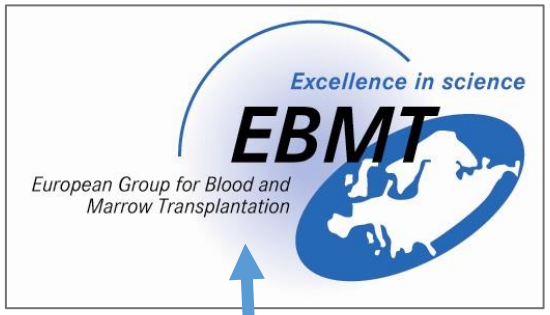
Ass. Prof. d-r Aleksandra Pivkova Veljanovska
University Clinic for Hematology, Skopje

19 YEARS OF STEM CELL TRANSPLANTATION IN REPUBLIC OF NORTH MACEDONIA: EXPERIENCE AND RESULTS

First allogeneic and autologous stem cell transplant in AML and CML patient



Regenerative medicine in intracoronary administration of BM derived stem cells 36 days post AMI

First hploidenthical transplants in AML and CML

First unrelated donor transplant in AML patient

2000 **2002** **2003** **2004** **2007** **2009** **2012** **2018** **2019**

Cryopreservation of stem cells

First pediatric transplant (autologous)

First allogeneic sibling pediatric transplant in SAA

First haploidenthical transplants with PTCY

First unrelated transplant in pediatric setting

The Beginning

25.09.2000 – first transplant procedures for two patients with AML (autologous and allogeneic sibling transplantation) with bone marrow as stem cell source

Be someone's marrow

The Collaboration

During 2000-2003 collaboration with G. Papanikolau Hospital , Thessaloniki, Greece

Total number of stem cell transplants 2000-2019

520
transplants

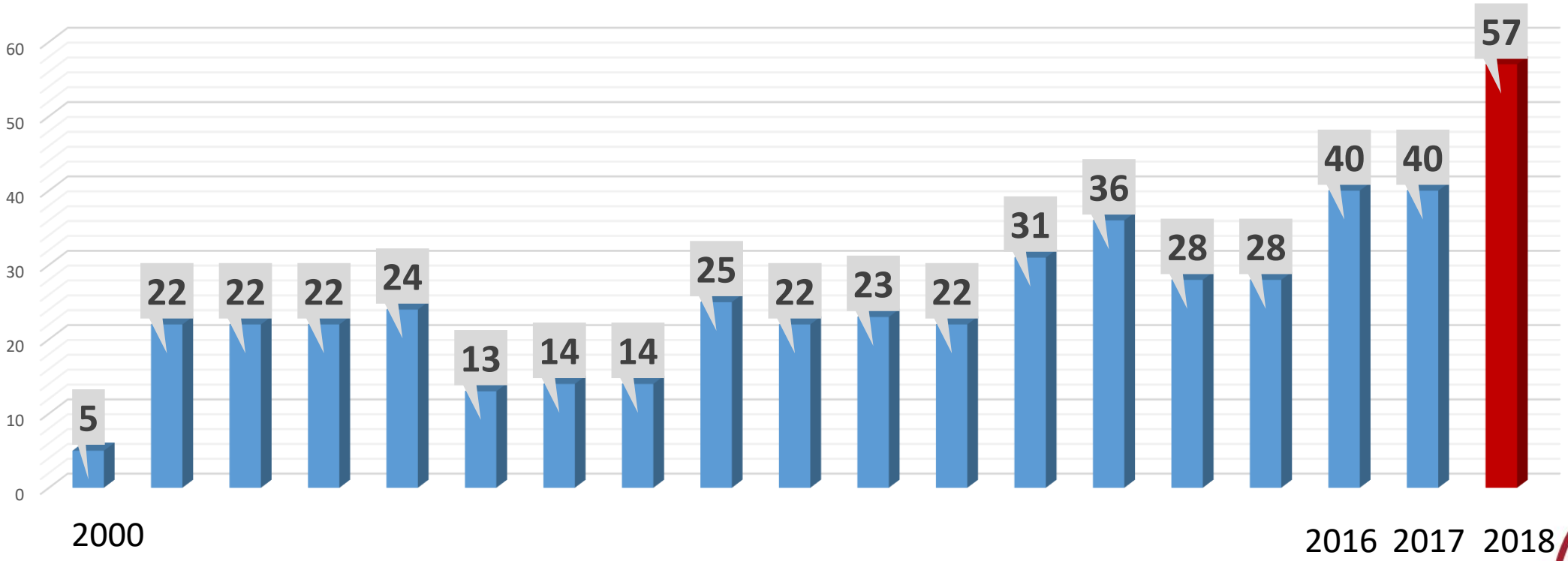
400 autologous
- 376 PBSC
- 24 BM

120 allogeneic
- 116 PBSC
- 4 BM

Excellence in science
EBMT
European Group for Blood and Marrow Transplantation

500
Be someone's marrow

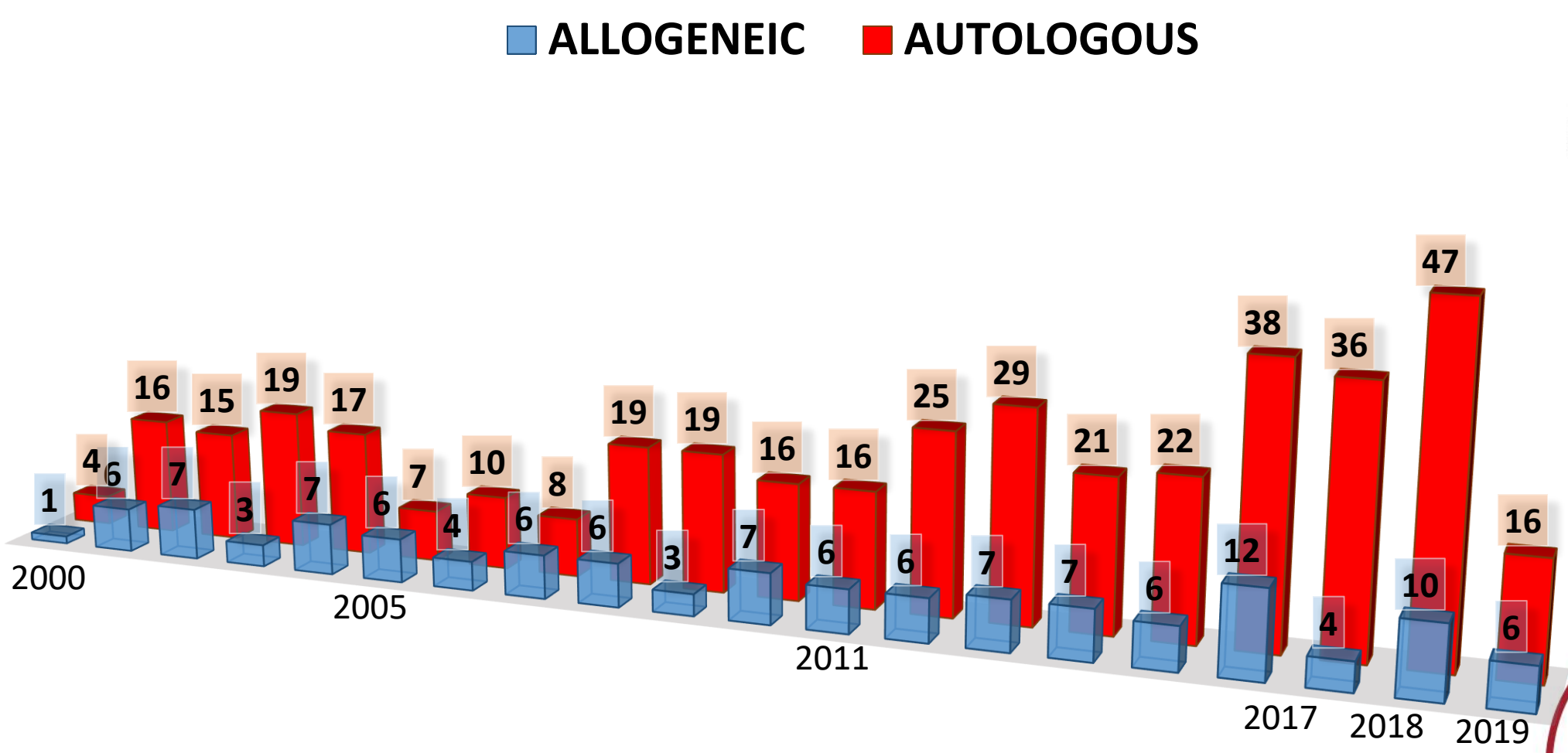
Number of transplants by year
2000-2018



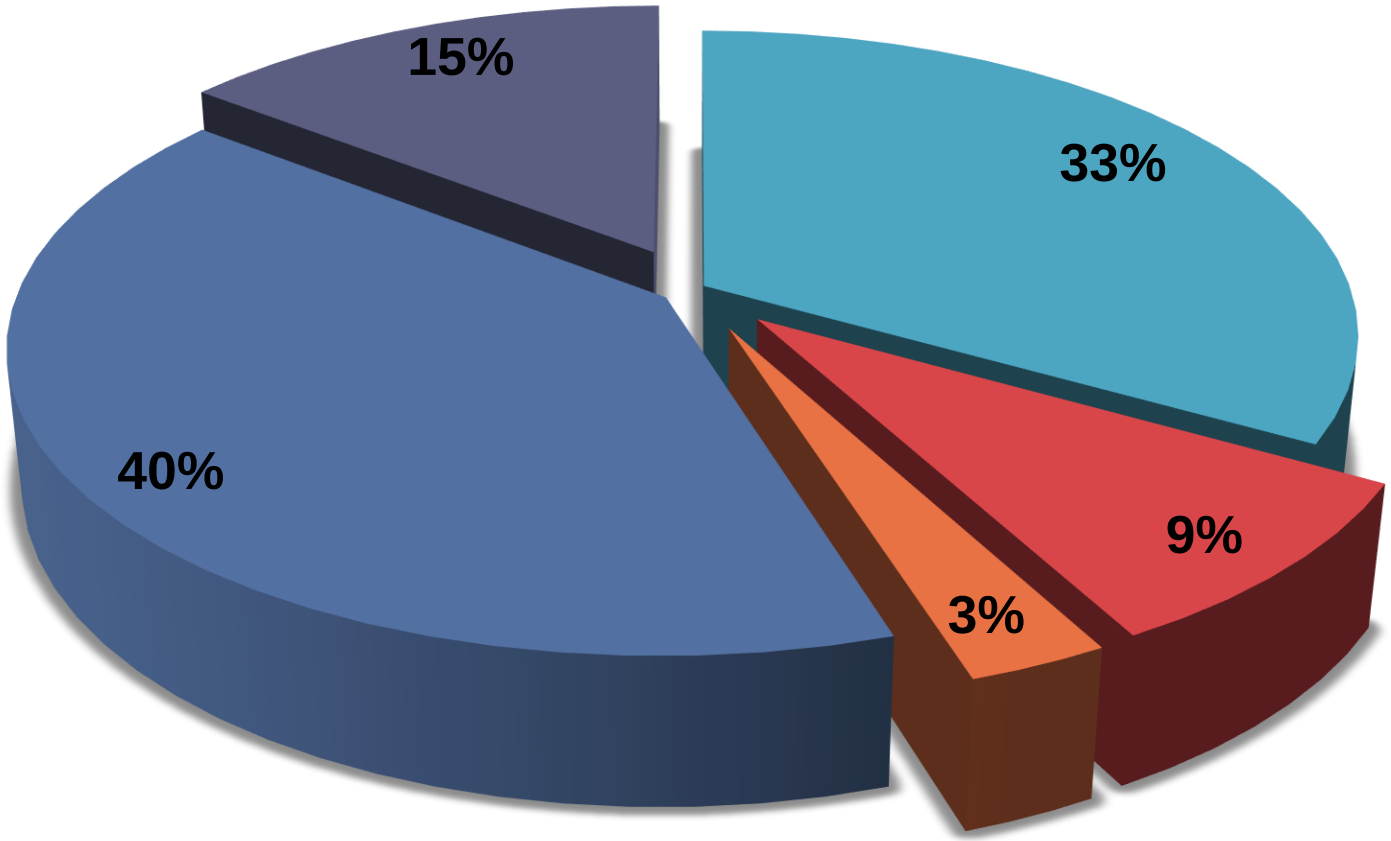
КЛИНИКА ЗА ХЕМАТОЛОГИЈА
УНИВЕРЗИТЕТСКА КЛИНИКА

500
Be someone's marrow

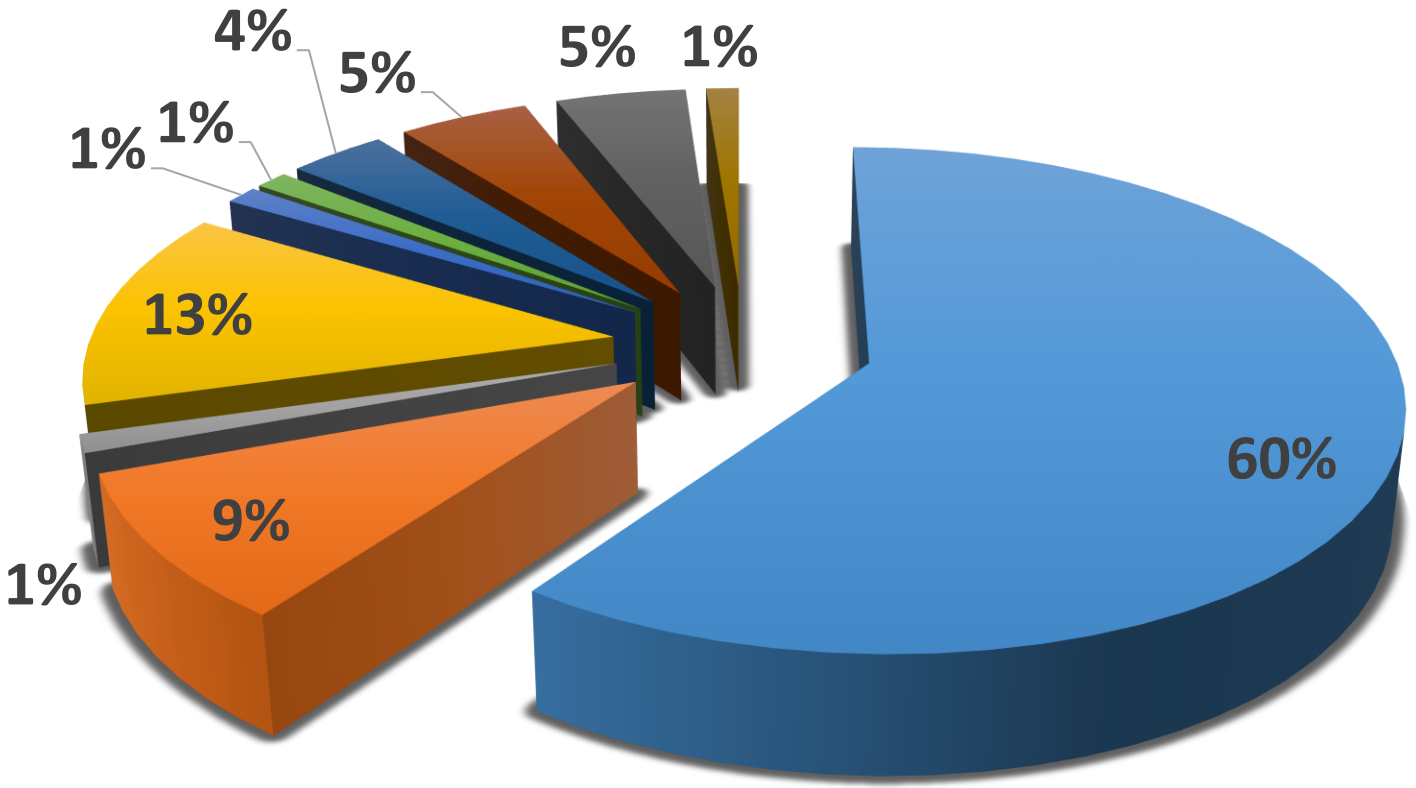
Number of transplants by transplant type 2000-2018



