the hematopoietic system**, including some disorders of the immune system

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

Passweg JR et al., BMT 2016

Indications for allo- and auto-HCT

- ✓ 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):** HCT as a valuable option for individual patients after carefull discussion of risks and benefits with the patient
3. **Developmental (D):** limited experience with this indication, additional research is needed to define role of HCT
4. **Generally not recommended (GNR):** disease in a phase or status in which pts are conventionally not treated by HCT

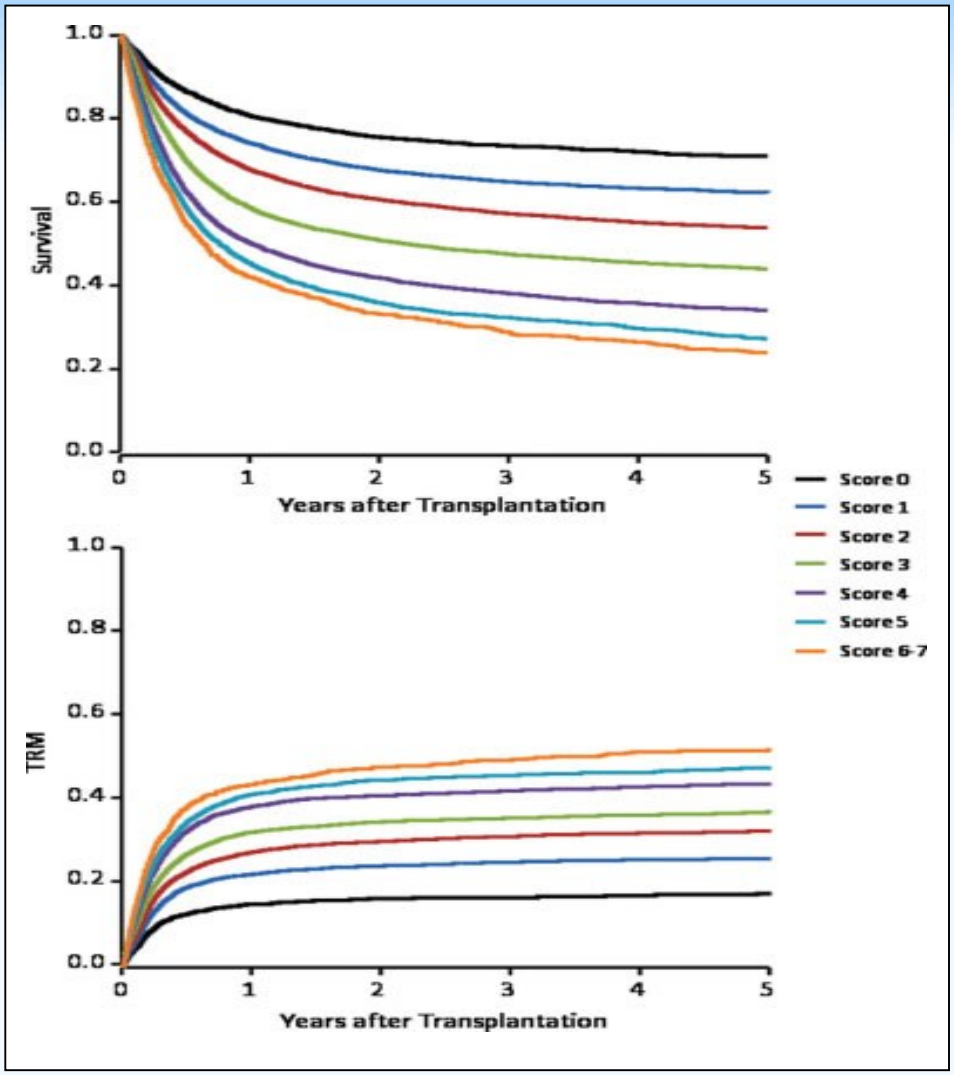
***Evidence grading**: evidence from randomized trial (I), evidence from well-designed clinical trial (II), other possibilities (III)*

Sureda A et al., BMT 2015

HCT – complications

1. Performance of HCT – this procedure has got a lot of risk for pts, the major problems – infections, toxicity, GvHD.
   Transplants may be performed in a specialized centre with experience with HCT 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 HCT- influence of many factors – whole clinical status, presence of comorbidities, age, status of main disease, prognostic factors, availibility of donor and others
3. Allogeneic HCT - 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-HCT against the risk factors and course of disease in each individual patient

EBMT transplant risk score

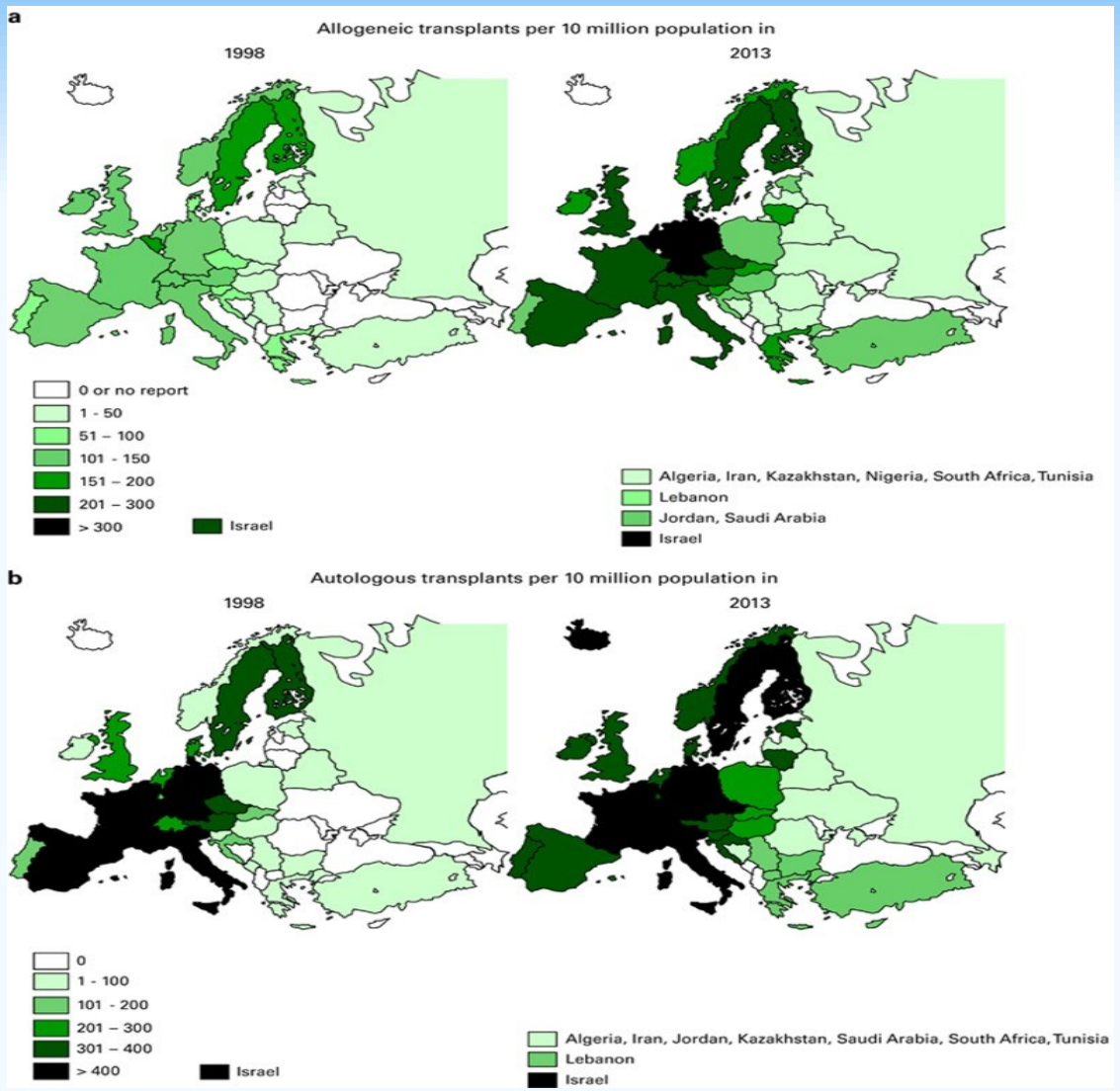


Survival and TRM of 56,605 patients with an allogeneic hematopoietic stem cell transplantation for an acquired hematological disorder is shown by risk score.