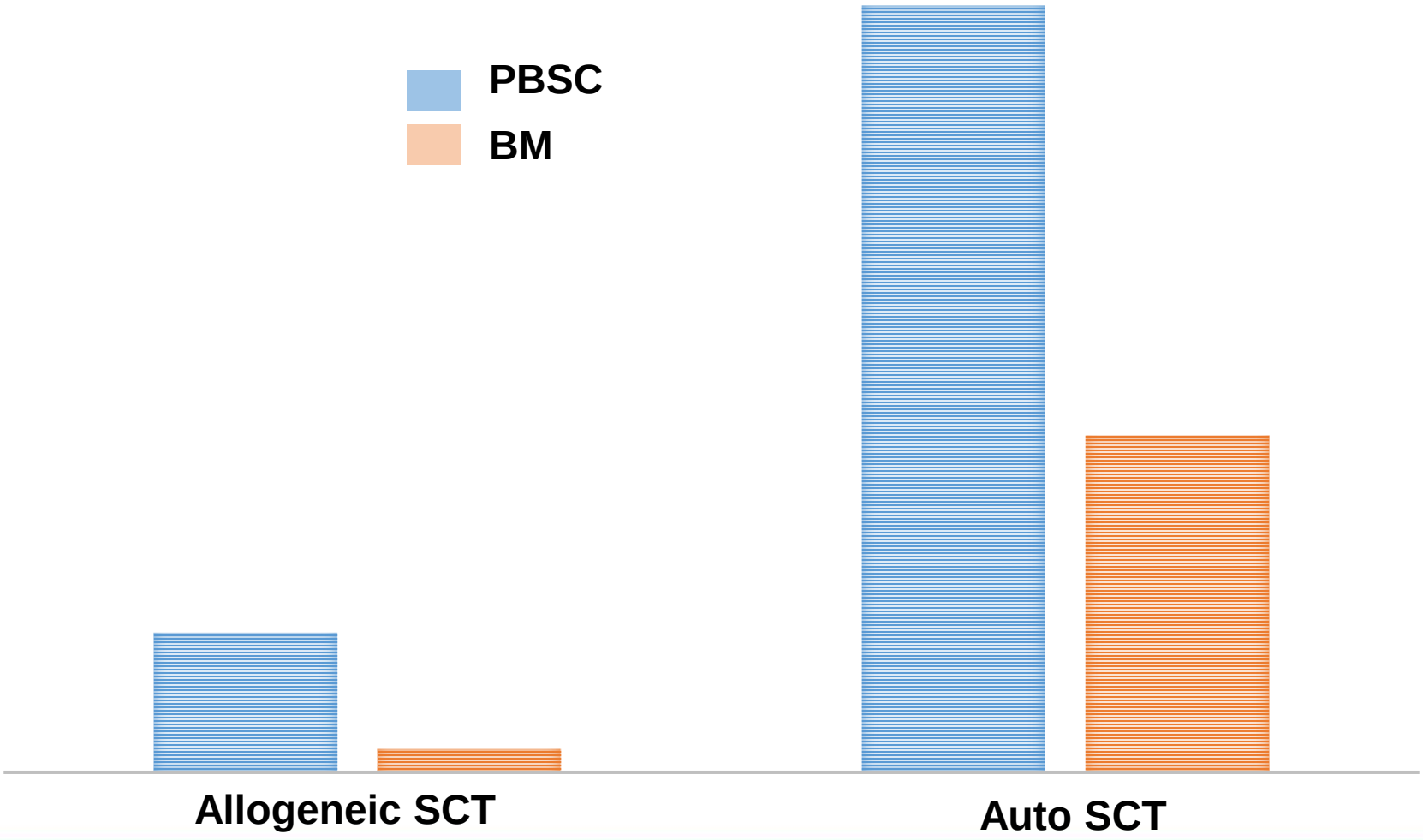
Autologous transplants according to diagnosis



Allogeneic transplants according to diagnosis

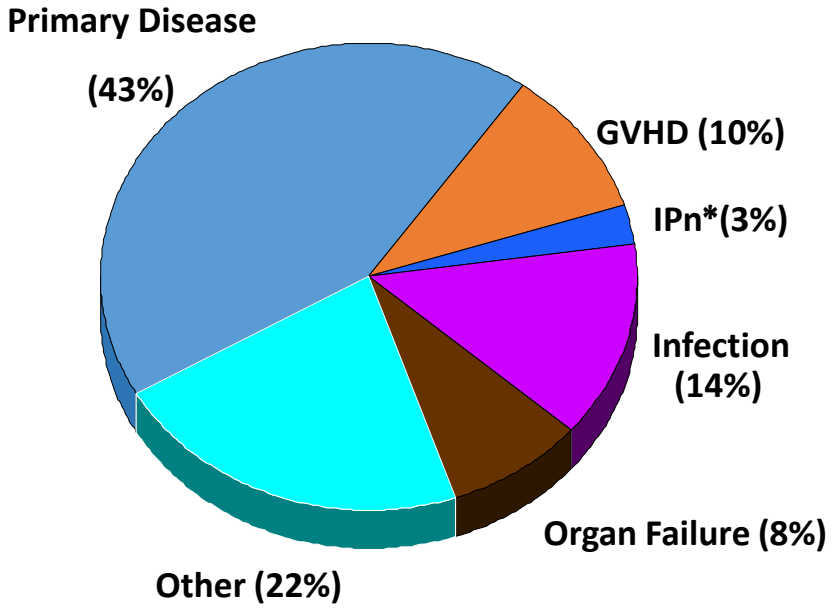


Source of stem cells during allogeneic and autologous transplantation

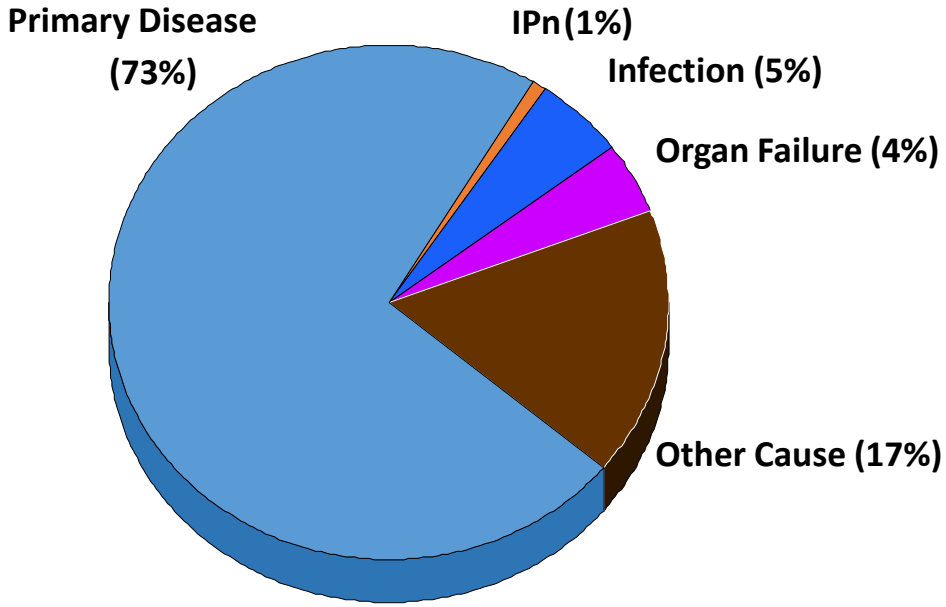


Causes of death after SCT
2000-2018

Allogeneic SCT



Autologous SCT



Mobilisation and cryopreservation of PBSC with 10-20% DMSO at University Clinic of Hematology during 2000/2001 (first procedures)

Initials	Dg	Mobilisation	Apheresis	MNC/10 (8)kg	CD34+/10(6)kg	viability
Z.A	CLL	G-CSF+Cy	1	1.2	1.2	40%
J.B	Pre-B ALL	G-CSF+hemo	2	1.8	1.8	30%
A.T	Pre B ALL	G-CSF+hemo	3 1	3.2 2.5	2.5	40% >80%
K.D	M.M	G-CSF+Cy	2	4.4	16	>80%
M.K	Pre B ALL	G-CSF+hemo	1	2.6	2.1	>80%
S.A	DLBCL	G-CSF	1	3.6	2.9	>80%

Characteristics of 540 grafts of cryopreserved autologous PBSC

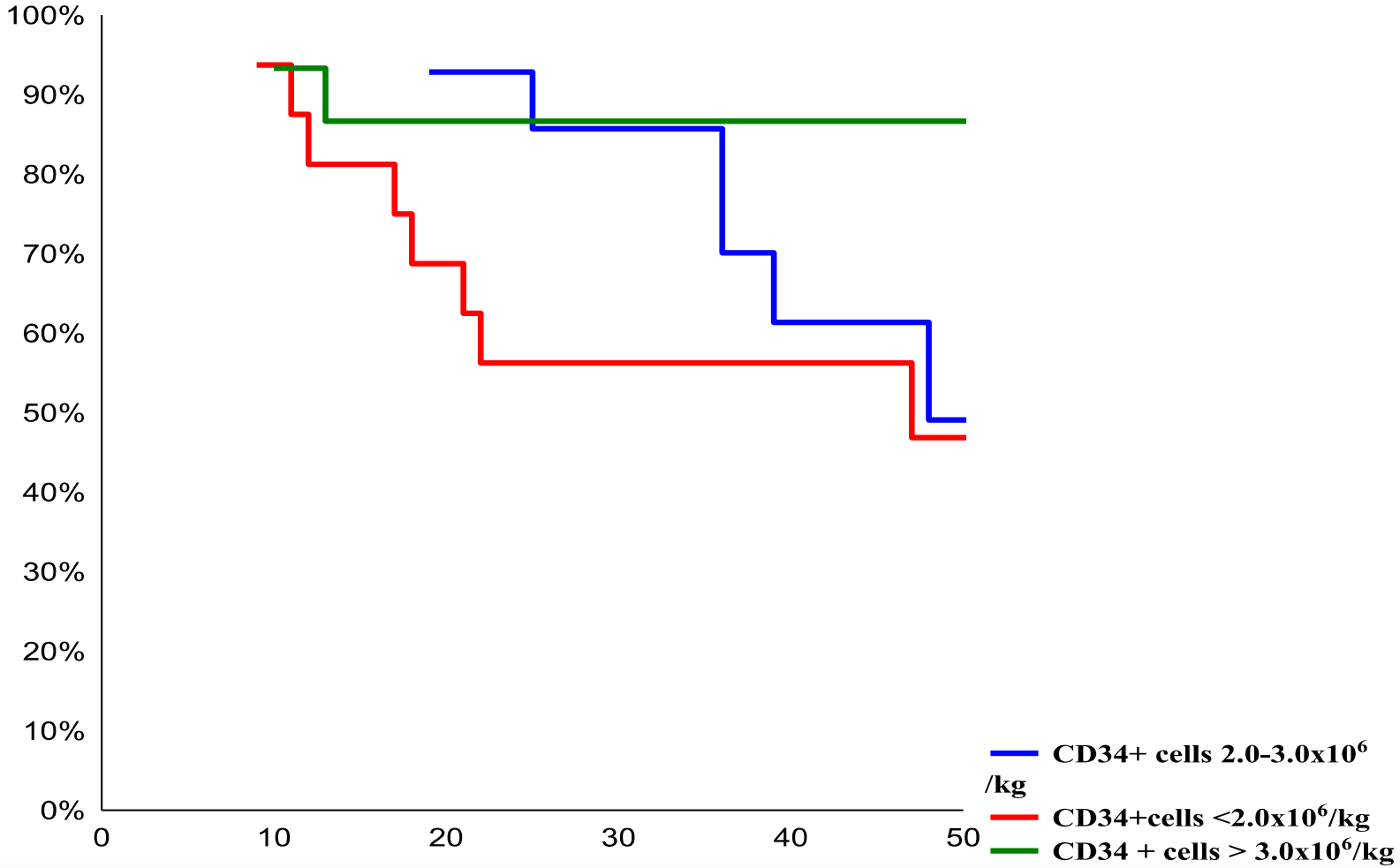
Vaiable	Mean	Interval	Mediana	S.D
Vol(ml) before freezing	149.62	60-1000	126.00	114.77
Vol (ml) after freezing.	327.51	50-2232	320.00	196.56
WBC before cryopreservation	170.67	19-400	165.00	58.06
WBC after cryopreservation	154.45	50-300	151.00	42.53
Days in liquid nitrogen	33.89	2-330	25.00	35.91
Hospital stay	13.22	7-34	8.00	7.69
Apheresis procedures	2.15	1-6	2.00	0.68
Number of cryobags	4.41	2-8	4.00	1.98
MNCx10^8/kg	2.95	0.6-7.5	2.70	1.21
CD34+x10^6/kg	2.34	0.1-5.7	2.00	1.09

Be someone's marrow

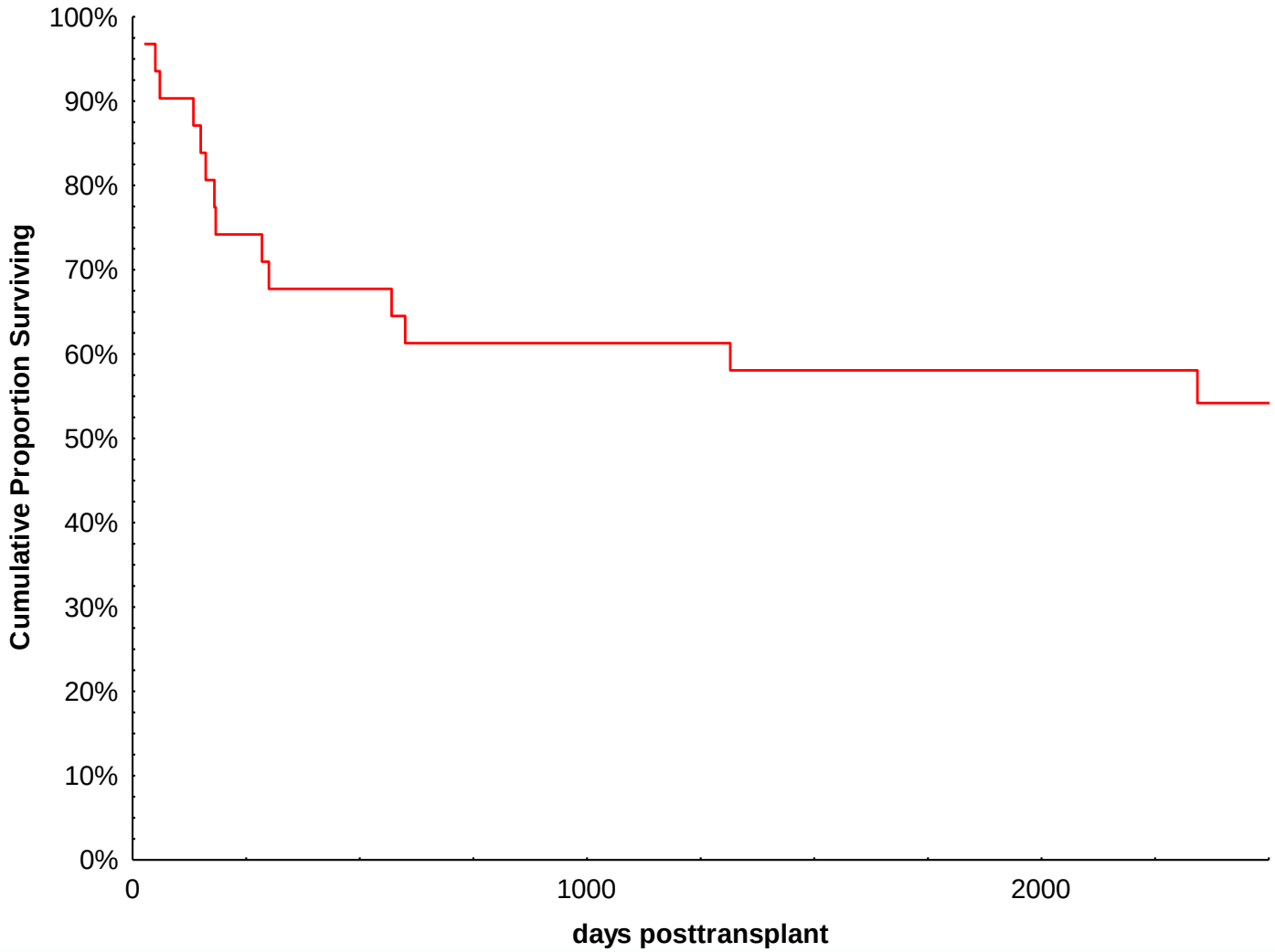
BM vs PBSC in autologous transplantations

variable	PBSC	BM	p
Weight (kg)	12779.50	1585.50	0.006
Age	12549.50	1815.50	0.085
Months to transplant	12610.00	1586.00	0.007
MNCx10^{8}/kg	11527.50	2837.50	0.006
CD34+x10^{6}/kg	13838.50	526.50	0.000
Erytrhocyte transfusion	11608.50	2756.50	0.017
Plt transfusions	12078.50	2286.50	0.738
Hospital stay	11700.50	2664.50	0.047
High teperature	11818.50	2546.50	0.142
Engraftment	11210.00	3155.00	0.000
Oral mucositis	12497.00	1868.00	0.136
Parenteral antibiotic	11324.00	3041.00	0.000
Parenteral antimicotic	11340.00	3025.00	0.000
Microbiological isolates	11514.50	2850.50	0.005

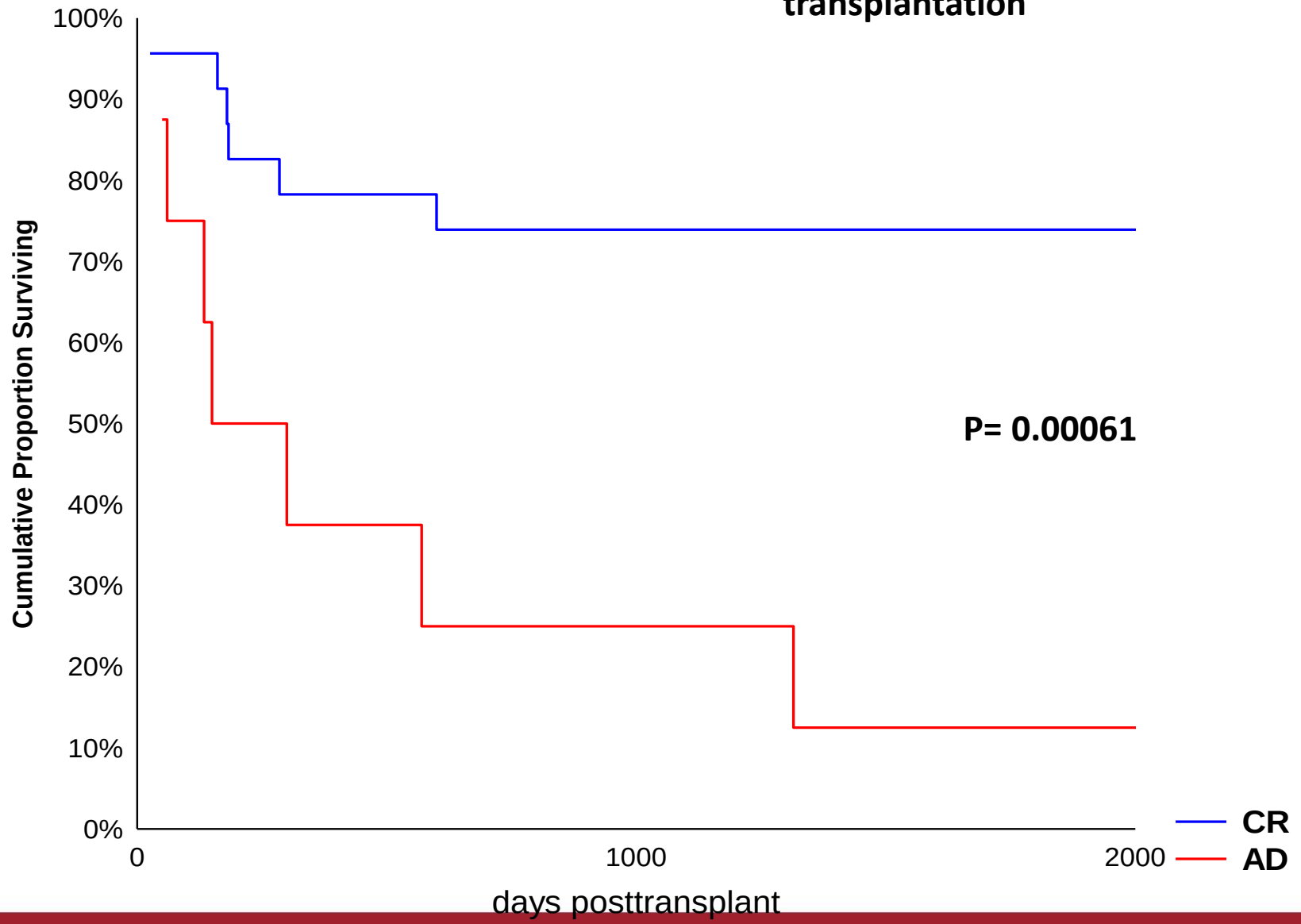
Survival according to number of CD34+ cells in myeloma patients during autologous transplantation



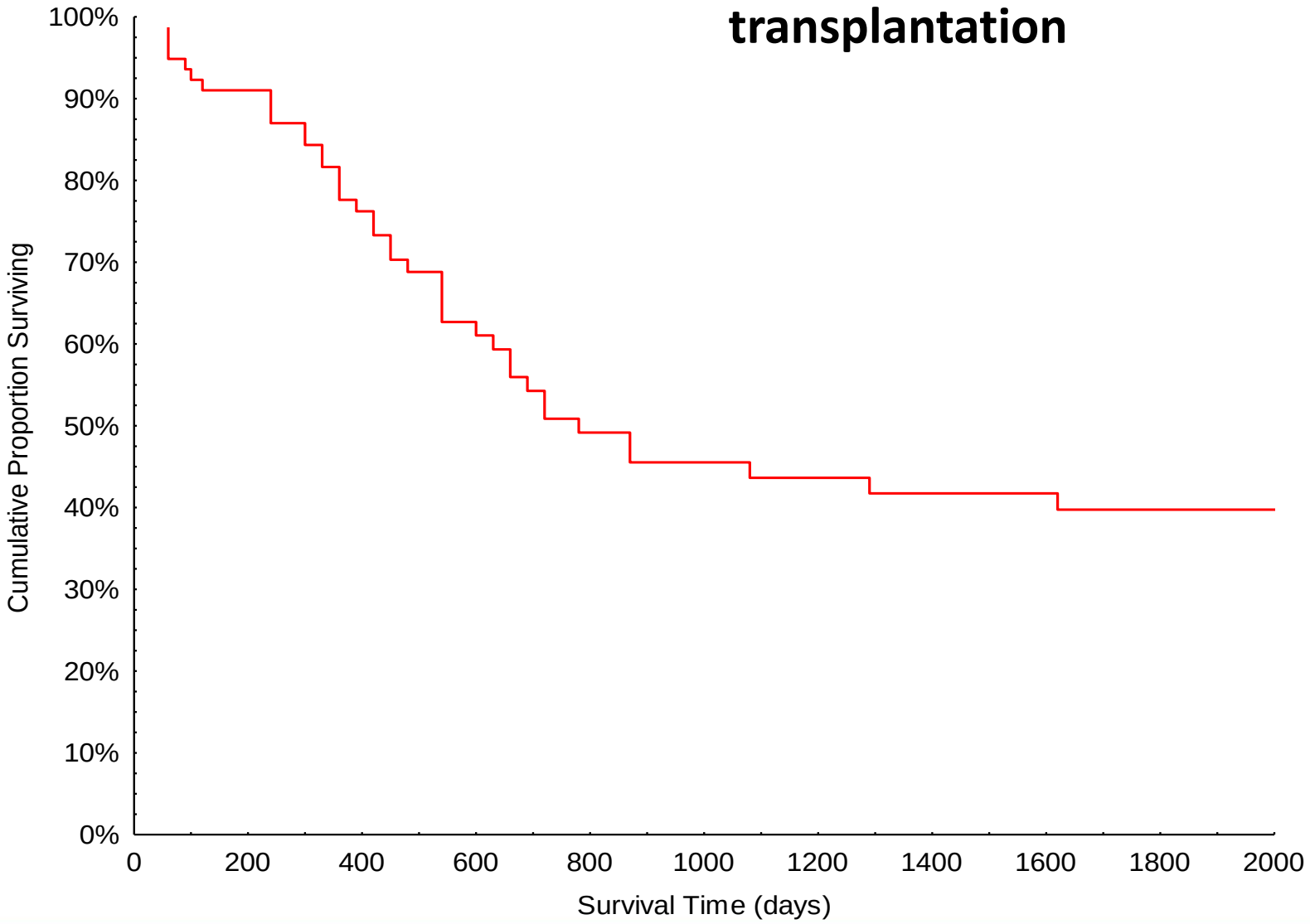
5 years OS in AML in CR1 treated with allogeneic sibling transplantation



5 years OS in AML according to disease status before allogeneic sibling transplantation



5 years OS in AML in CR1 treated with autologous transplantation



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Combined delivery approach of bone marrow mononuclear stem cells early and late after myocardial infarction: the MYSTAR prospective, randomized study

Mariann Gyöngyösi[1*], Irene Lang[1], Markus Dettke[2], Gilbert Beran[1], Senta Graf[1], Heinz Sochor[1], Noémi Nyolczas[3], Silvia Charwat[1], Rayyan Hemetsberger[1], Günter Christ[1], István Édes[4], László Balogh[4], Korff Thomas Krause[5], Kai Jaquet[5], Karl-Heinz Kuck[5], Imre Benedek[6], Theodora Hintea[6], Róbert Kiss[3], István Préda[3], Vladimir Kotevski[7], Hristo Pejkov[7], Sholeh Zamini[1], Aliasghar Khorsand[1], Gottfried Sodeck[8], Alexandra Kaider[9], Gerald Maurer[1] and Dietmar Glogar[1]

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AHJ
American Heart Journal

Volume 153, Issue 2, Pages 212.e1-212.e7 (February 2007)