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

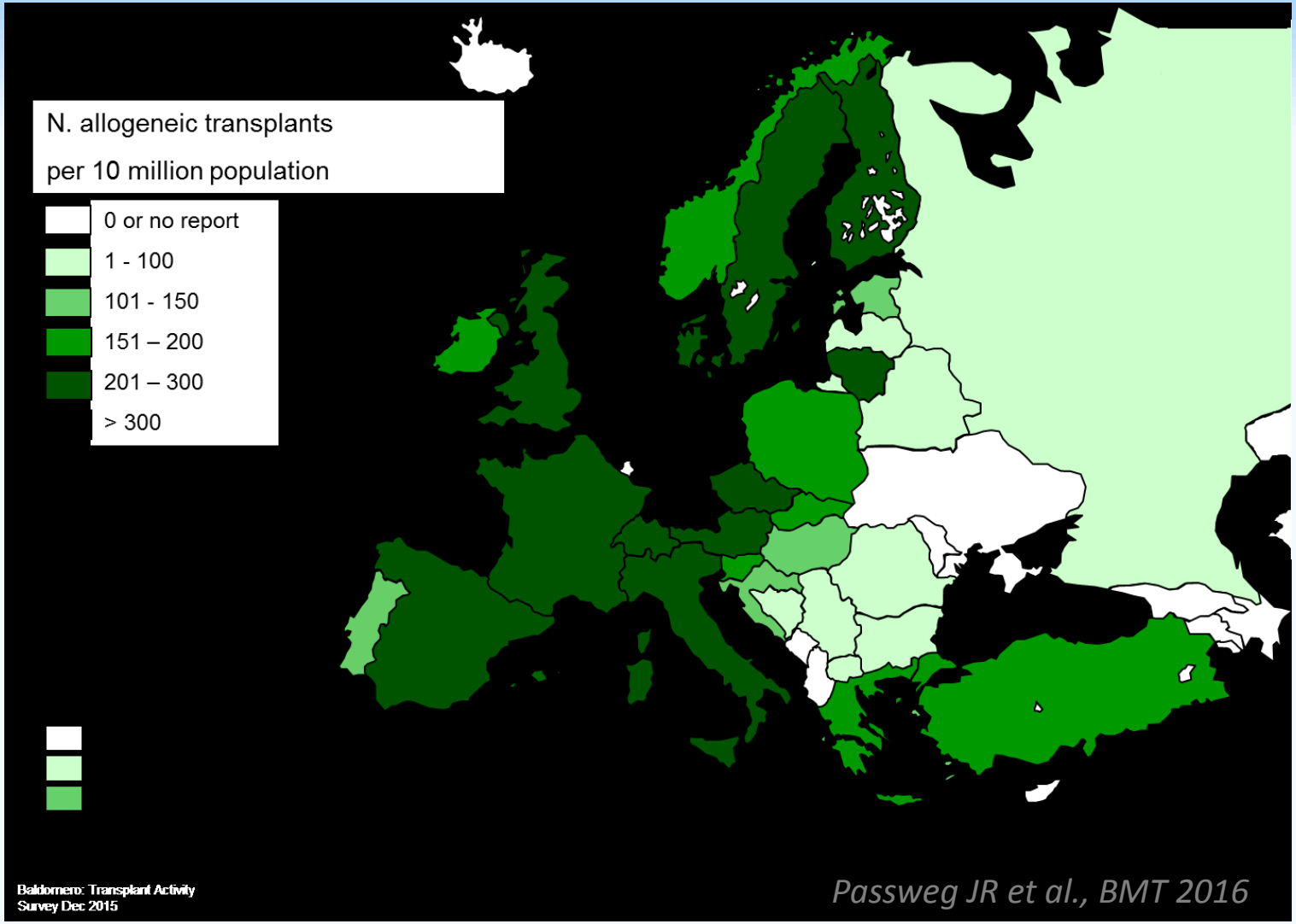
Gratwohl A et al, Cancer, 2009

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

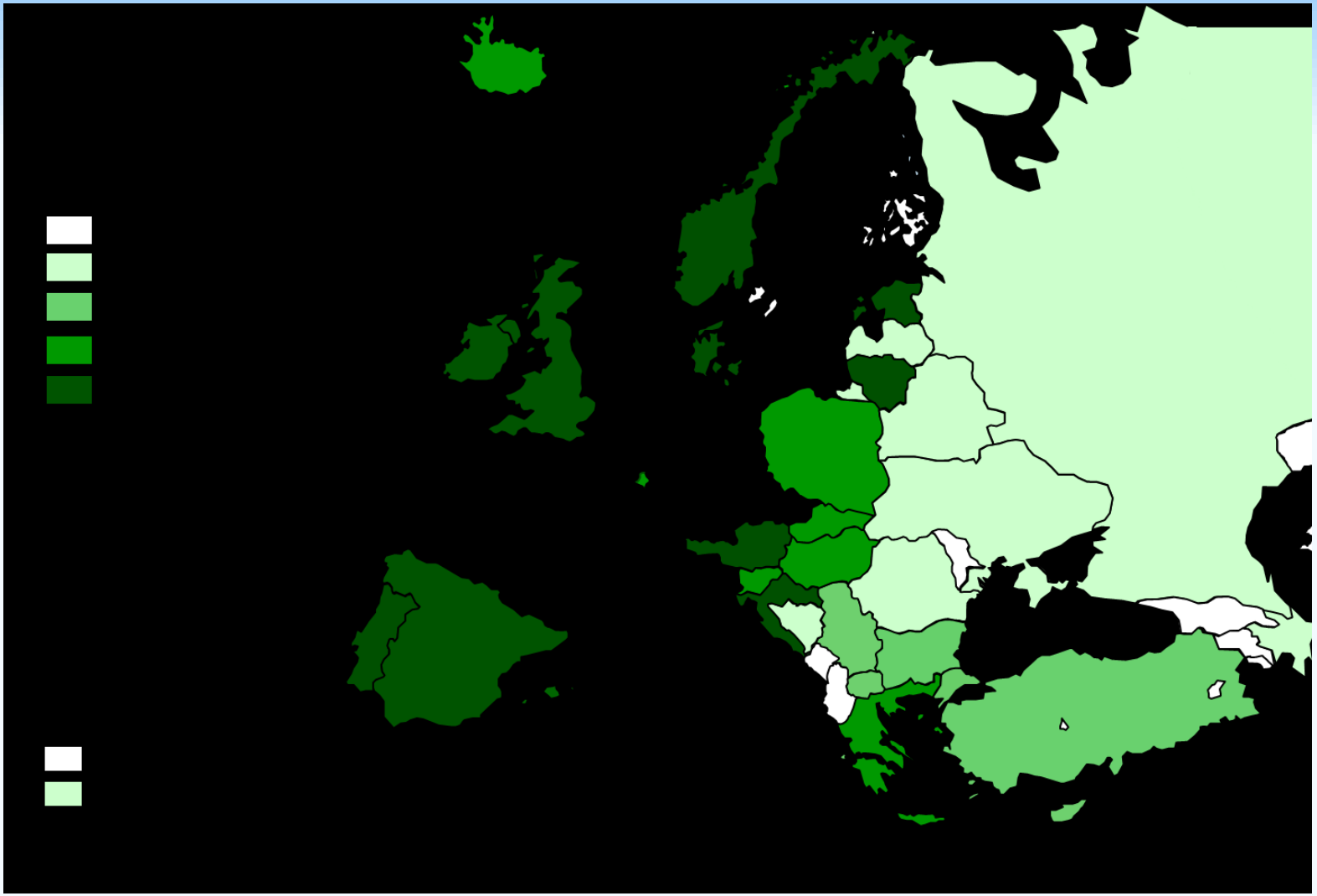


Passweg JR et al., BMT 2016

Allogeneic HCT – rates in Europe 2014



Autologous HCT – rates in Europe 2014



Passweg JR et al., BMT 2016

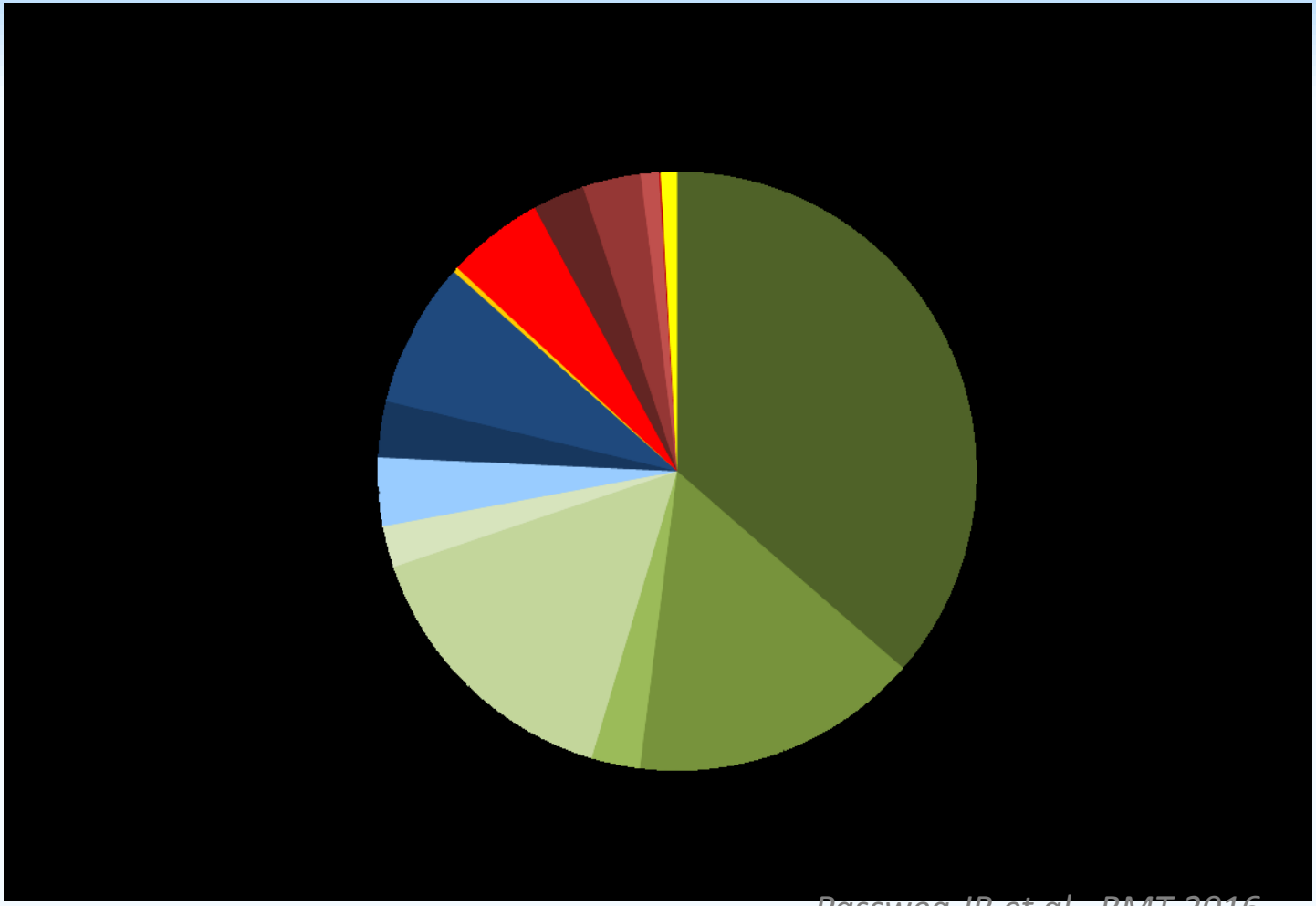
EBMT Activity Survey in 2014:

Main indications

Indication	Allogeneic 1st HCT	Autologous 1st HCT	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

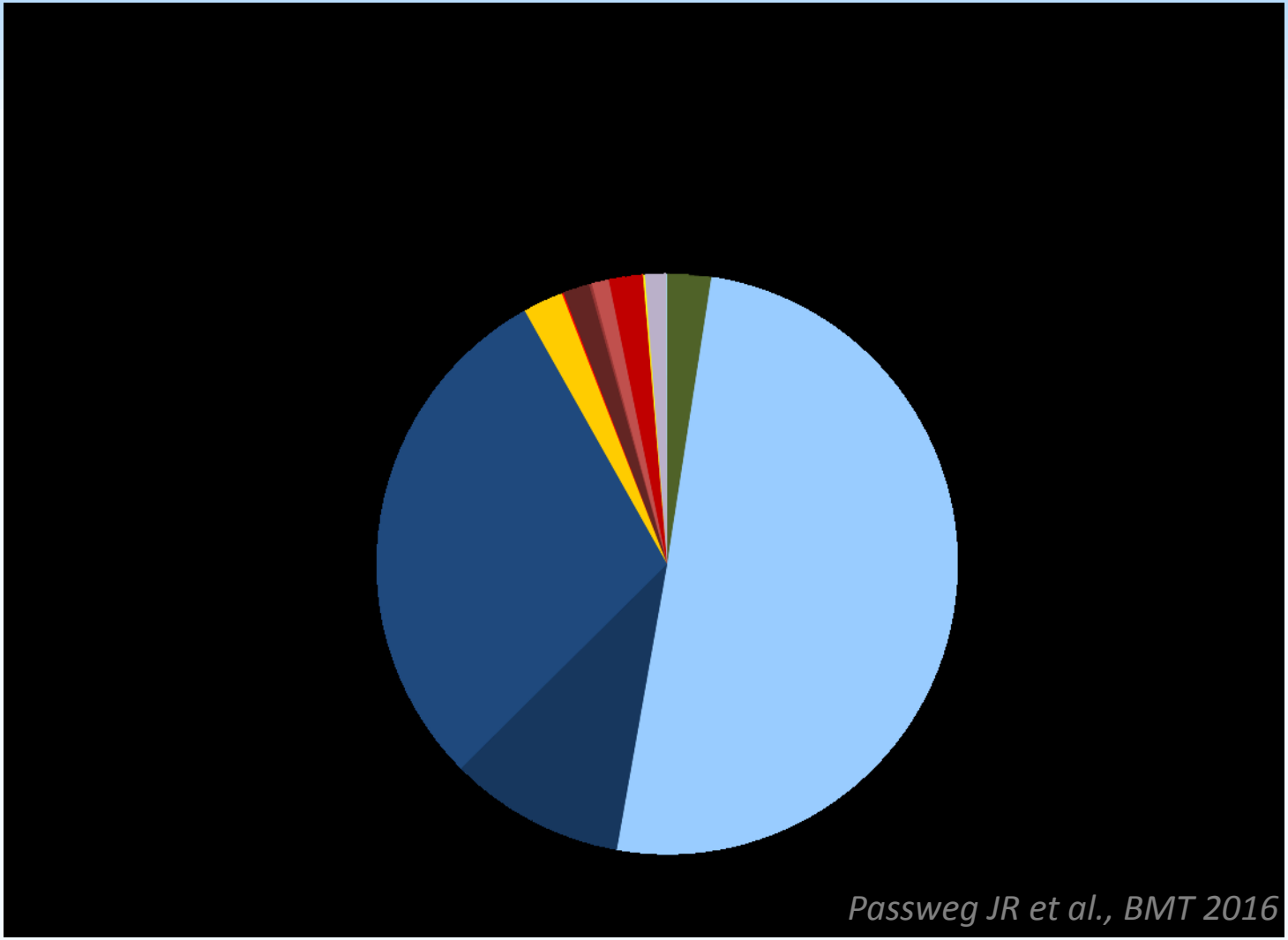
Allogeneic HCT in Europe 2014 - indications and diagnoses