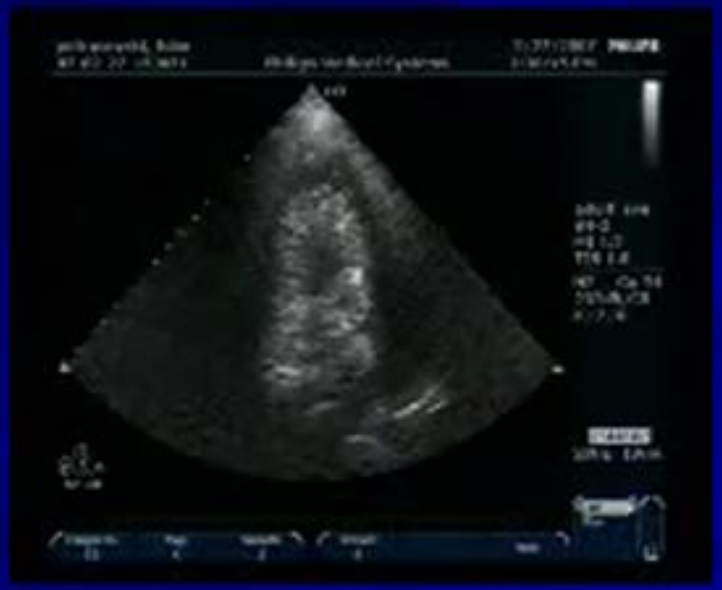
previo

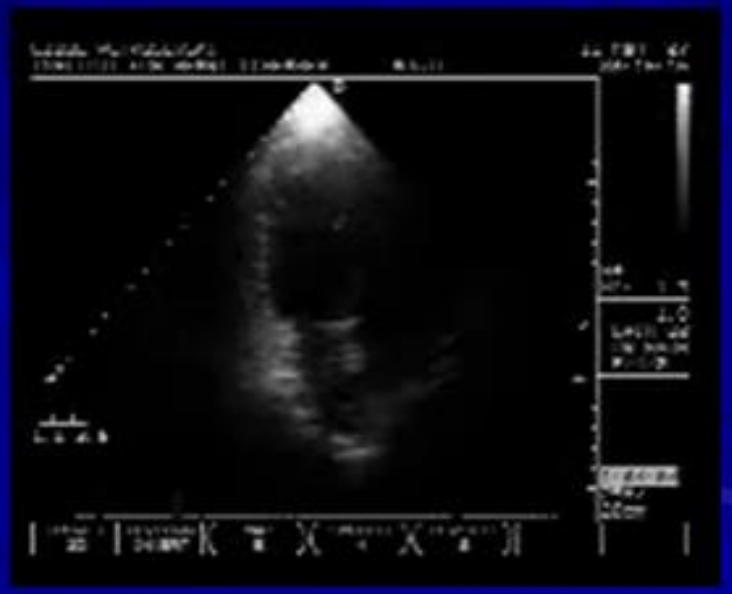
Design and rationale for the Myocardial Stem Cell Administration After Acute Myocardial Infarction (MYSTAR) Study: A multicenter, prospective, randomized, single-blind trial comparing early and late intracoronary or combined (percutaneous intramyocardial and intracoronary) administration of nonselected autologous bone marrow cells to patients after acute myocardial infarction

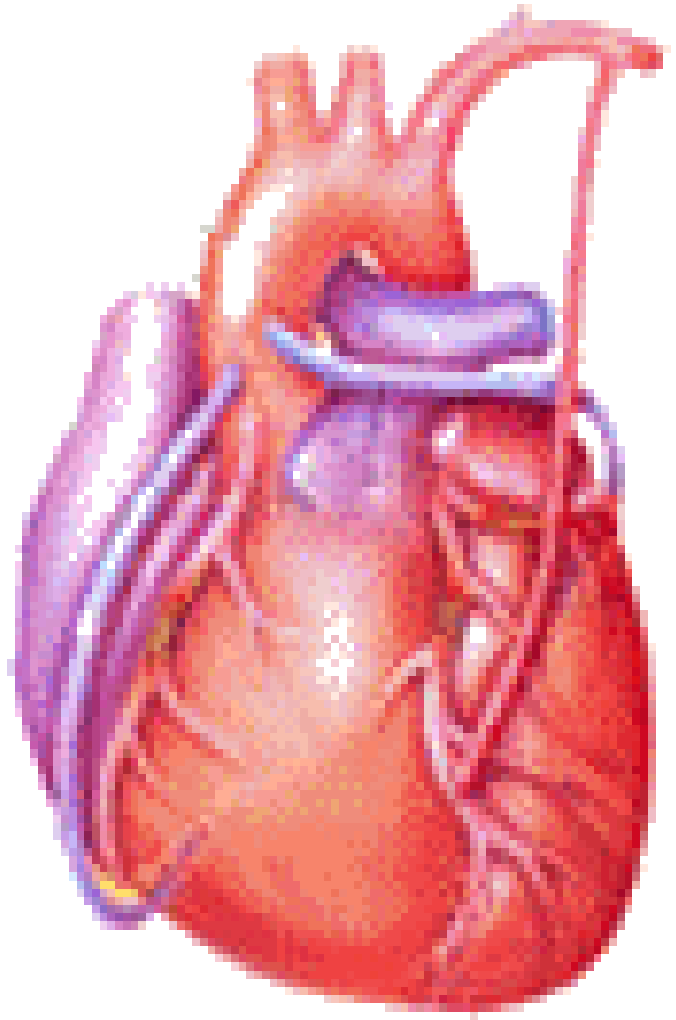
Noémi Nyolczas, MD, FESC[ab], Mariann Gyöngyösi, MD[a], Gilbert Beran, MD[a], Markus Dettke, MD[c], Senta Graf, MD[a], Heinz Sochor, MD, FESC[a], Günther Christ, MD[a], István Édes, MD, PhD, FESC[d], László Balogh, MD[d], Korff T. Krause, MD[e], Kai Jaquet, MD[e], Karl-Heinz Kuck, MD[e], Imre Benedek, MD[f], Theodora Hintea, MD[f], Róbert Kiss, MD, PhD[b], István Préda, MD, PhD, FESC[b], Vladimir Kotevski, MD, FESC[a], Hristo Pejkov, MD[a], Darius Dudek, MD[h], Grzegorz Heba, MD[h], Christer Sylven, MD[i], Silvia Charwat, MD[a], Ronaldo Jacob, MD[a], Gerald Maurer, MD, FACC[a], Irene Lang, MD[a], Dietmar Glogar, MD, FESC[a]

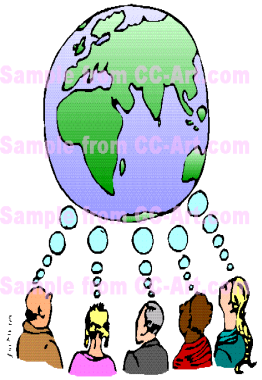
Echocardiographic assessment also showed improvement of global left ventricular function 3 months after the infarction

LVEF = 44% (pt 1) and 46% (pt 2)









785 patients screened

68 excluded for participation in another trial
494 excluded LVEF >45 %
141 refused to participate

82 patients provided written informed consent and randomized

Early group (*n*=41)

Late group (*n*=41)

2 patients crossed over to early group for logistic reasons

5 patients withdrew consent (excluded)

5 patients withdrew consent (excluded)

6 patients spontaneous improvement of LVEF to >45% (excluded)

2 patients spontaneous improvement of LVEF to >45% (excluded)

2 patients excluded for complications (left ventricular thrombus, severe allergy)

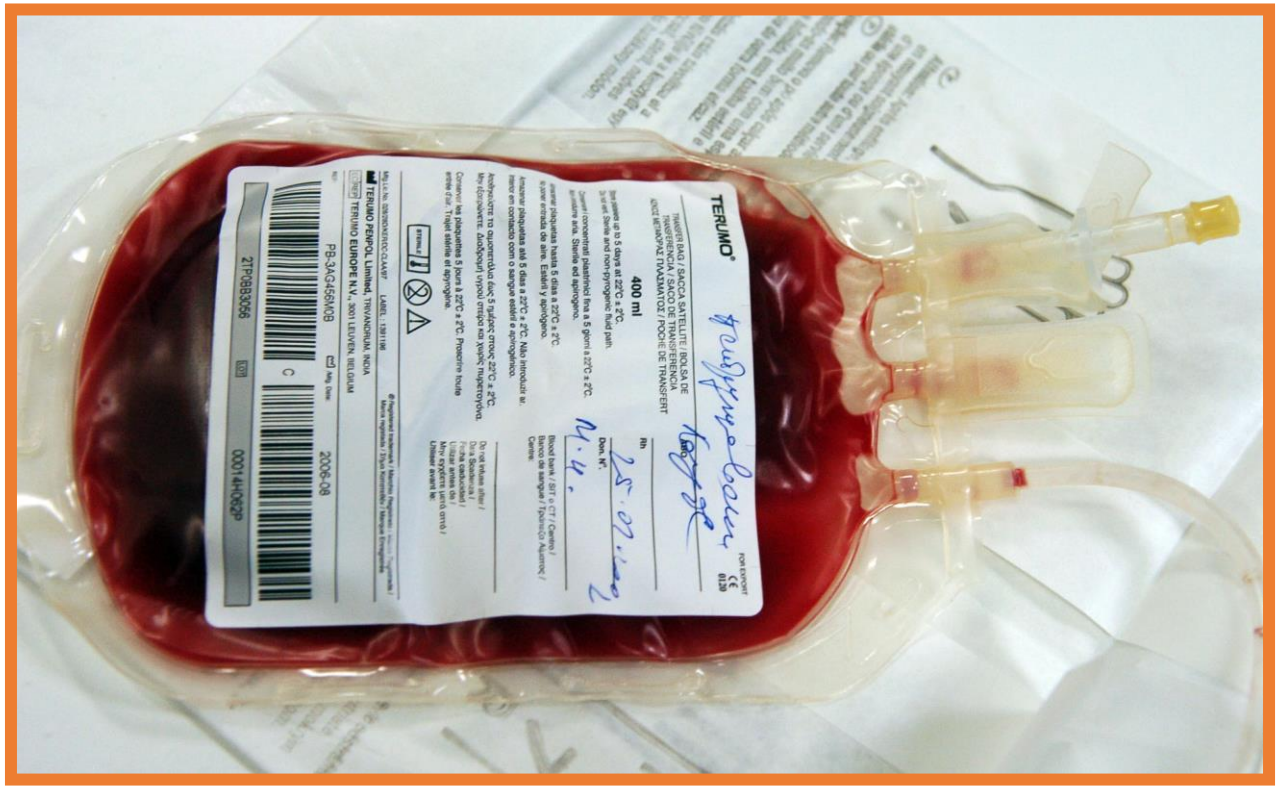
2 patients excluded for complications (left ventricular thrombus, aortic dissection)

30 patients underwent stem cell therapy and included in the analysis

30 patients underwent stem cell therapy and included in the analysis

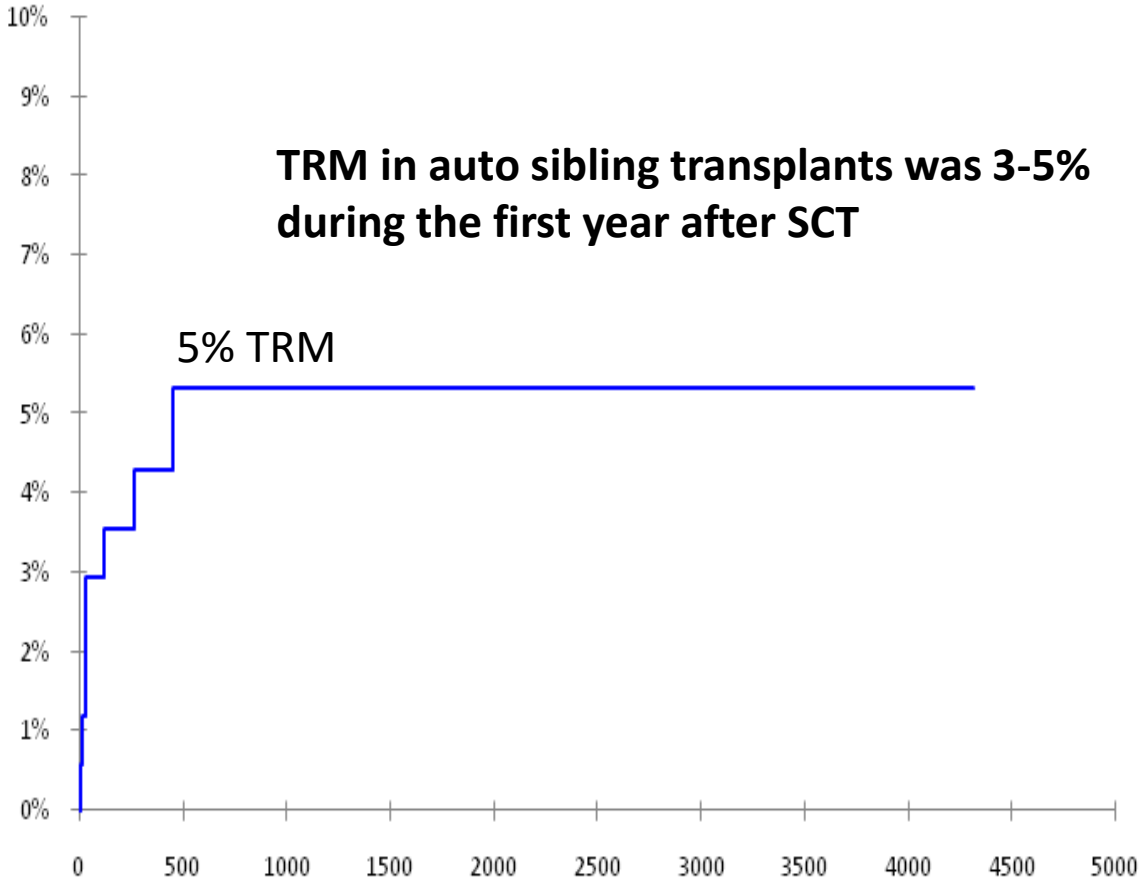
Intracoronary aplication

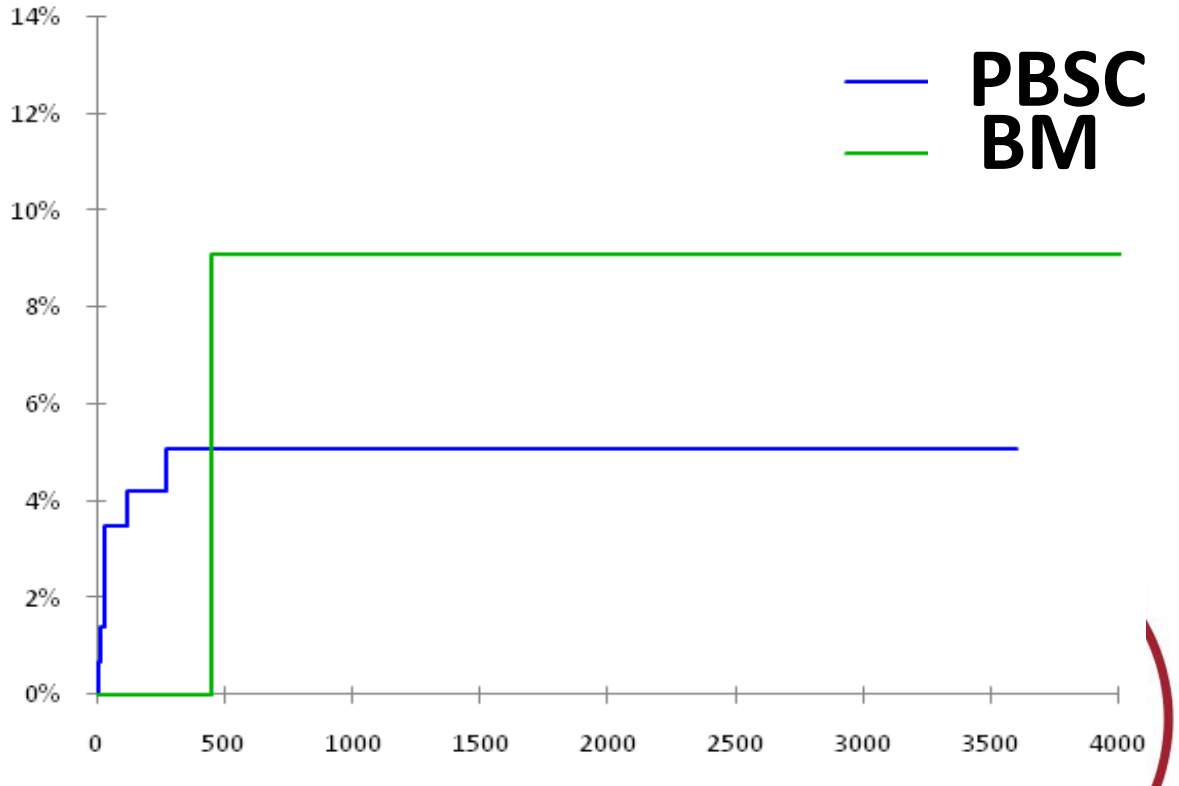
Buffy coat: 69ml;
Mononuclear cells = $3.9x10^8$/kg
CD34+cells = $1,2x10^6$



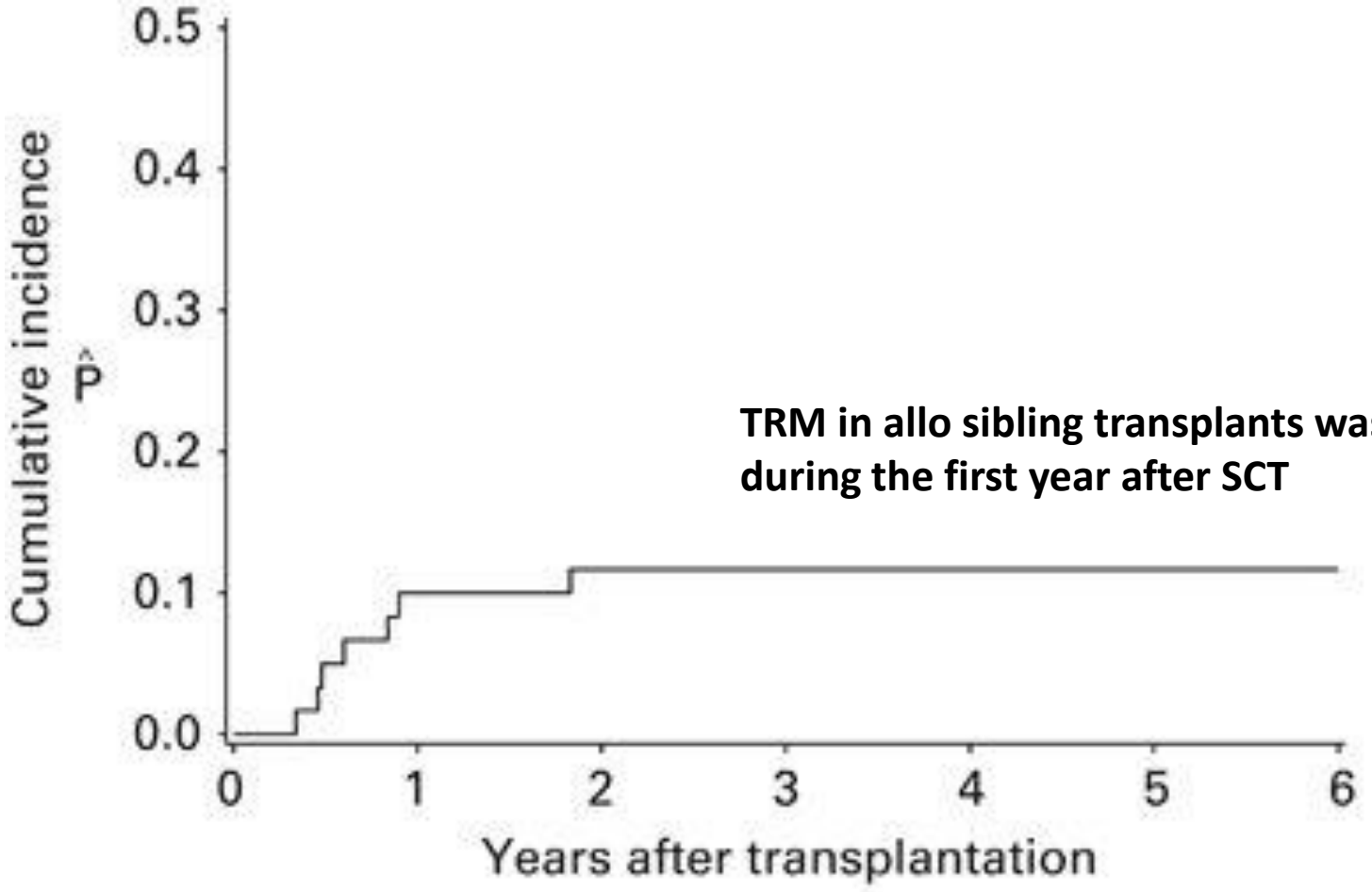
TRM in autologous transplantation (2000-2018)

TRM in auto sibling transplants was 3-5% during the first year after SCT



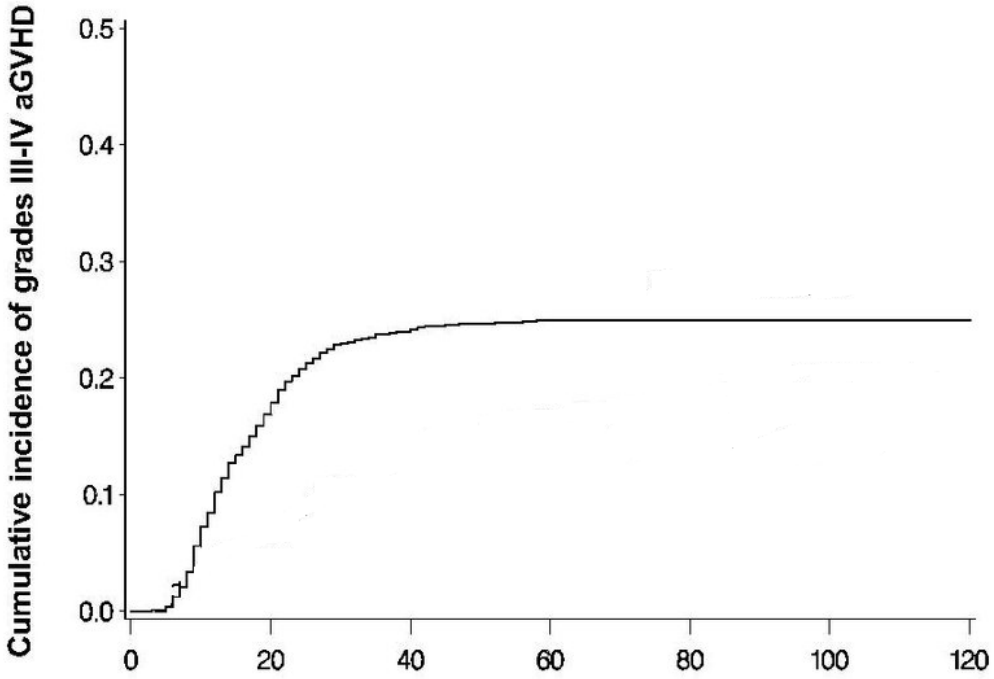


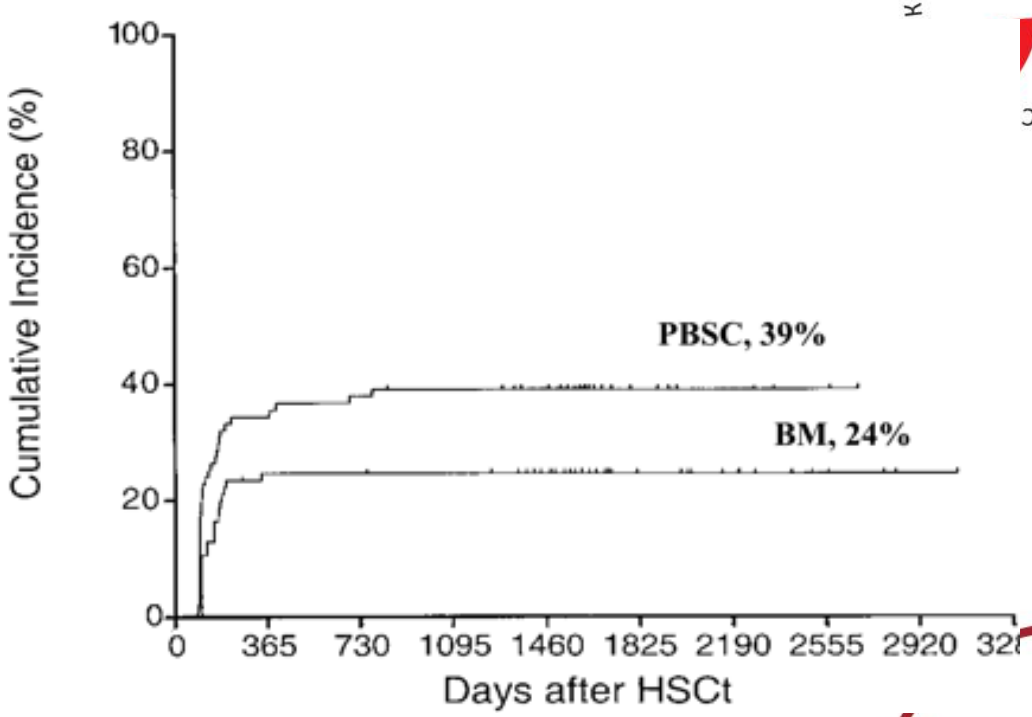
TRM in allogeneic transplantation in AML wity BuCy conditioning (2000-2018)



TRM in allo sibling transplants was 10% during the first year after SCT

Incidence of GVHD (2000-2018)





MUD

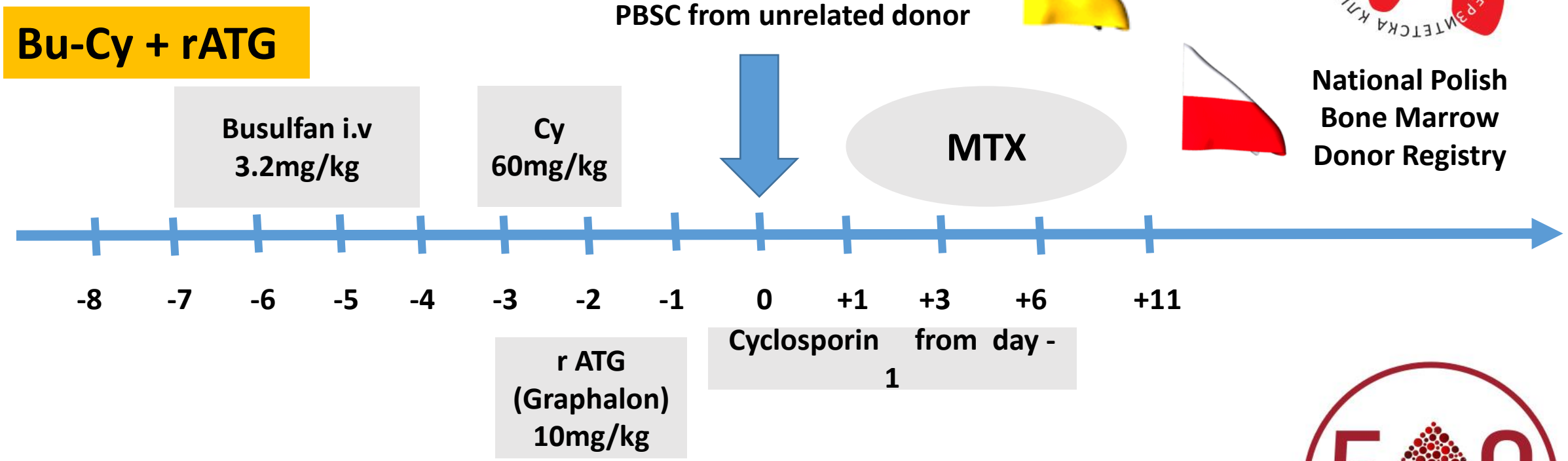
3 patients (2AML, 1 SAA with monosomy 7)

ZKRD

National Polish Bone Marrow Donor Registry

Bu-Cy + rATG

PBSC from unrelated donor



Be someone's marrow

Haploidenthical transplantations with PTCY

3 patients with no family (10/10) and no unrelated donor 10/10 in the WMDA and high risk disease (1AML, 1 MDS, 1 ALL)

TBF regimen (2 pts)
PBSC as source of SC

Thiotepa 5mg/kg i.v. x2 (Day -6,-5)
Fludarabin 50 mg/m^2 i.v. x 3 (Day -4,-3,-2)
Busulfan 3,2 mg/kg i.v. x3 (-4,-3,-2)
Cyclophosphamide 50mg/kg Day +3 und +4