Passweg JR et al., BMT 2016

Baldomero Transplant Activity Survey Dec 2015

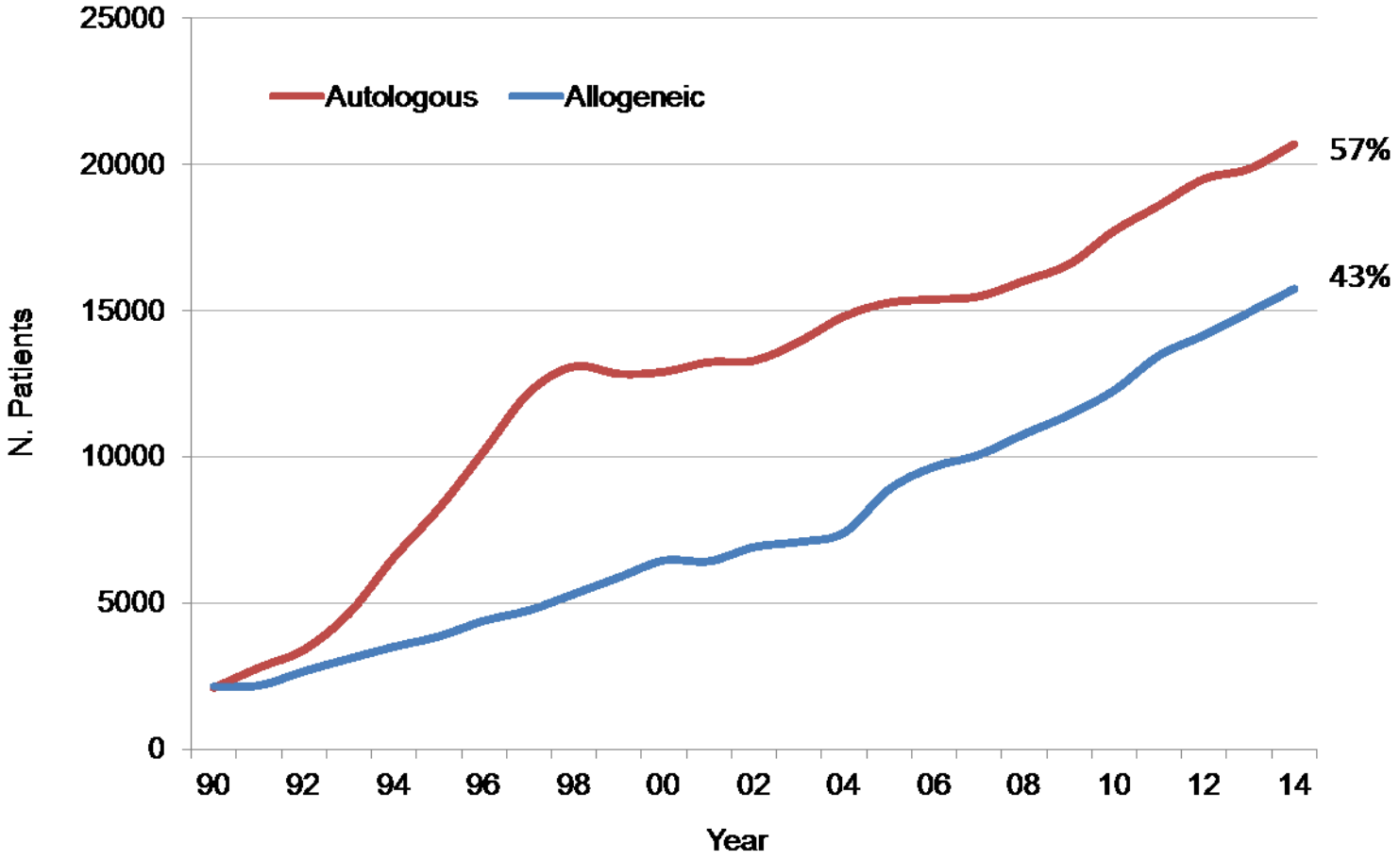
Autologous HCT in Europe 2014 - indications and diagnoses



Baldomero Transplant Activity Survey Dec 2015

HCT activity in Europe 1990 - 2014:

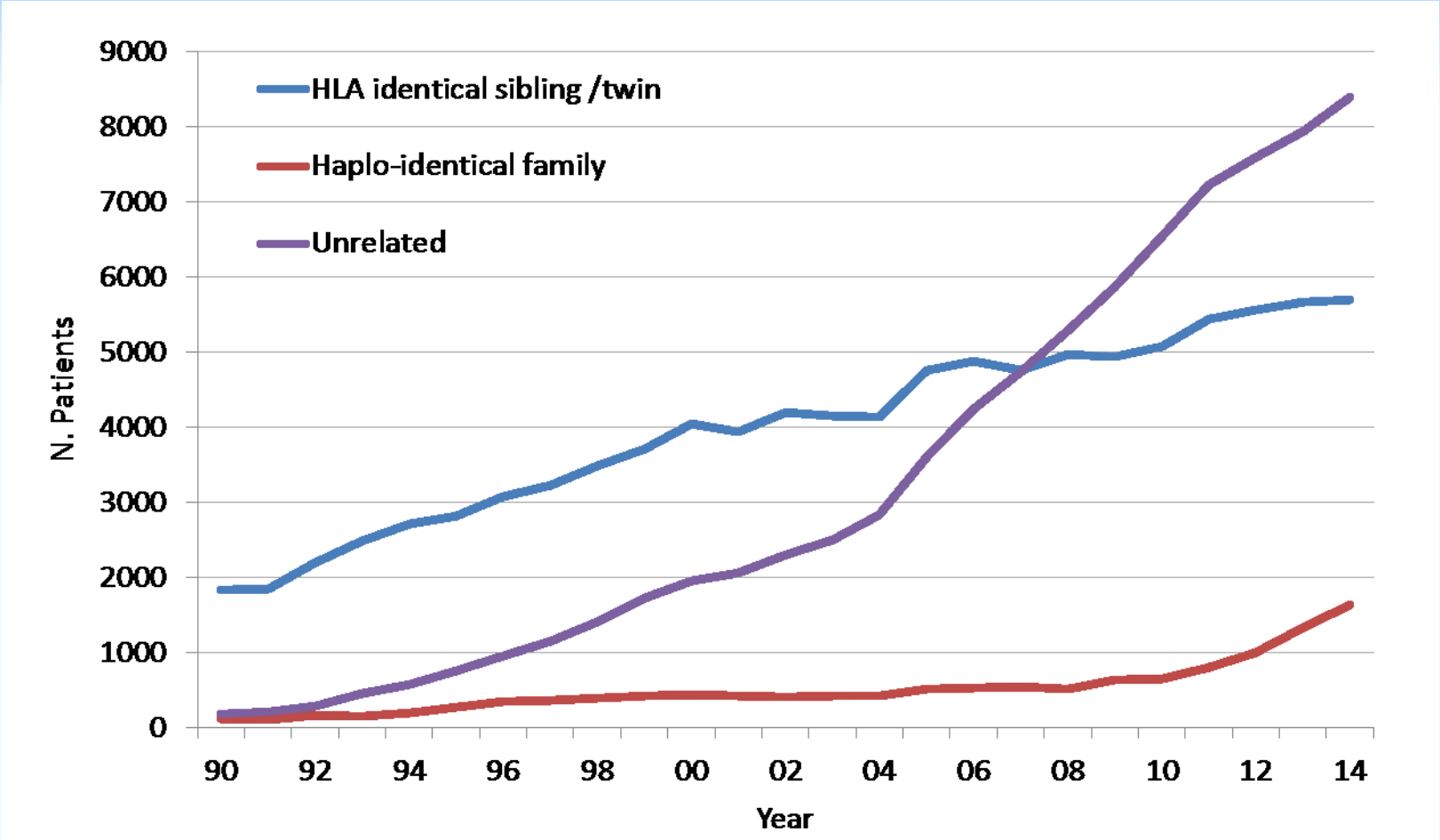
Transplant type 1st HCT



Passweg JR et al., BMT 2016

HCT activity in Europe 1990 - 2014:

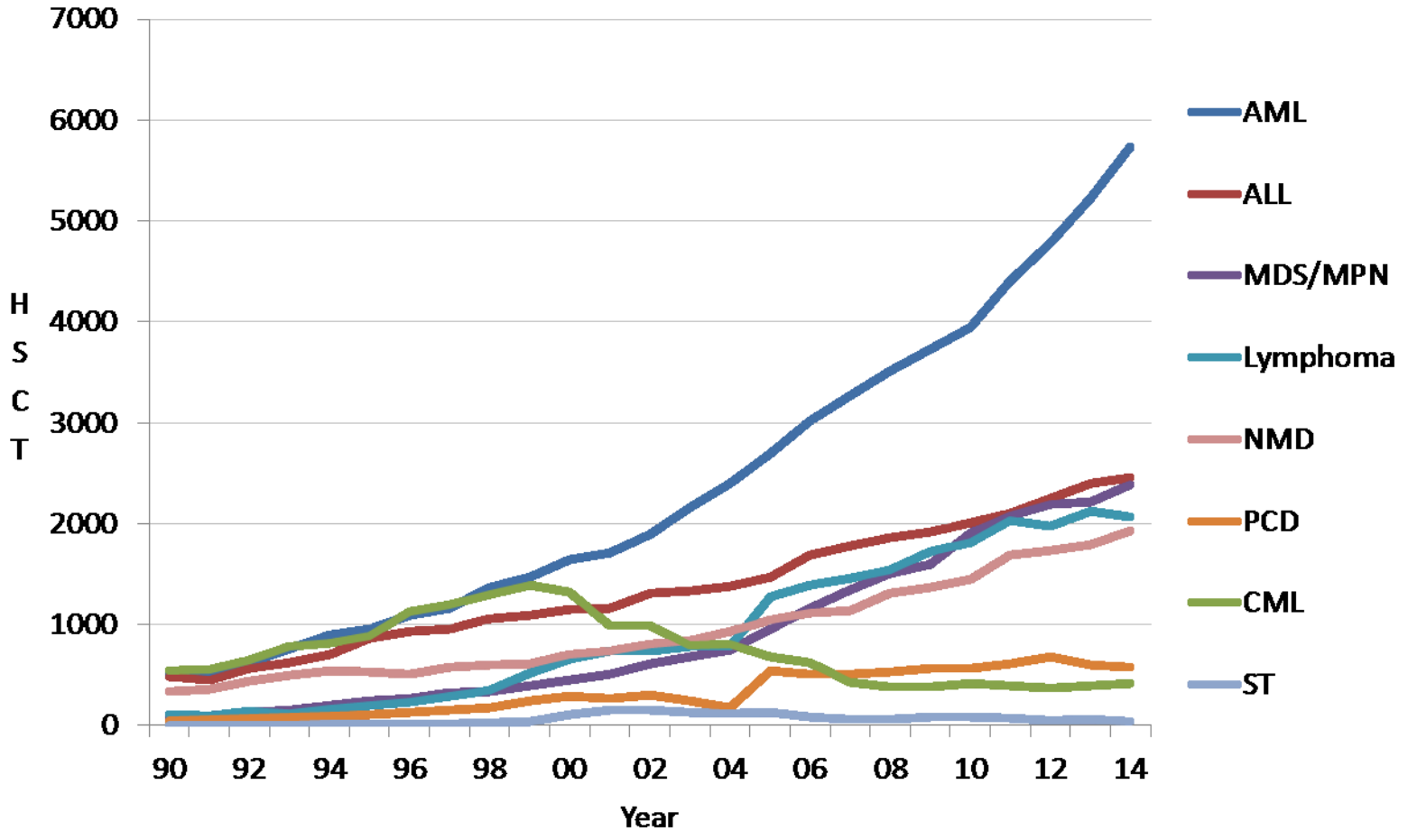
Donor origin: 1st HCT



Passweg JR et al., BMT 2016

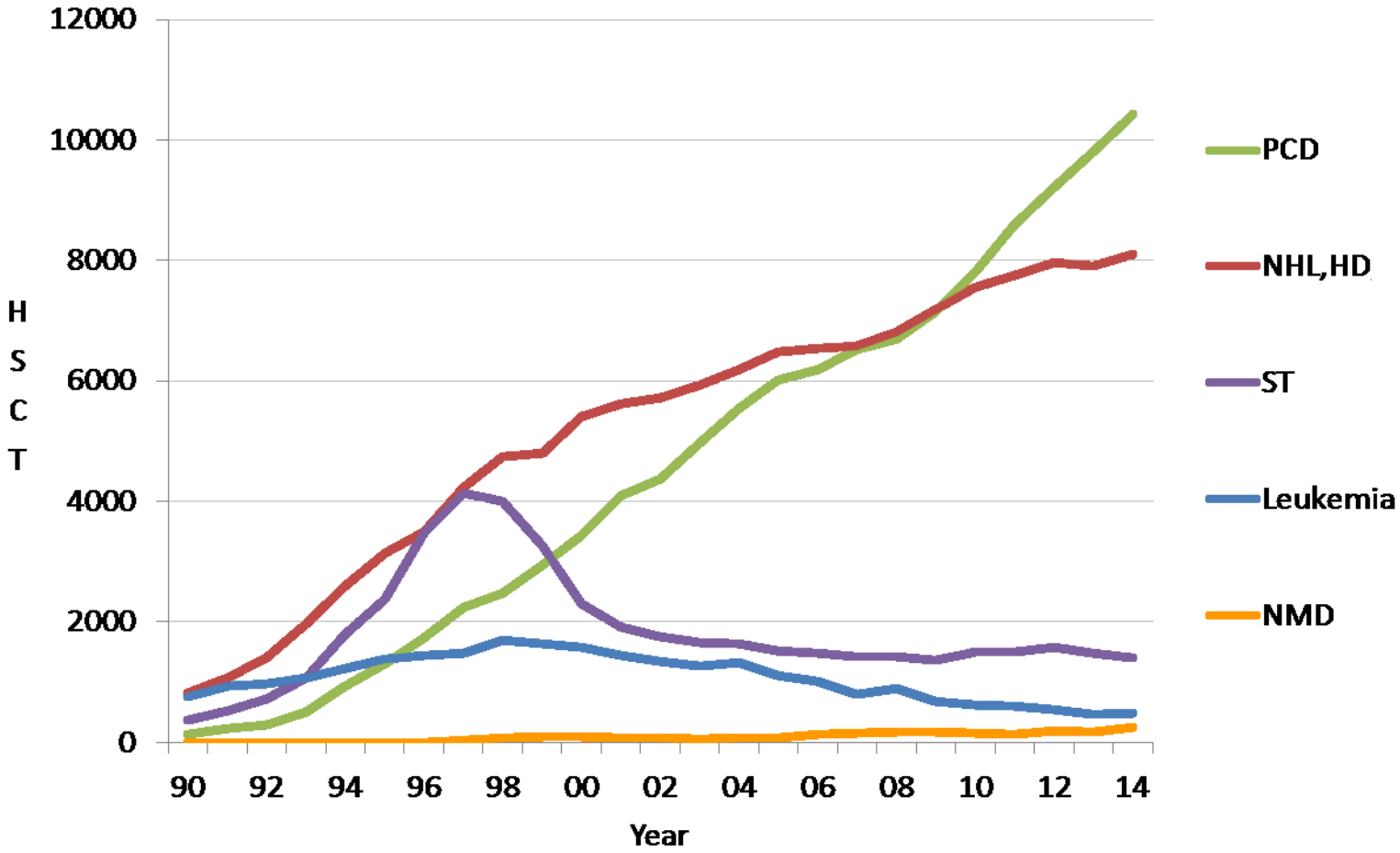
HCT activity in Europe 1990 - 2014:

Main indications: allogeneic



HCT activity in Europe 1990 - 2014:

Main indications: autologous



Main indications of HCT in Europe - year 2014 -

- ✓ Leukemia: 11 853 (33% of all HCT; 96% allogeneic), mostly AML+ALL (acute leukemia)
- ✓ Lymphoid neoplasias: 20 802 (57% of all HCT; 89% autologous), mostly PCD (multiple myeloma) and NHL (lymphomas)
- ✓ 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

HCT - trends in Europe
- year 2014 -

- ✓ **Increasing numbers of both auto- and allo-HCTs**
- ✓ **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 HCT: a report by the EBMT – I

- ✓ Hematopoietic stem cell transplantation (HCT) is used with increasing frequency in Europe with 40 000 transplants reported in 2014.
- ✓ **Transplant-related mortality remains high in allogeneic HCT (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 HCT, whereas others may function as a 'bridge to transplant'.

Passweg JR et al., BMT 2017

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

- ✓ We analyzed HCT 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 HCT in early **CML.**
- ✓ In **myelodysplastic syndromes**, hypomethylating agents show no effect on HCT 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 HCT 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 for autologous HCT.
- ✓ **Drug development data show different effects on HCT use; highly effective drugs may replace HCT, whereas other drugs may improve the patient's condition to allow for HCT**.

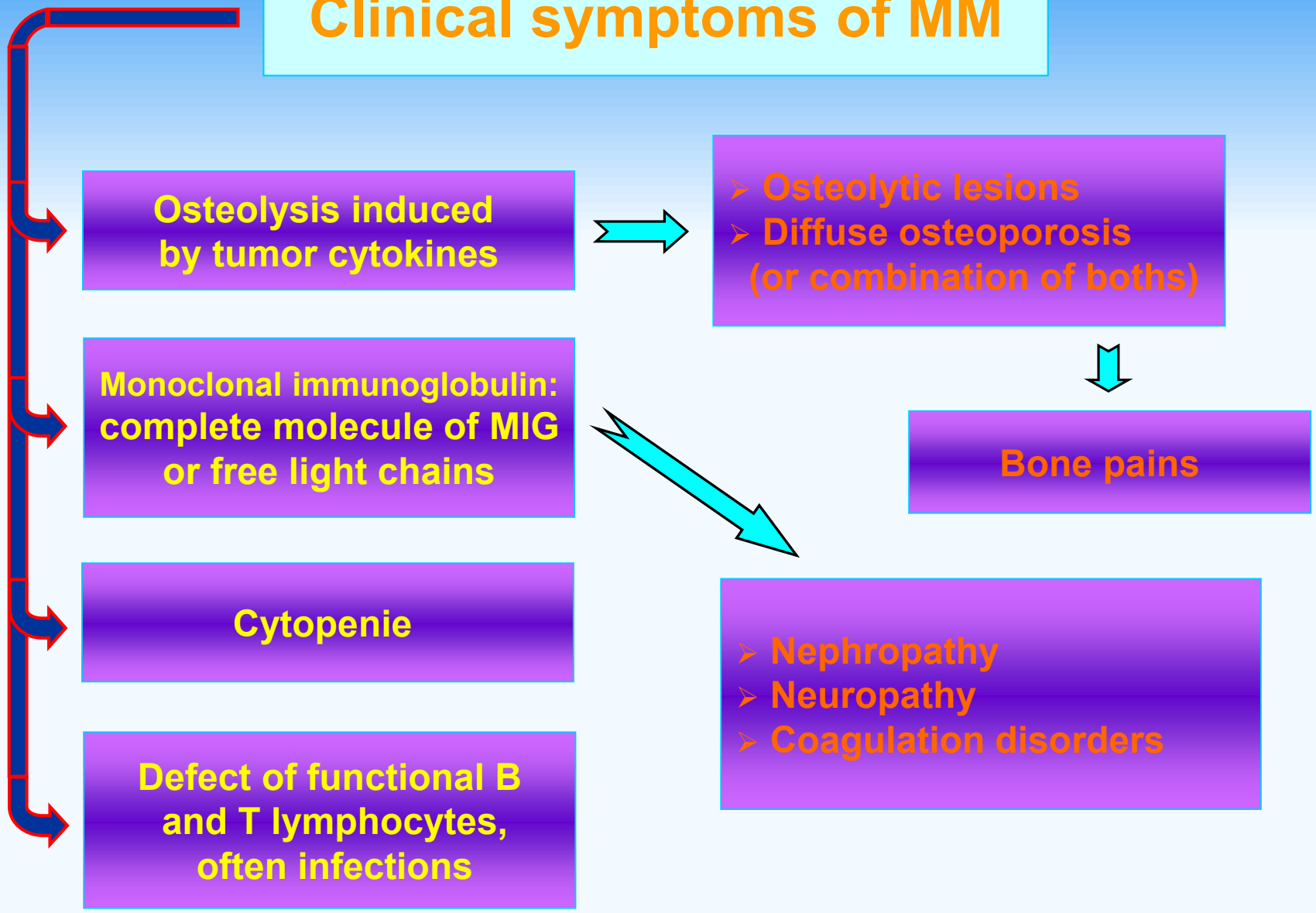
Passweg JR et al., BMT 2017

Multiple myeloma (MM)

- 1% of all cancer disorders, 10% of all hematological malignancies
- Median age at diagnosis: 65-70 years; only 2% of pts are younger than 40 years
- MM - uncurable chronic cancer disease
- Median of overall survival from MM diagnosis: 3-4 years with standard treatment, 5-7 years with treatment including autologous transplantation
- MM still remains the main indication for autologous transplantation (over 50% of all autologous transplantations).

Moreau P et al. Annals of Oncol, 2017; 28:52-61.

Clinical symptoms of MM

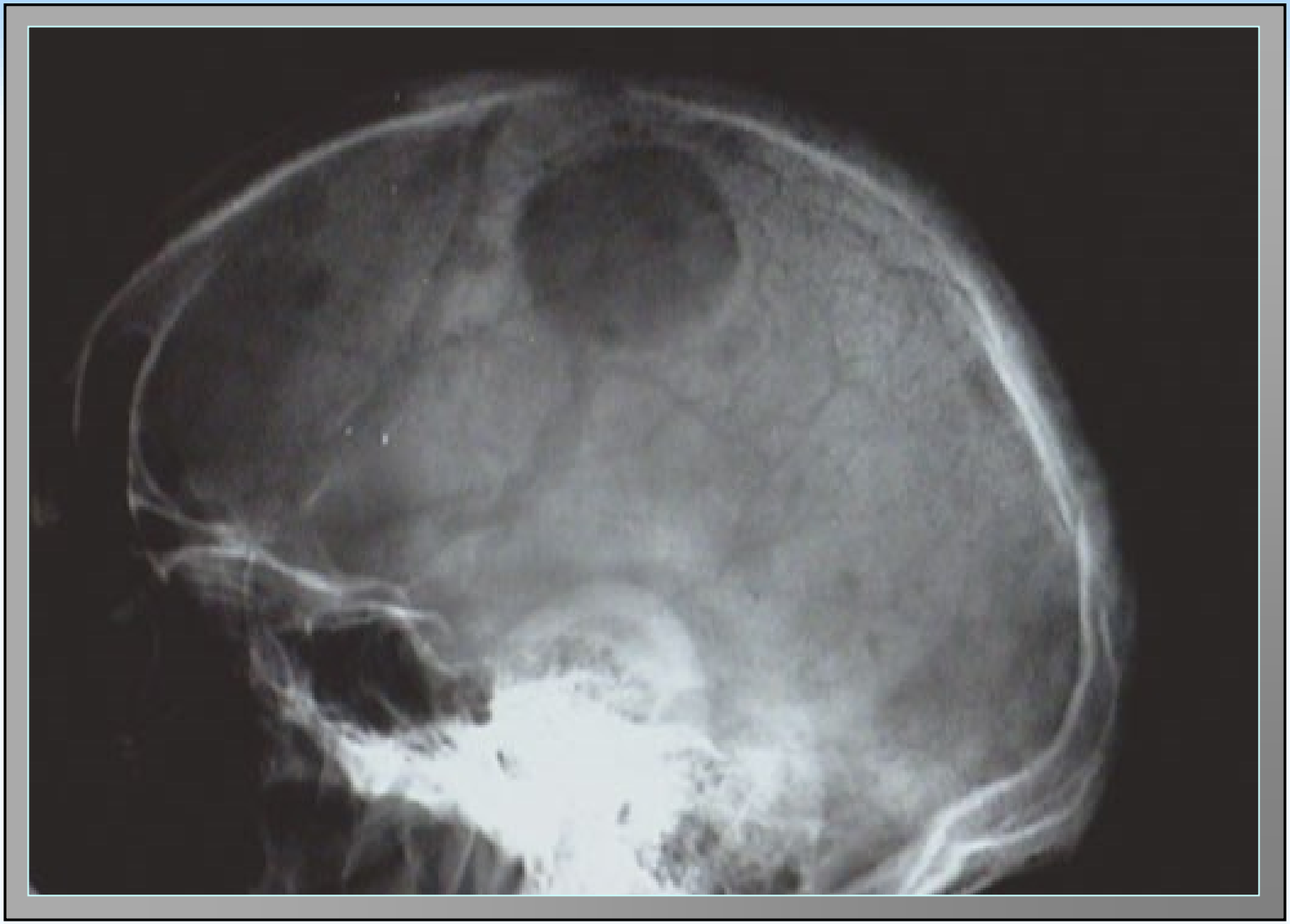


Diagnostic criteria for multiple myeloma - IMWG (2014)