Day	Conditioning			CSA	MMF	PTCY
-7						
-6	Thio					
-5	Thio					
-4		Flu	Bu			
-3		Flu	Bu			
-2		Flu	Bu			
-1				X		
0	PBSC			X	X	
+1				X	X	
+2				X	X	
+3				X	X	X
+4				X	X	X

Paediatric transplant data in Republic of North Macedonia

Year	Age prior SCT	Diagnosis	Type of transplant	Status after SCT
2013	5 years	MDS	Allo sibling BM	Death GVHD + 4 months
2009	10 years	AA	Allo sibling PBSC	Alive in CR
2012	10 years	ALL	Autologous BM	Alive in CR
2006	8 years	Juing Sarcoma	Autologous PBSC	Death in Relapse +9 months
2004	7 years	NHL	Autologous PBSC	Death in Relapse +2 months
2014 2019	3 years 13 years	Juing Sarcoma AA	Autologous BM MUD	Death with relapse at +6 months Alive + 3 months

Institutions collaborators

Macedonian Bone Marrow Donor Registry (MBMDR)

Institute for immunology and human genetics, Skopje

Institute for transfusion medicine Skopje

University children hospital , Medical faculty, Skopje

Faculty of pharmacy, Skopje

University Clinic for nephrology, Skopje

University Clinic for intensive care and reanimation, Skopje

Institute for microbiology, Medical faculty, Skopje

EBMT CIC 381

EBMT

CIC 0381 : 1 details

Georgievski, Borce Chevreska, Lidija Stojanovski, Zlate Panovska Stavridis, Irina Pivkova, Aleksandra Chadievski, Lazar Trajkovska, Gabriela Bozinovska, Gordana Trajkovska-Ancevska, Zaklina	University Clinic for Haematology BMT Unit Majka Tereza 17 1000 Skopje Macedonia Tel.:389 23110548 Fax:389 23110548 E-mail:georgievskib@yahoo.com

1ST BONE MARROW
TRANSPLANT WORKSHOP
OF REPUBLIC OF NORTH MACEDONIA
FUTURE PERSPECTIVES AND CHALLENGES

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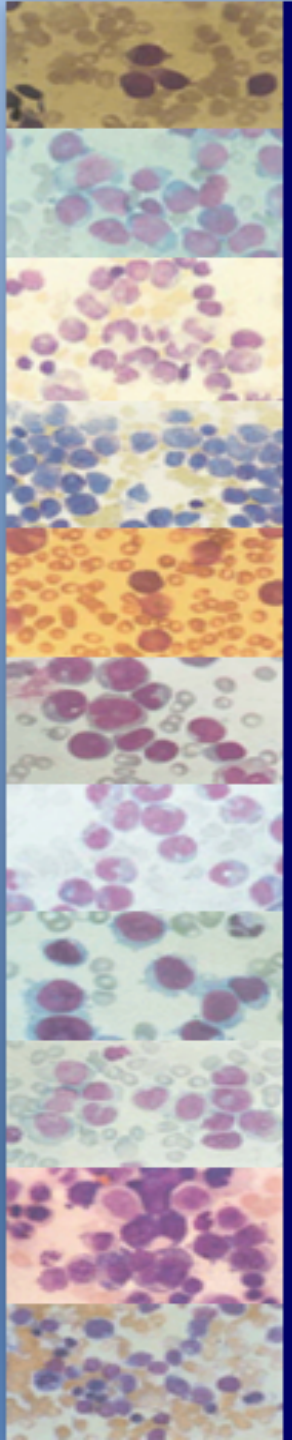
Thank you for your attention



Принципи на лекување на малигни хемопатии

Науч. сор. д-р Александра Пивкова Велјановска

ЈЗУ Универзитетска Клиника за Хематологија

HISTORY OF CANCER

History of Cancer Treatment

- 1550 BC – Egyptian papyrus written by p is the first documentation of cancerImhote
- 460 BC – Hippocrates “names” cancer using the terms carcinos & carcinoma from the Greek word for crab
- 160 AD – Medical conditions were explained by the four humors (blood, black bile, yellow bile, white bile)
- 1775 – British surgeon Percival Pott reported increased scrotum cancer among chimney sweeps
- 1846/1865 – Anesthesia & antiseptic (carbolic acid) discovered
- 1878 – Paul Erlich discovers the principle of what will later be known as chemotherapy
- 1895 – Discovery of x-ray & experiments in treating cancer
- 1937 – National Cancer Institute Act signed by President Roosevelt

History of Cancer Timeline www.cancerfilms.org, The History of Cancer www.cancer.org

History of Cancer Treatment

- 1941 – WWII soldiers exposed to mustard gas found to have toxic changes to bone marrow
  - Led to development of alkylating agents in 1943 at Yale
- 1945 – American Cancer Society founded
- 1948 – Sidney Farber, the “father of chemotherapy” used aminopterin (methotrexate) to treat leukemia patients
- 1952 – Screening being done using pap smear, colonoscopy & mammography
- 1955 – Marlboro Man ad campaign; sales up 5000% over 8 months
- 1956 – First bone marrow transplant done in leukemia patient
- 1957 – US Surgeon General report that cigarette smoking is causative factor in lung cancer
- 1969/1971 – War on Cancer; Nixon signs National Cancer Act
- 1976 – Mammogram Screening Trial results in 20% reduction in deaths for women >55

History of Cancer Timeline www.cancerfilms.org, The History of Cancer www.cancer.org

History of Cancer Treatment

- 1982 – High-dose chemo + autologous HSCT in solid tumors; found to have no benefit by late 1990s
- 1992 – Breast cancer HER-2 gene identified
- 1999 – Imatinib (Gleevec®) trial – launch of targeted therapies
- 2003 – Human Genome Project completed – map of entire sequence of human DNA
- 2006 – Cancer Genome Atlas – gene sequencing of tumors
- 2010 – President's Cancer Panel – increased research
- 2011 – Emphasis on Oncology immunotherapy research (ie: ipilimumab for malignant melanoma)
- 2015 – President Obama's "Moonshot to Cure Cancer" – calls for expanded funding & screening, increased access to clinical trials, insurance coverage of gene testing, decreased prescription drug prices, & sharing of information

History of Cancer Timeline www.cancerfilms.org, The History of Cancer www.cancer.org, "Moonshot" article www.healthline.com

Евалуација на пациенти со малигни хематолошки заболувања и одговор на терапија

Историја на болеста

Први симптоми на малигното заболување и опис
Промена во телесна тежина последните 3 месеци

Клинички иследувања

Одредување на големина на туморската маса
Физикален преглед

Лабораториски иследувања

ESR, KKS, периферна размаска, стернална пункција, проточна цитометрија, коскена биопсија
Биохемиски иследувања

Радиодијагностички, сцинтиграфски и сонографски иследувања

Општи прогностички фактори

Фактори поврзани со малигното заболување

- Хистологија, хистолошки субтип и градација
- Туморска маса и број на туморски клетки
- Пролиферативен индекс (фракција на раст)
- Стадиум на болеста

Фактори поврзани со пациентот

- Возраст и пол
- Работна способност
- Губиток во телесна тежина
- Интервал од дијагноза до почеток со лекување
- Анемија, тромбоцитопенија
- Температура, инфективни компликации
- Целуларност на коскената срцевина
- Инсуфициентност на другите органи
- Ухранетост

Евалуација на субјективните параметри и работен капацитет на болниот

Karnofsky score

100	Без знаци за болест, нормален капацитет
90	Минимални знаци за болест
80	Присутни знаци за болест, нормална активност
70	Намалена работна способност, може да се грижи за себе
60	Потребна повремена помош за дневните активности
50	честа медицинска нега
40	Неспособен пациент, потребна нега
30	Хоспитализација
20	Тешка општа состојба
10	Прогресија на фаталниот процес
5	Смрт

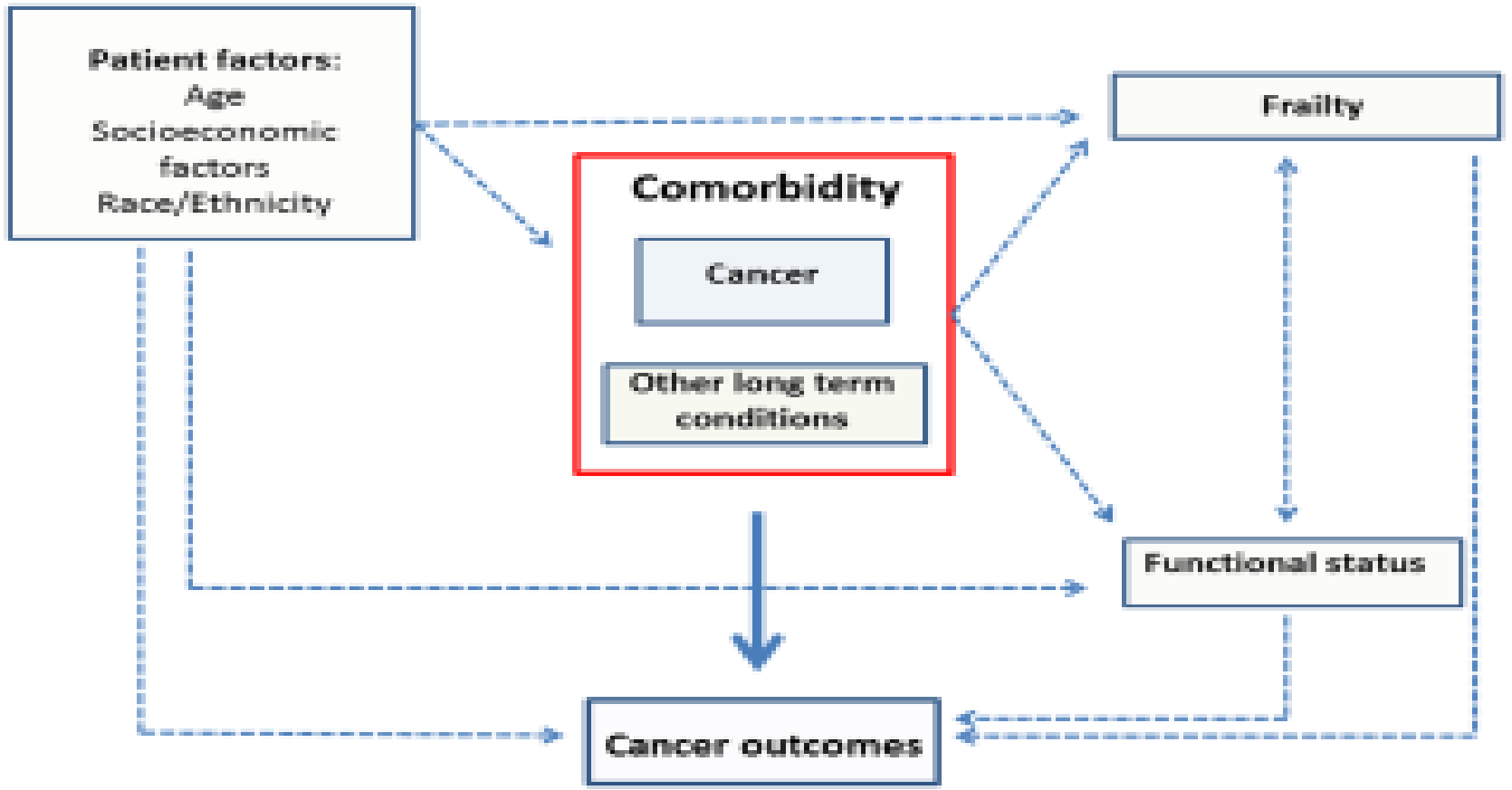
Коморбидни состојби и малигни хематолошки заболувања

- **Коегзистирачка медицинска состојба која е присутна наспроти малигното хематолошко заболување која има влијание врз исходот на лекувањето**

- **Не постои златен стандард**

Sorensen HT. Clin Epi 2013:5 (suppl1):1-2.
Ritchie CS. J Oncol Practice 2011;7:371-4.

The impact of comorbidity on cancer and its treatment



CA: A Cancer Journal for Clinicians
Volume 66, Issue 4, pages 337-350, 17 FEB 2016 DOI: 10.3322/caac.21342
http://onlinelibrary.wiley.com/doi/10.3322/caac.21342/full#caac21342-fig-0001

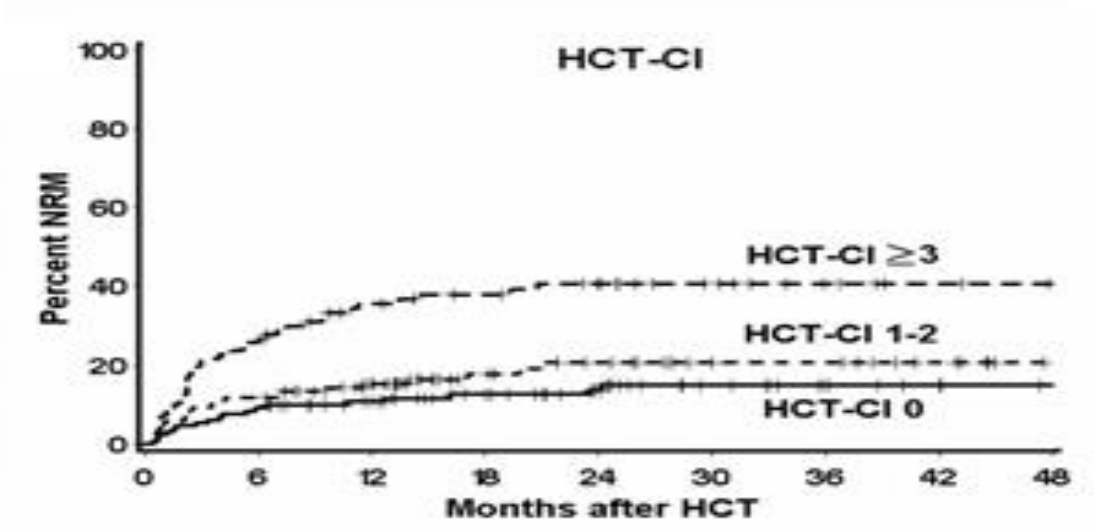
Евалуација на субјективните параметри и работен капацитет на болниот