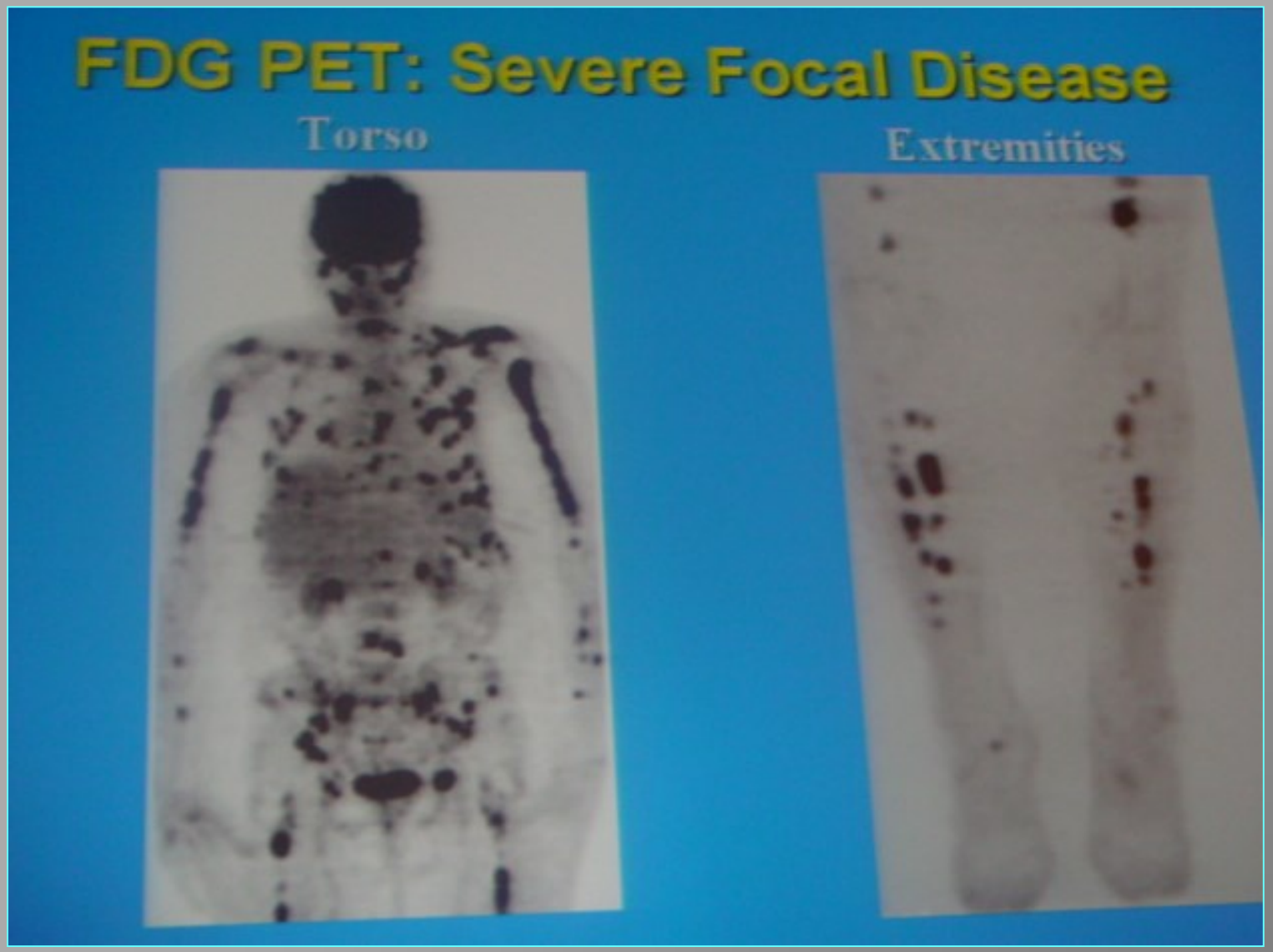
- Number of clonal plasma cells
  in bone marrow over 10% or biopsy-proven bone or extra-medullary plasmacytoma
- Evidence of serum M protein (IgG or IgA) over 30g/l or urinary M protein over 500 mg per 24 h
- Evidence of end stage organ damage that can be attributed to the MM, specifically:

C – calcium over 2.8 mmol/l (hypercalcemia)
R – renal insufficiency – serum creatitine over 177 umol/l
A – anemia (hemoglobin value under 100 g/l)
B – bone osteolytic lesions on skeletal radiography, CT or PET-CT or multiple focal lesions on MRI studies

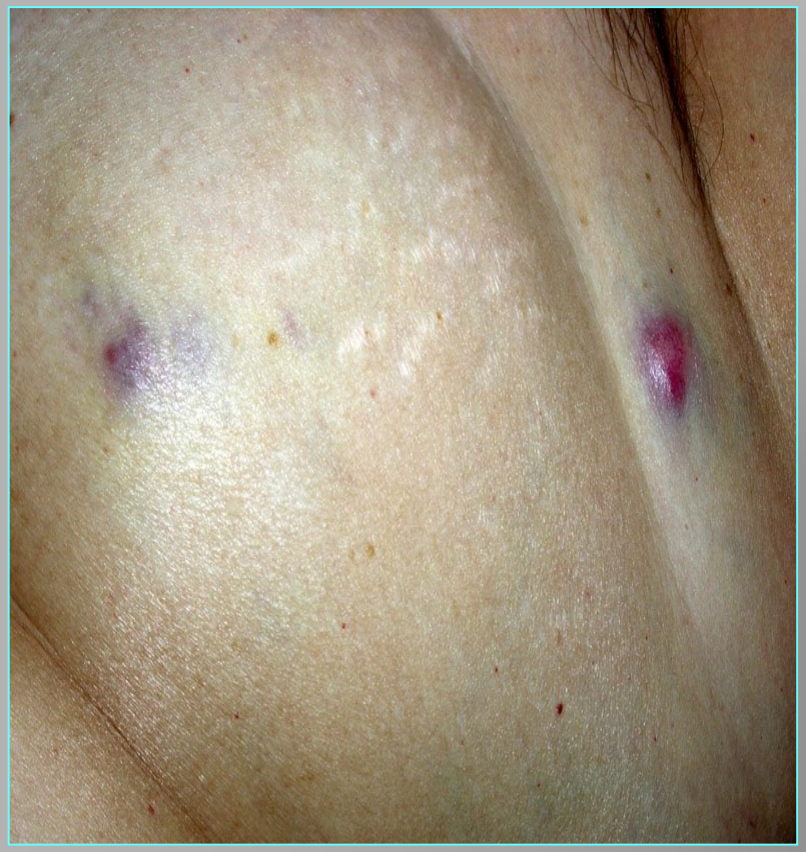
Myeloma osteolytic lesions (radiography of skull)