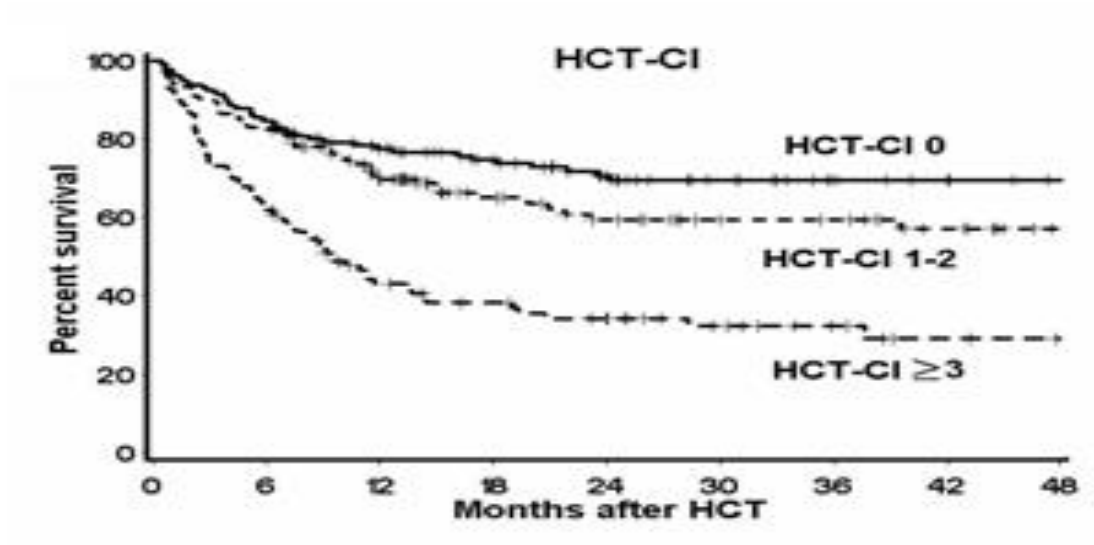
Table 3. Hematopoietic Stem Cell Transplant Comorbidity Index

Comorbidity	Definition	Weight
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1
Cardiovascular comorbidity	Coronary artery disease, congestive heart failure, myocardial infarction, or EF < 50%	1
Inflammatory bowel disease	Chronic disease or ulcerative colitis	1
Diabetes or steroid-induced hyperglycemia	Diabetes or steroid-induced hyperglycemia requiring insulin or an oral hypoglycemic drug	1
Cerebrovascular disease	Transient ischemic attacks or cerebrovascular accident	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment	1
Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN	1
Obesity	Body mass index > 35 kg/m^2	1
Infection	Documented infection or fever of unknown origin or pulmonary nodules of fungal pneumonia or prophylaxis against tuberculosis	1
Rheumatologic	SLE, RA, polymyositis, mixed connective tissue disease, polymyalgia rheumatic	2
Peptic ulcer	Presence of prior endoscopic or radiologic diagnosis	2
Renal, moderate/severe	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Pulmonary, moderate	DLco and/or FEV_1 66%–80% or dyspnea on slight activity	2
Prior malignancies	Treated at any time, excluding nonmelanoma skin cancer	3
Heart valve disease	Moderate to severe degree of valve stenosis, prosthetic mitral or aortic valve, or systematic mitral valve prolapse	3
Pulmonary, severe	DLco and/or FEV_1 < 66% or dyspnea at rest or requiring oxygen	3
Hepatic, moderate/severe	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	3

Note. EF = ejection fraction; ULN = upper limit of normal; AST = aspartate transaminase; ALT = alanine transaminase; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis; DLco = percentage of measured-to-predicted diffusion capacity of carbon monoxide; FEV_1 = percentage of measured-to-predicted forced expiratory volume in 1 second. Adapted from Sorror (2013).

Преѓивување после трансплантација и влијание на коморбидитети врз преживувањето





Евалуација на субјективните параметри

Table 1. Charlson Comorbidity Index Scoring System

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.

Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Основни принципи

ЦИТОХЕМОТЕРАПИЈА

БИОЛОШКИ МОДИФИКАТОРИ

ИМУНОТЕРАПИЈА

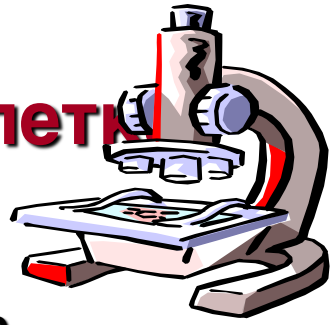
ТРАНСПЛАНТАЦИЈА НА ХЕМАТОПОЕТСКИ СТЕМ КЛЕТКИ

ГЕНСКА ТЕРАПИЈА

ЦИТОХЕМОТЕРАПИЈА

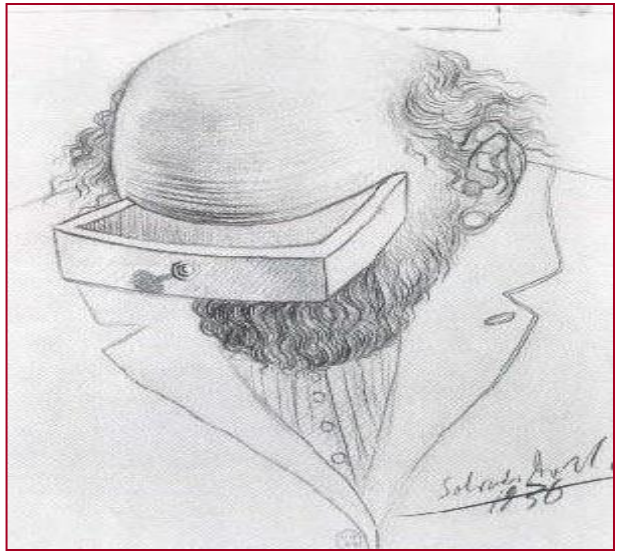
- се користат околу 50 хемотерапеутици
- 1943- mechlorethamine hydrochlorid (Nitrogen Mustard) за M.Hodgkin
- тераписки синергизам: комбинирана хемотерапија од неколку цитостатици
- со примена на дополнителна терапија и комплетно излекување

Патофизиологија и кинетика на малигната клетка



- малигните клетки потекнуваат од еден клон и дел од нив се во G0 (непролиферативна) фаза кога цитостатиците немаат ефект

- пролиферативна фаза : G 1; G 2 и M кога клетките се размножуваат (од 1-100 дена за различни заболувања)



- со циклично давање на цитостатикот може да се уништат сите малигни клетки

- биолошка резистентност: дозите да се максимални, но и тераписки (во m^2)

Класификација на цитостатици

- **Во сите фази**: алкилирачки лекови, BCNU; DTIC и др.
- **Во фаза G1**: L-asparaginasa, Amscacrine
- **Во фаза G2**: Bleomycin
- **Во митоза M**: Vincristine, Vinblastine
- **Комбинирано**: Daunoblastine, Adriamycin, Idarubicin, Mitoxantrone

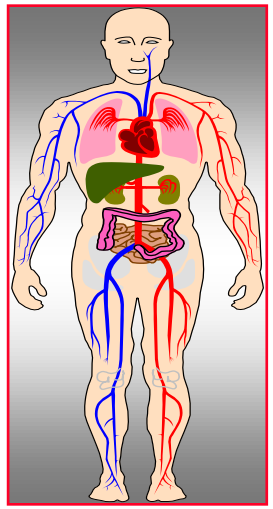
БИОЛОШКИ МОДИФИКАТОРИ

ЦИТОКИНИ: ја зголемуваат одбрамбената способност: INF, CSF

МОНОКЛОНАЛНИ АНТИТЕЛА

СТИМУЛАТОРИ НА КЛЕТОЧНА ДИФЕРЕНЦИЈАЦИЈА

Alltrans retinoid acid (АМЛ-М3)



МОНОКЛОНАЛНИ АНТИТЕЛА

MabThera: Глувчешко/Хумано Химерично Моноклонално Антитело

Варијаблен регион: глувчешкото IgG1 kappa анти-CD20

Константен регион: хуман IgG1 тежок ланец и kappa лесен ланец

Анти-CD20 антитело

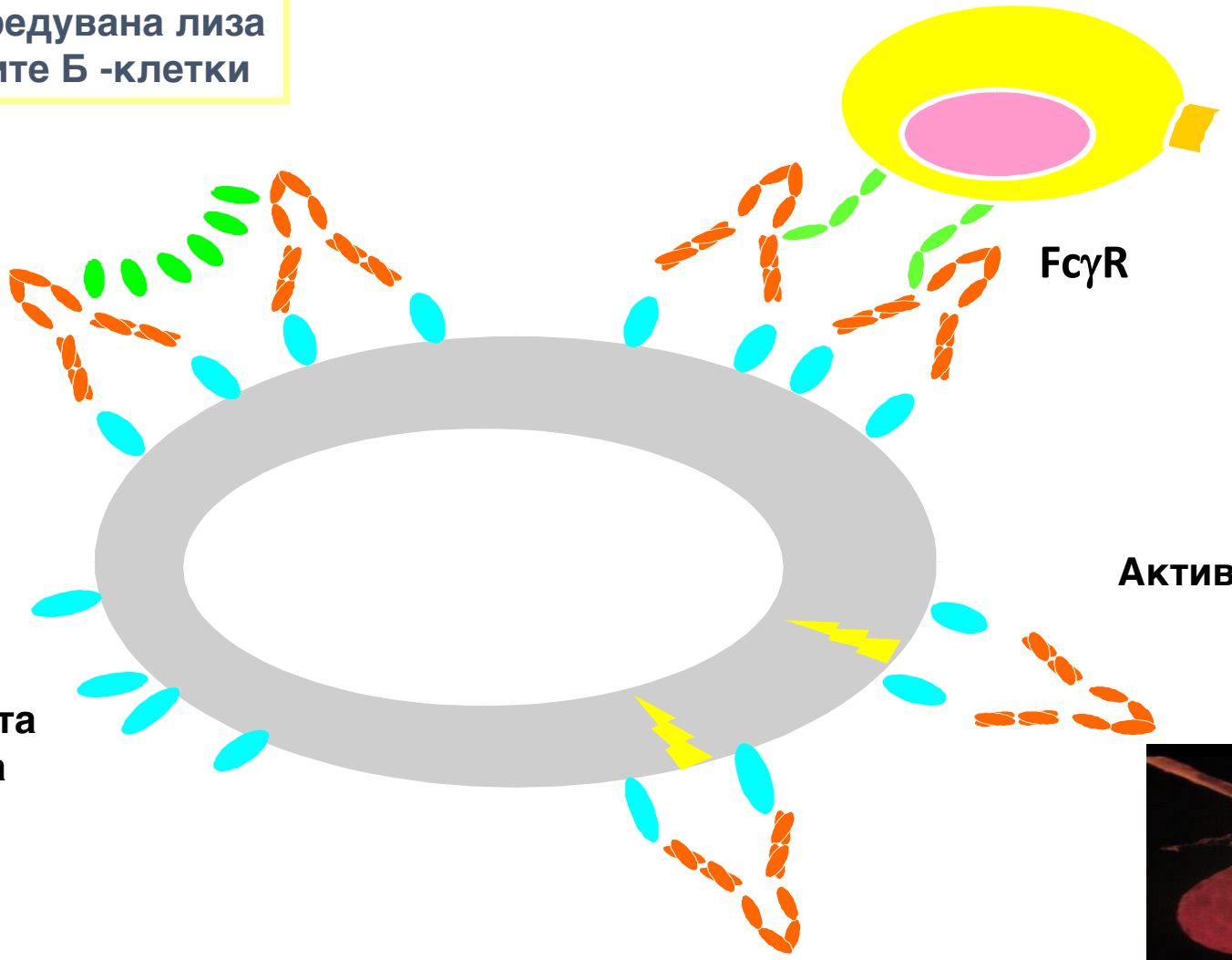
- се врзува за ЦД20 антигенот на површината на сите неопластични клетки од Б-тип и овозможува директна клеточна цитотоксичност и комплемент-медиирана цитотоксичност
- во комбинација со стандардните хемотераписки протоколи обезбедува поголем процент на позитивни одговори кон терапија, подолго преживување и подобар квалитет на живот кај сите пациенти
- инхибира пролиферација на лимфомската линија
- покачува чувствителност на лимфомските клетки кон хемотерапевтиците
- несаканите ефекти се минимални и незначителни

Механизам на дејство на моноклоналното антитело

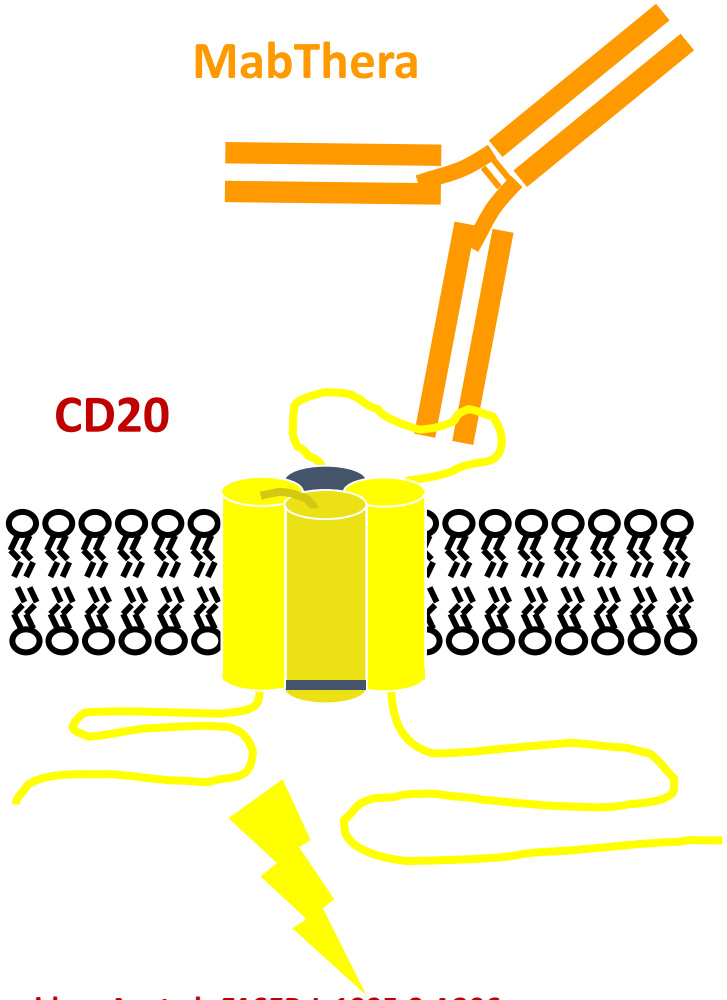
Антитело зависна клеточна цитотоксичност