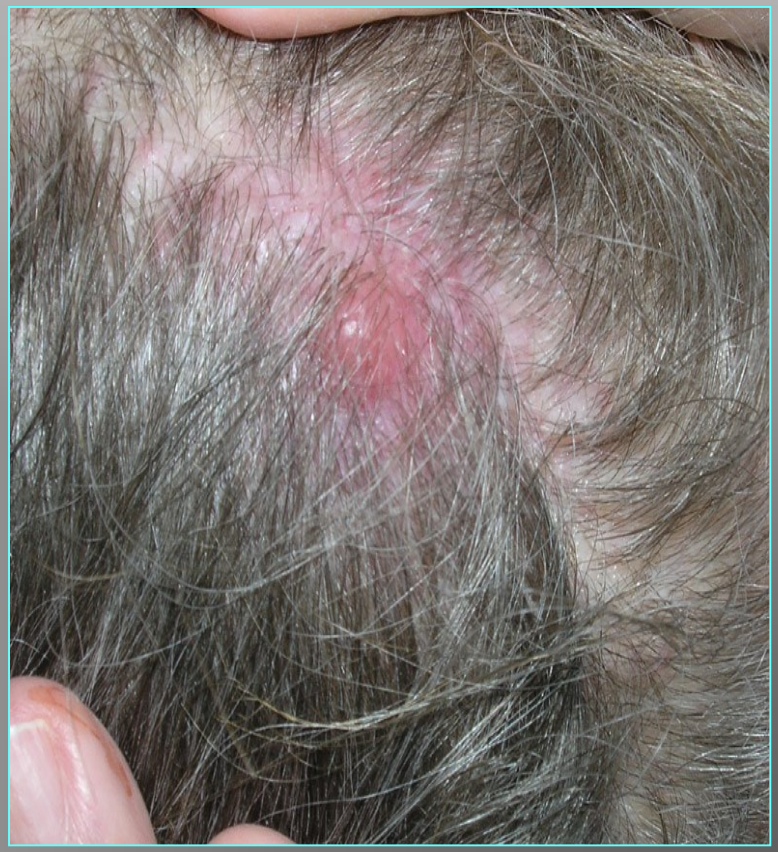


FDG PET: Severe Focal Disease

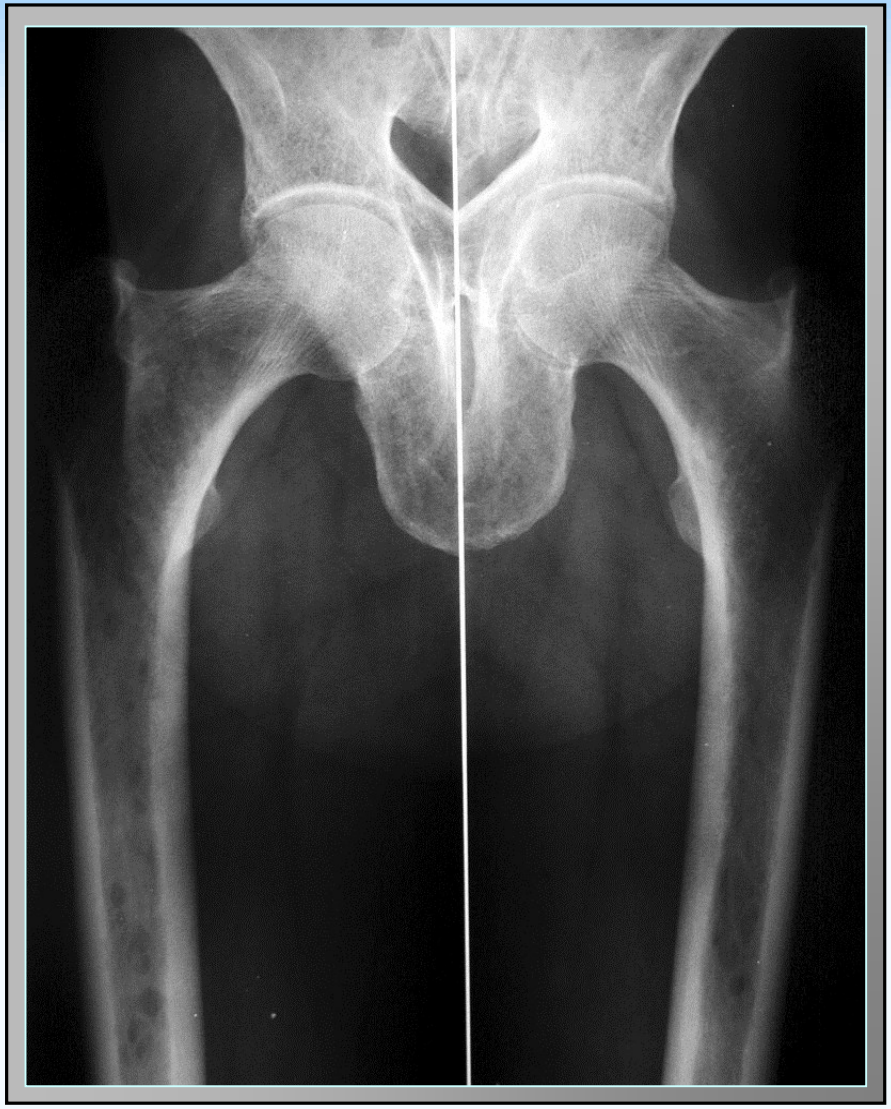


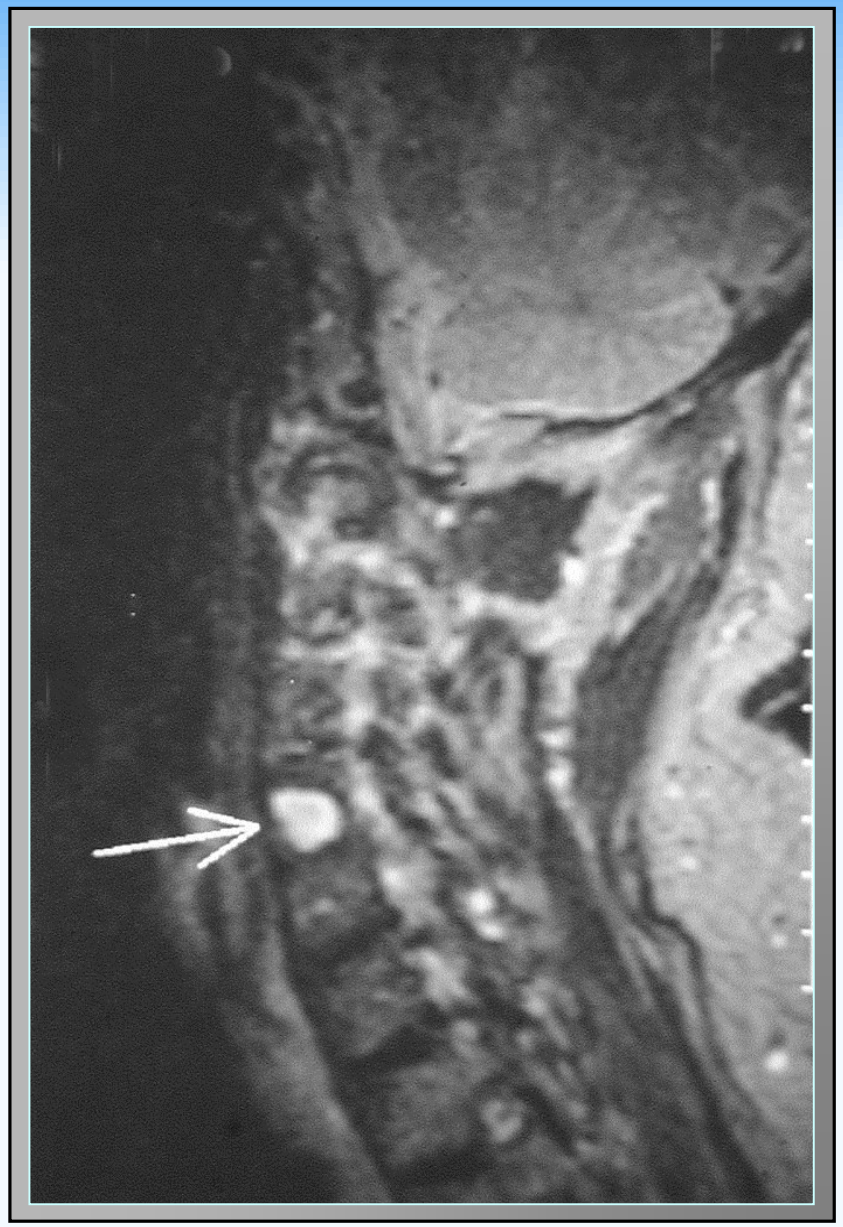
Extramedullary myeloma lesions of skin and soft tissues (biopsy-proven)





Bone lesions on skeletal radiography of femoral bones and MRI of spine





Autologous transplantation in MM: case report 1

Female, 62 years

- **Diagnosis of carcinoma ovarii** pT2a pN0 M0, treatment with surgery and chemotherapy from 10/2014, status of disease after treatment – remission of disease
- **PET/CT from 9/2015: new osteolytic lesions** - in os sacrum 20 mm and spine corpus of L4 - 21x14x19 mm, unknown etiology, bone pains
- In 10/2015 – **biopsy from osteolytic lesion in L4 was performed, diagnosis of plasmocellular myeloma was established**
- Complete examination was done in our department in 12/2015, diagnosis **MM, IIA according to DS criteria, ISS1, type IgG lambda, with CRAB criteria**
- **Treatment:** 4 cycles of bortezomib-based regimen (VTD), autologous PBSC mobilisation and harvest in 5/2016, autologous HCT in 6/2016, conditioning MEL200, hospitalization after autologous HCT: 16 days
- **Treatment response:** remission of MM, PET/CT from 10/2017 and 1/2019 – without abnormal metabolic active skeletal lesions. In 2/2019: remission of MM.

Allogeneic transplantation in ALL: case report 2 – ZR, male born on 1991 - I

- ✓ **First symptoms of disease** – 8/2016: fatigue, weakness, bleeding, fever, infection of upper respiratory tract; acute disease – symptoms appeared in several days
- ✓ **Hyperleukocytosis** 437x10^9/l (normal value 4-10x10^9/l); **anemia** Hb 47,9 g/l (normal value of Hb: 135-175g/l); **trombocytopenia** 42x10^9/l (normal value: 150-350)
- ✓ In peripheral blood: presence of blasts (95%), normal value: 0% of blasts
- ✓ Diagnosis of acute lymphoblastic leukemia was established
- ✓ **Diagnosis of acute leukemia: over 20% of blasts** in peripheral blood or bone marrow

Allogeneic transplantation in ALL: case report 2 – ZR, male born on 1991 - II

- ✓ **Therapy: several courses of chemotherapy –** combination of cytostatic drugs + corticosteroids: 2 courses of induction and 1 course of consolidation (8-10/2016), response - complete response of ALL
- ✓ **HLA typing was done in patient and his 3 siblings,** only 1 sister is completely HLA identical (10/10)
- ✓ **In 1/2017 allogeneic transplantation of PBSC from HLA identical sibling was performed after myeloablative conditining** Cy/TBI, day 0 (application of PBSC) was 31.1.2017
- ✓ **Hospitalization after allo-HCT** : 24.1.-7.3.2017, infectious complications, febrile neutropenia, GIT mucositis, upper GIT acute GvHD, pneumonia
- ✓ **2/2019**: patient alive, in good clinical condition, in remission of ALL, without immunosupressive therapy, he is observed in out-patient department, now he is preparing to study in university

Allogeneic transplantation in AML: case report 3 - PM, born on 1952, female - I

- ✓ **First symptoms of disease** – 10/1996: fatigue, weakness, bleeding, fever; acute disease – symptoms appeared in several days
- ✓ Age at diagnosis of AML: 44 years
- ✓ **In peripheral blood count:** leukocytosis, anaemia, thrombocytopenia
- ✓ **Diagnosis of AML:** from bone marrow examination (sternal puncture - BM aspiration from sternum) – 77% of blasts in bone marrow
- ✓ **Therapy**: chemotherapy – induction, 2 courses of consolidation, effect of CR, HLA typing of 2 siblings, 1 HLA identical brother
- ✓ In 4/1997 allogeneic HCT was performed, after MAC BuCy, hospitalization for allo-HCT: 2 months

Allogeneic transplantation in AML: case report 3 - PM, born on 1952, female - II

- ✓ **Complications in the first year after allogeneic HCT**: reccurent infections (CMV, EBV), acute GvHD, hemorhagic cystitis by viral BKV etiology and others
- ✓ **Status to 2/2019: 22 years after allo-HCT**, patient alive, remission of AML, in good clinical condition, without specific therapy
- ✓ Patient returned to her job 2 years after allogeneic transplant – she is teacher on the university. She worked on the university to her 62 years. Now (2/2019) she is retired, but she is living very active life.

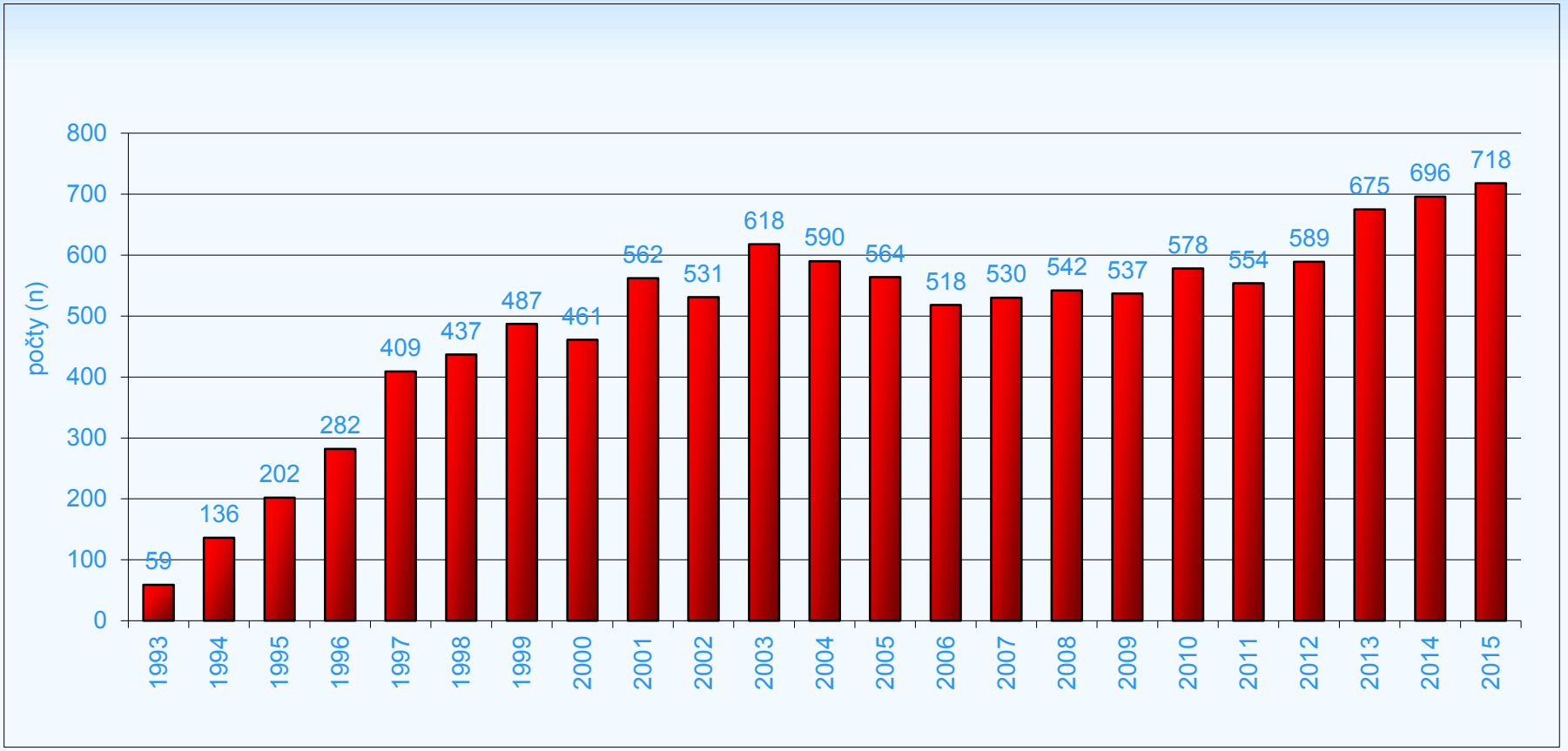
Allogeneic transplantation in CLL: case report 4 - RK, female, born in 1968, high-risk CLL – part I

- ✓ **Diagnosis of CLL:** 6/2000, Rai stage IA, progression to stage IIB in 11/2012, p53 mutation from 6/2016
- ✓ **Treatment before HCT - 4 lines:** 4x FCR, alemtuzumab, bendamustin+R, ibrutinib
- ✓ **Status of disease at transplant:** stable disease
- ✓ **Age at transplant:** 48
- ✓ **Conditioning:** FC-RIC protocol, **day 0:** 31.8.2016
- ✓ **Donor:** unrelated donor 9/10
- ✓ **Regular monitoring after HCT:** examinations of blood count, biochemistry and bone marrow; CsA levels; chimerism; PCR-CMV; MRD – flow, PCR; PET/CT scans

Allogeneic transplantation in CLL: case report 4 - RK, female, born in 1968, high-risk CLL – part II

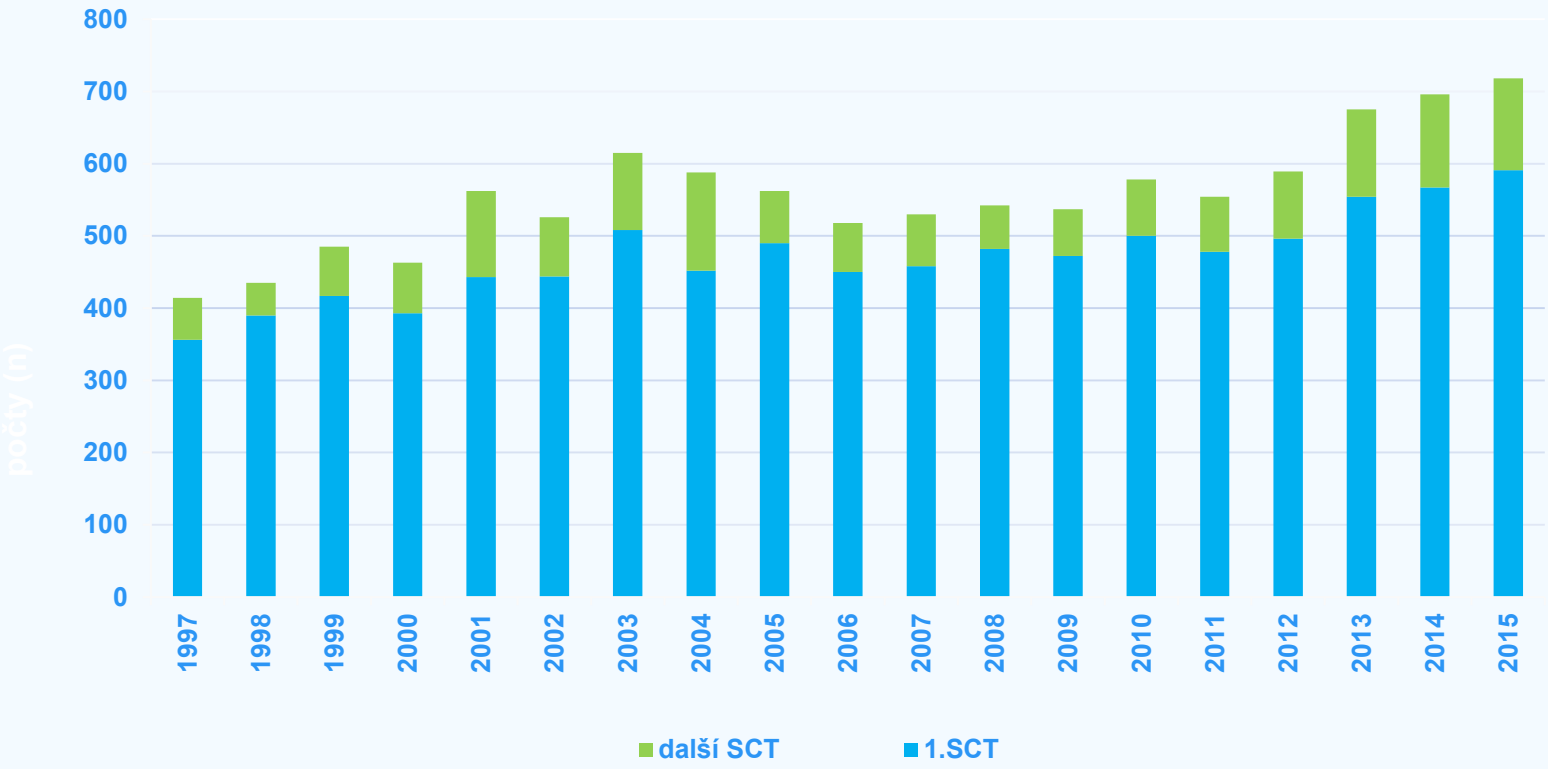
- ✓ **Complications after allo-HCT:** febrile neutropenia, infections
- ✓ **Treatment response:** hematological remission
- ✓ MRD-flow negativity from peripheral blood and bone marrow, complete chimerism was achieved
- ✓ **Follow-up from HCT to February 2019:** 30 months, patient is alive and disease free, she returned to her job after 9 months from alo-HCT

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



Survey on Transplant Activity, EBMT

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

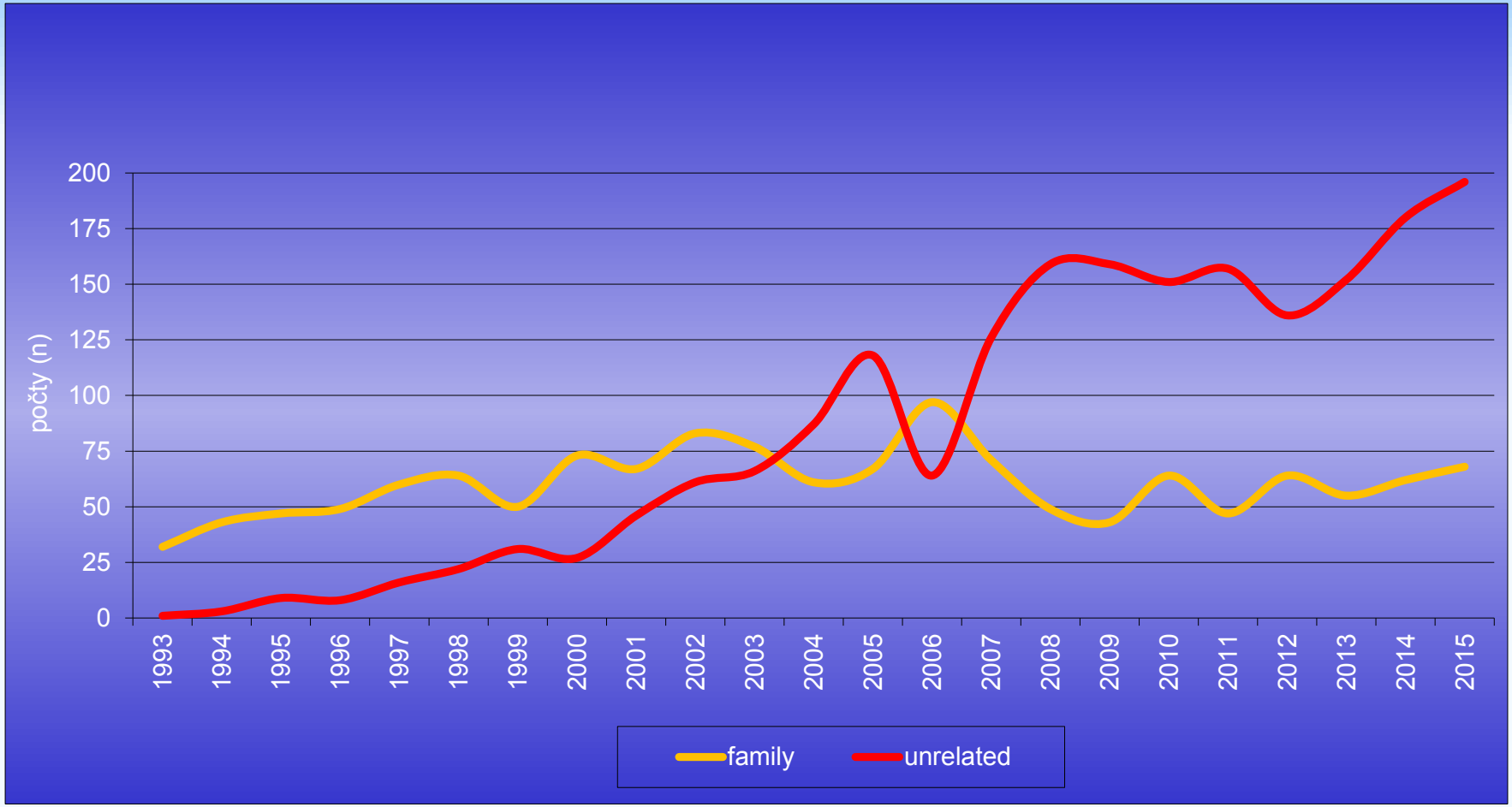


Survey on Transplant Activity, EBMT

HCT activities in Czech Republic in 2015

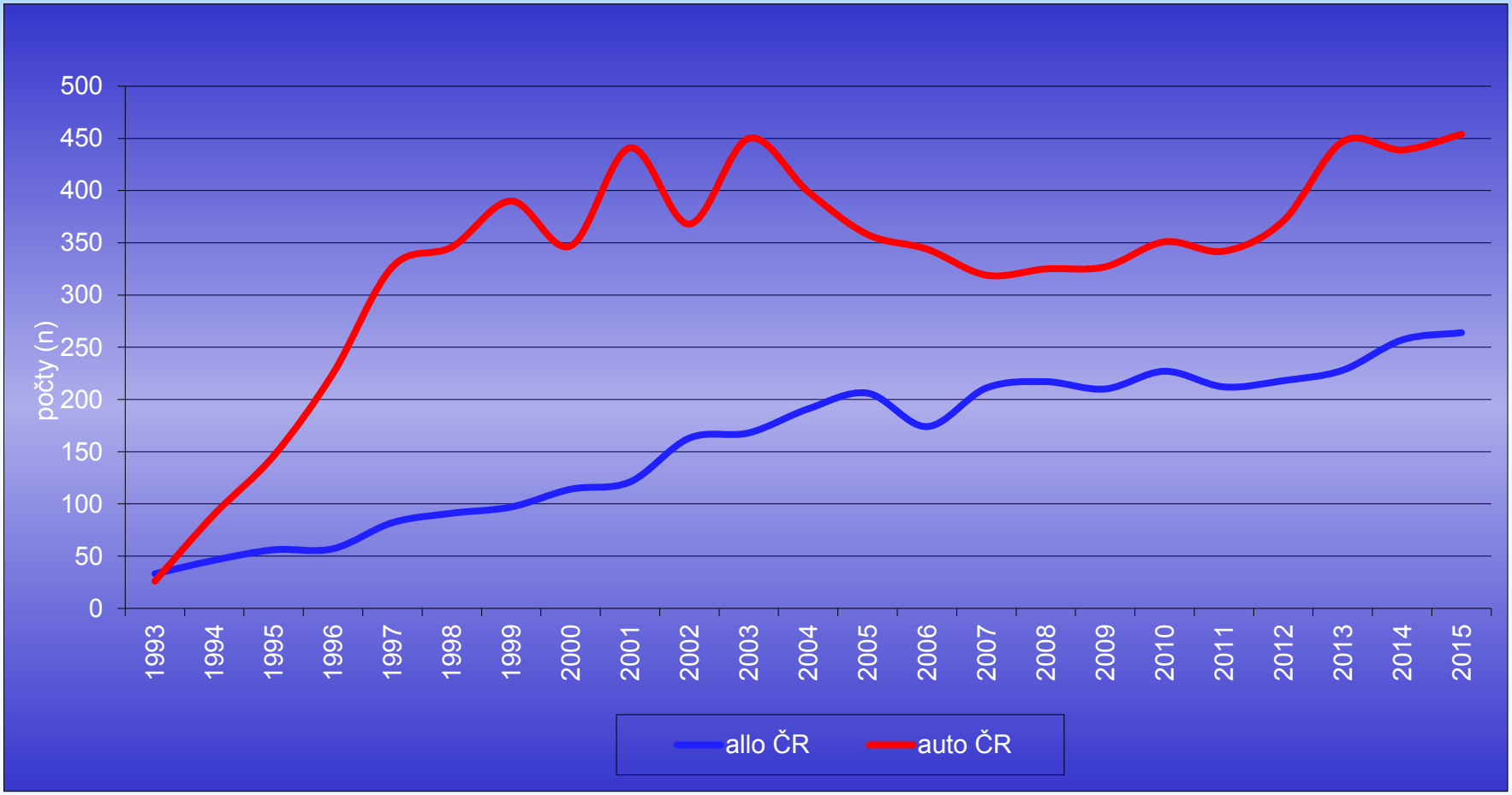
- ✓ 718 HCTs were performed in 2015 in Czech Republic in 10 transplant centres
  - 264 allogeneic HCT
  - 454 autologous HCT
- ✓ The first HCTs: 591 (83%)
  - 348 autologous HCT
  - 243 allogeneic HCT
  - Number of non-myeloablative HCT: 143
  - Number of DLI applications (donor lymphocyte infusions):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

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



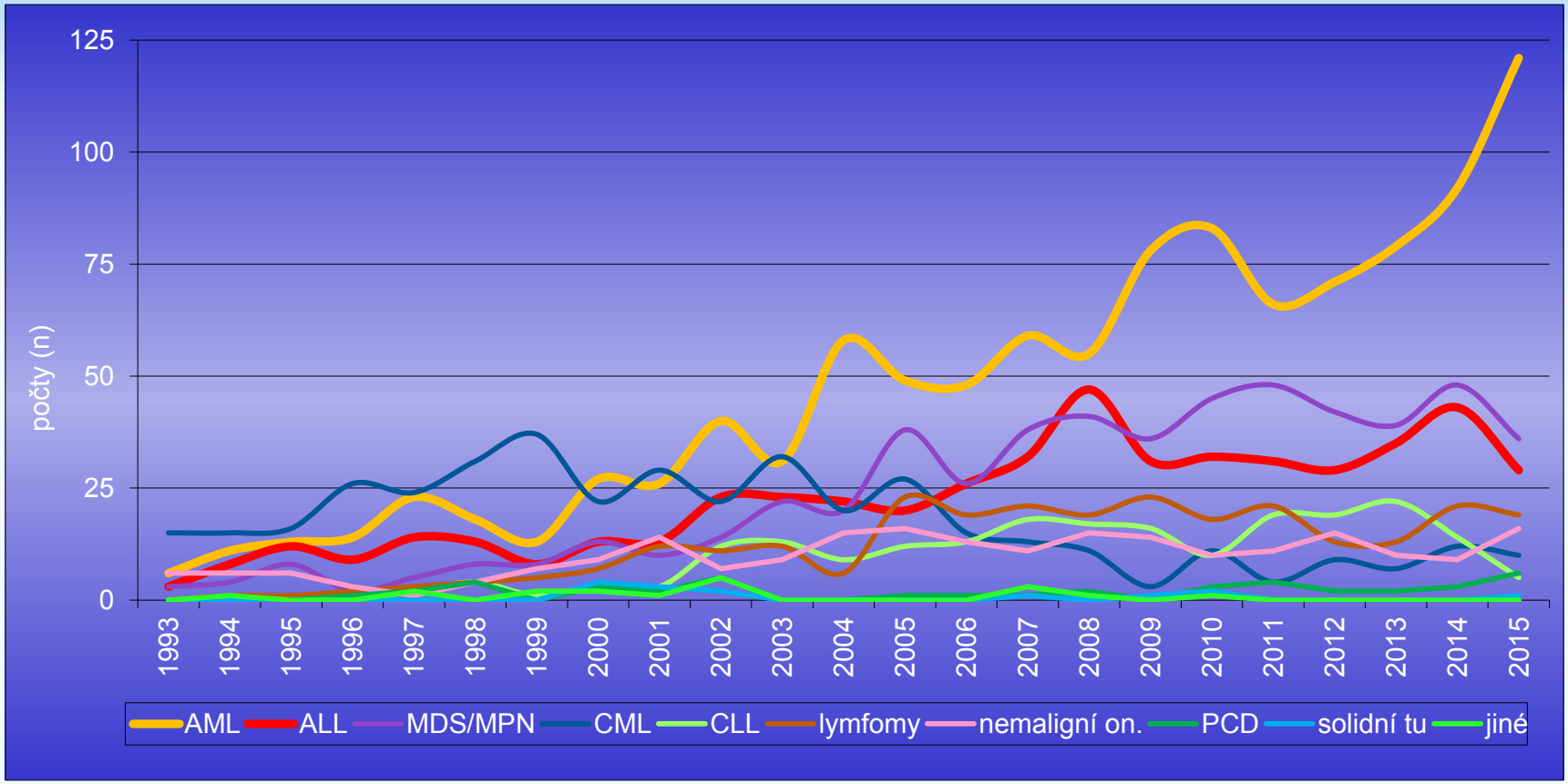
Survey on Transplant Activity, EBMT

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



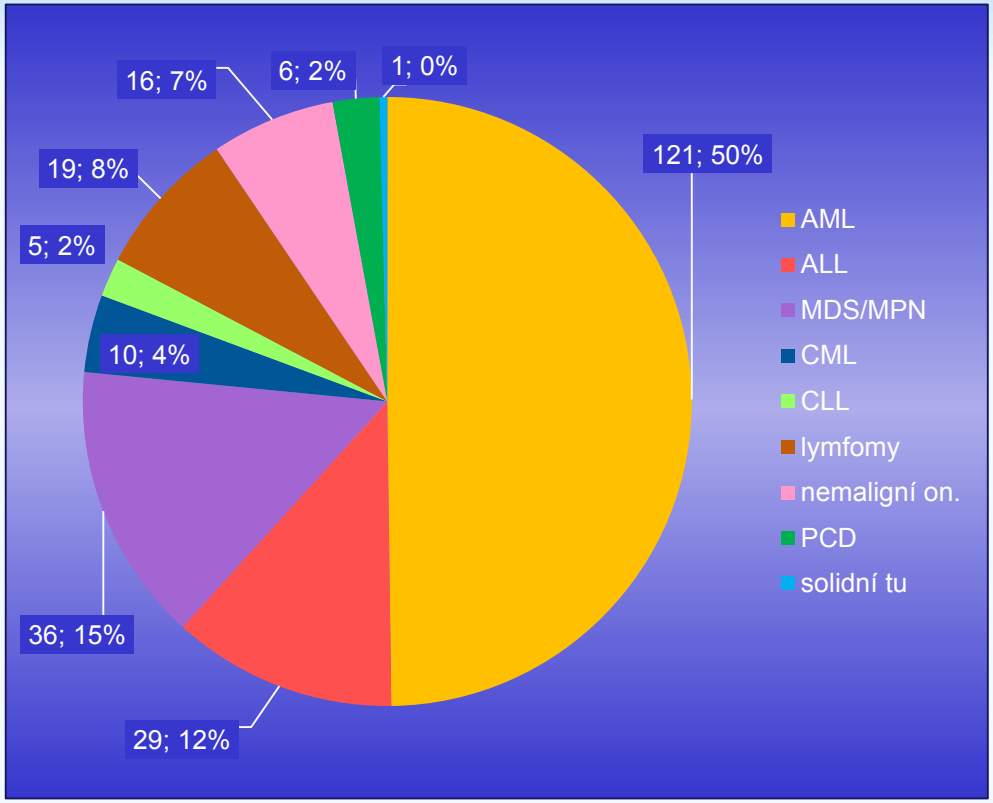
Survey on Transplant Activity, EBMT

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



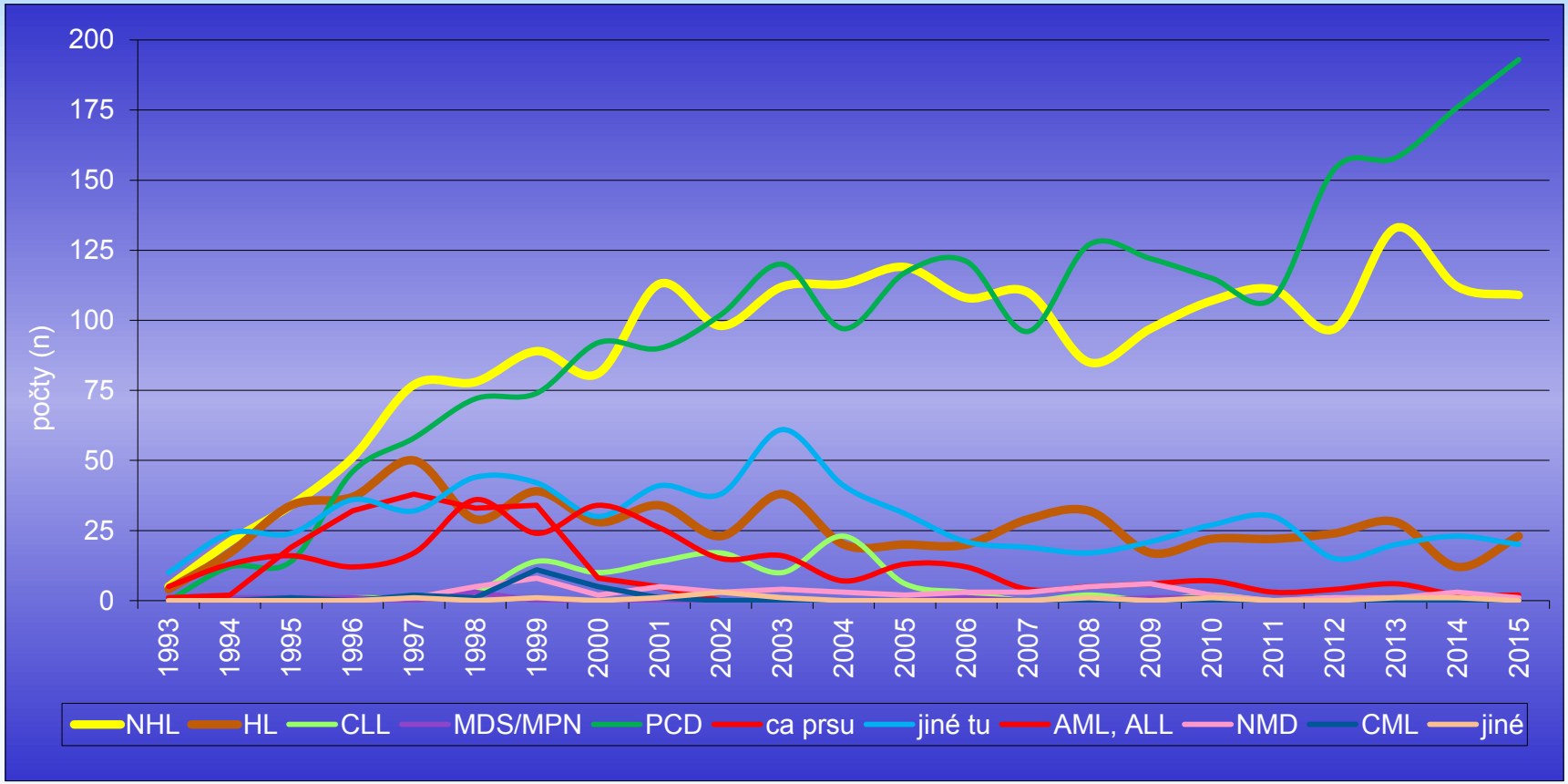
Survey on Transplant Activity, EBMT

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



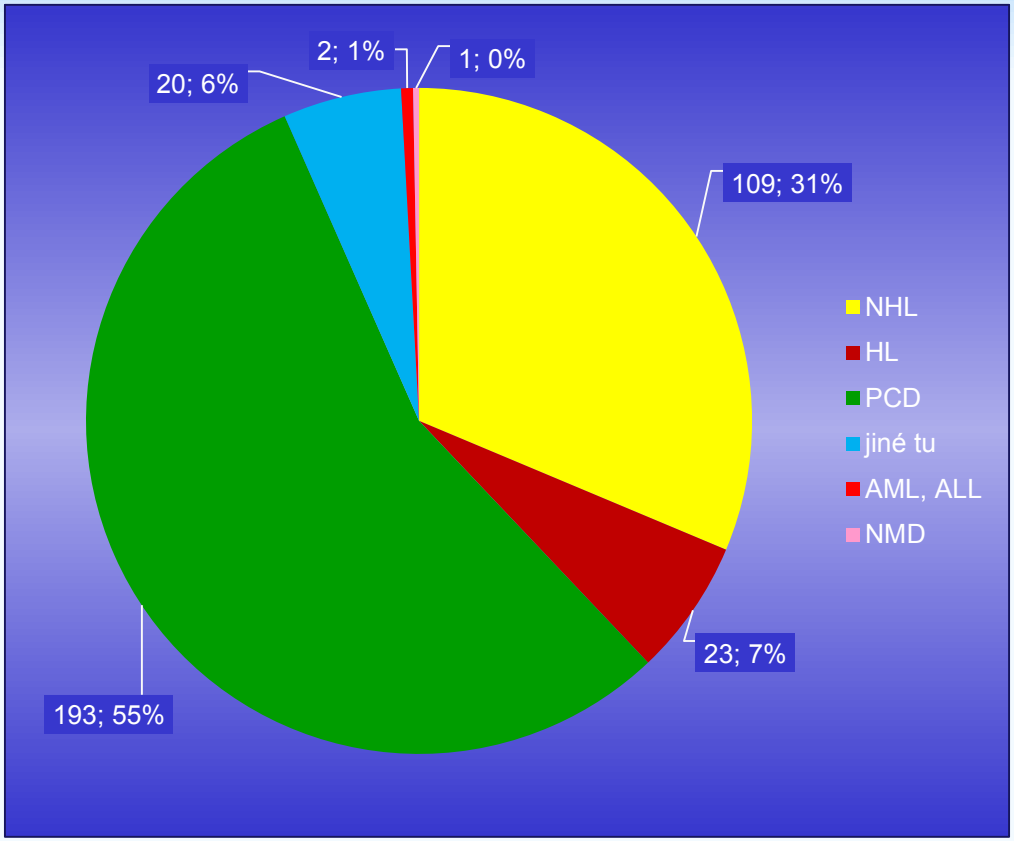
Survey on Transplant Activity, EBMT

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



Survey on Transplant Activity, EBMT

Main indications for autologous HCT in Czech Republic in 2015: PCD, NHL, HL – myeloma and lymphomas



Survey on Transplant Activity, EBMT

Hematopoietic stem cell transplantations at our department (IHOK) – summary of activities

- The first HCT was performed in 1993
- 25 years of IHOK hematopoietic stem cell transplant program in 2018

- **In summary, 2418 hematopoietic stem cell transplantations were performed in period 1993- 10/2018**
  Overall number of autologous transplantations: 1795
- Overall number of allogeneic transplantations: 623 *(relative donor in 295 patients, unrelated donor in 328 patients)*
- Numbers of HCTs per year at IHOK:
  (median for last 5 years)
  85 autologous transplantations, 35 allogeneic transplantations

Conclusions - I

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

Conclusions - II

- **Main indications for autologous HCT**: multiple myeloma and lymphomas, **86%** of all indications.
- **Main indications for allogeneic HCT**: 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-HCT against the risk factors and course of disease in each individual patient.
- HCT still remain in present time (year 2019) treatment method of choice in many hematological and non-hematological disorders at suitable patients.