Комплемент посредувана лиза на циркулирачките Б -клетки

Фиксација на комплемент



Дополнителни предложени механизми на дејство на MabThera



- Ја тригерира апоптозата (програмирана клеточна смрт) *ин витро*[1]
- Ја инхибира пролиферацијата на клеточната линија на лимфомот *ин витро*[2]
- Ги сензитизира резистентните клеточни линии на лимфомот кон хемотерапевтски агенси *ин витро*[1]
- Нема очигледна зависност од клеточниот циклус за активноста

1. Demidem A, et al. *FASEB J*. 1995;9:A206.
2. Maloney DG, et al. *Blood.* 1996;88(suppl 1):637A.

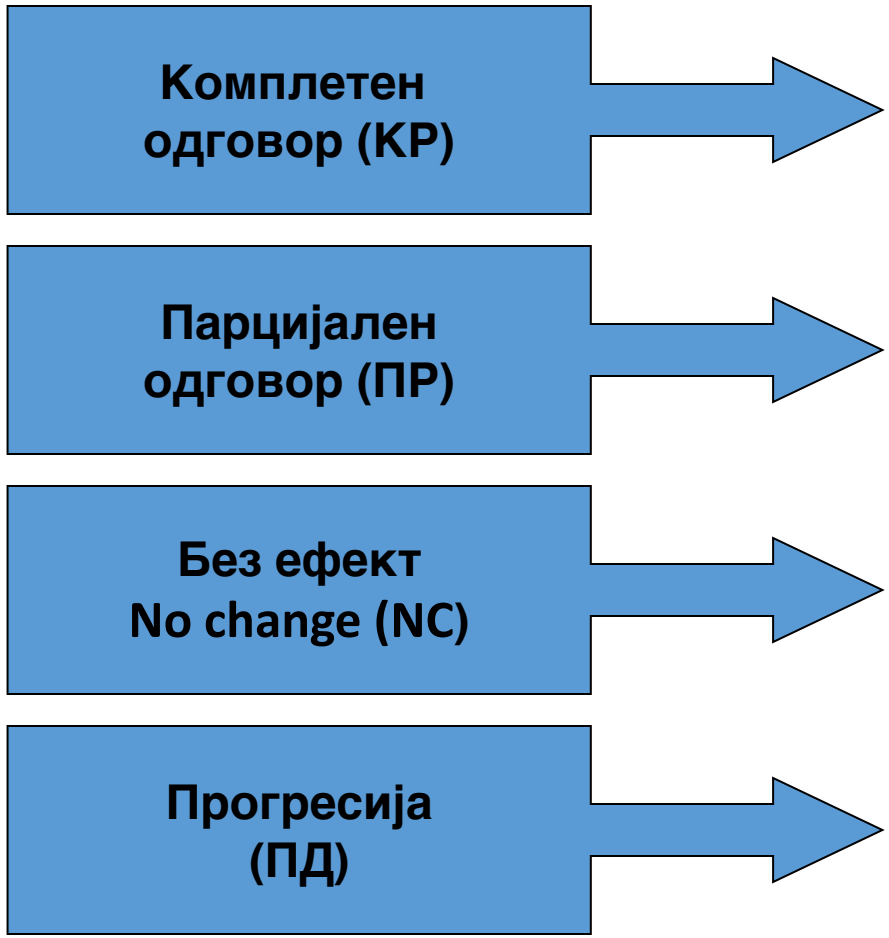
ГЕНСКА ТЕРАПИЈА

- Се користи за модифицирање на сите клеточни линии преку трансмисија на модифицирана генетска информација на наредната генерација
- Продукција на протеини со генетски инженеринг слободни од потенцијални контаминатори, а пурифицирани од природни извори како плазмата. Рекомбинантните ДНК технологии овозможуваат користење на овие протеини во тераписки цели: еритропоетин, G-CSF, тромбопоетин, фактори на коагулација итн.
- Векторски посредувана трансмисија на гени и формирање на трансген за овозможување на нормално клеточно функционирање, векторот содржи ДНК секвенци кои кодираат тераписки протеин контролиран од транскрипциски регулаторен механизам за генска експресија. Како вектори се користат аденовируси, ретровируси, други вирусни вектори, невирусни вектори.

План за лекување

- соработка со пациентот и негова психолошка подготвеност
- информаации за компликации и последици
- обезбедување на централна венска линија
- превенција од инфекции

Евалуација на туморскиот одговор на терапијата

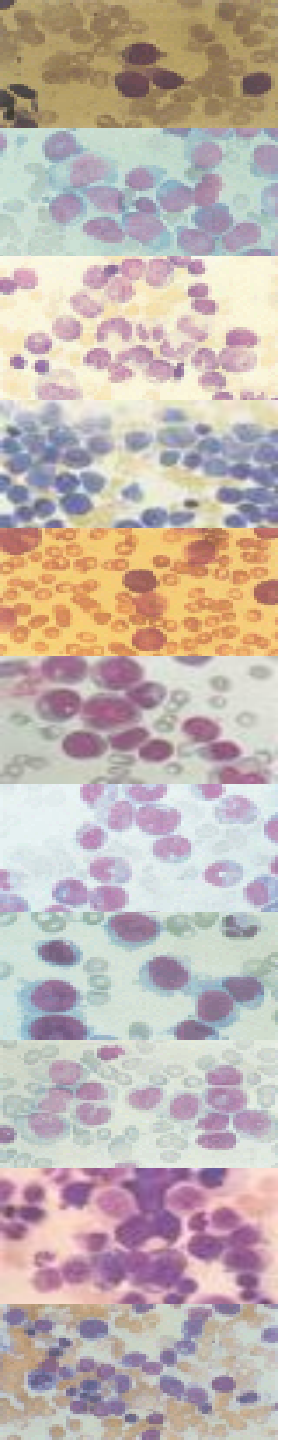


Отсуство на сите симптоми на заболувањето и губење на туморската маса

≥50% намалување на туморската маса, без појава на нови туморски лезии

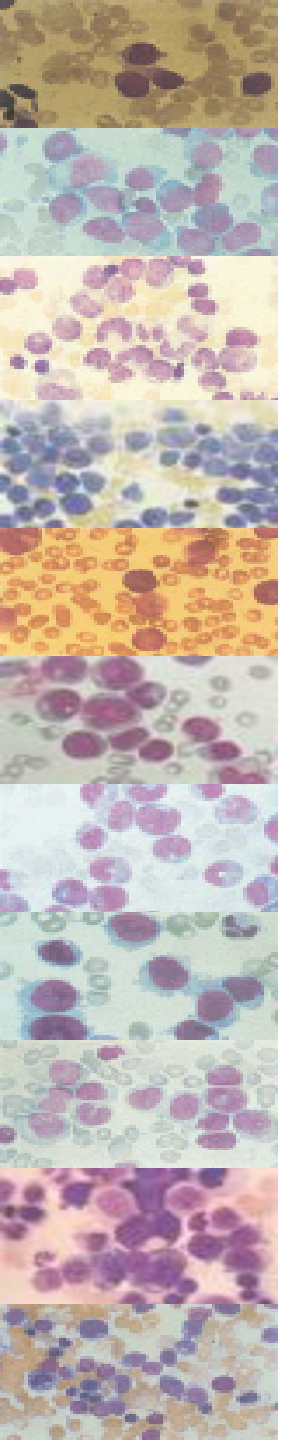
Тумор кој не се изменил помалку од 50% или зголемување на туморска лезија до 25%

≥25% зголемување на една или повеќе туморски манифестации или појава на нови лезии



The Cell Cycle

- G_1 phase: cell prepares for DNA synthesis
- S phase: cell generates complete copy of genetic material
- G_2 phase: cell prepares for mitosis
- M phase: replicated DNA is condensed and segregated into chromosomes
- G_0 phase: resting state



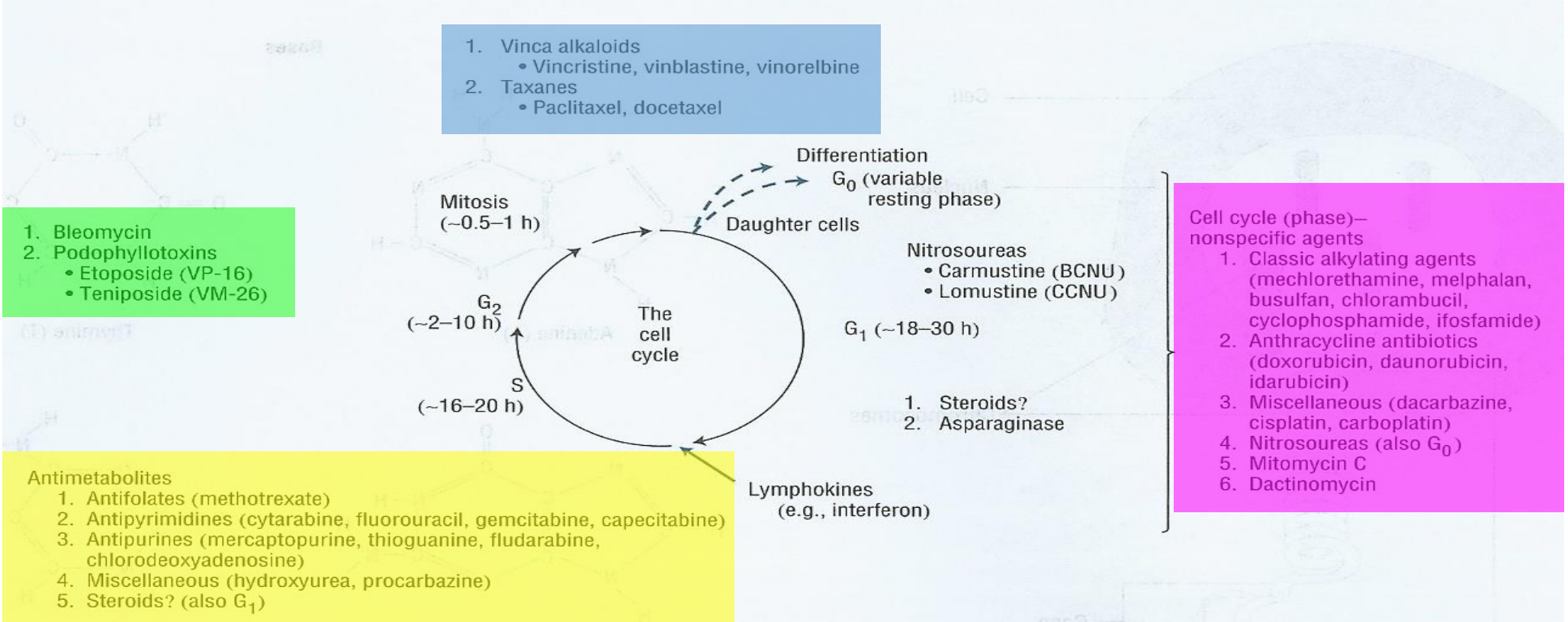
Chemotherapy

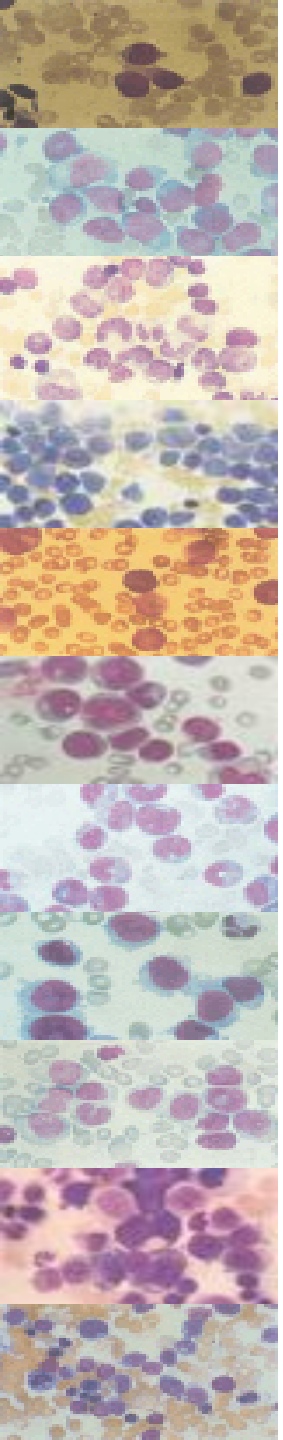
- **Cell cycle phase – specific**
  - agents with major activity in a particular phase of cell cycle
  - schedule dependent

- **Cell cycle phase – nonspecific**
  - agents with significant activity in multiple phases
  - dose dependent

Conventional Chemotherapy

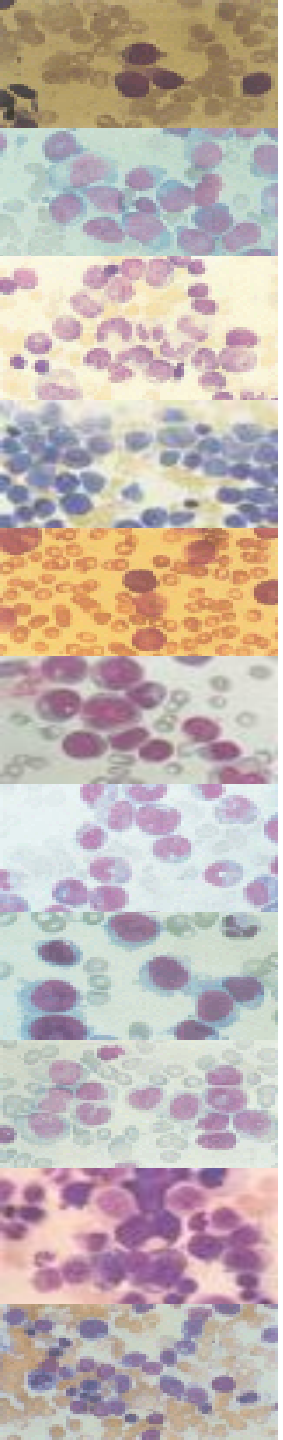
- Backbone of cancer chemotherapy regimens
- Cytotoxicity is not selective





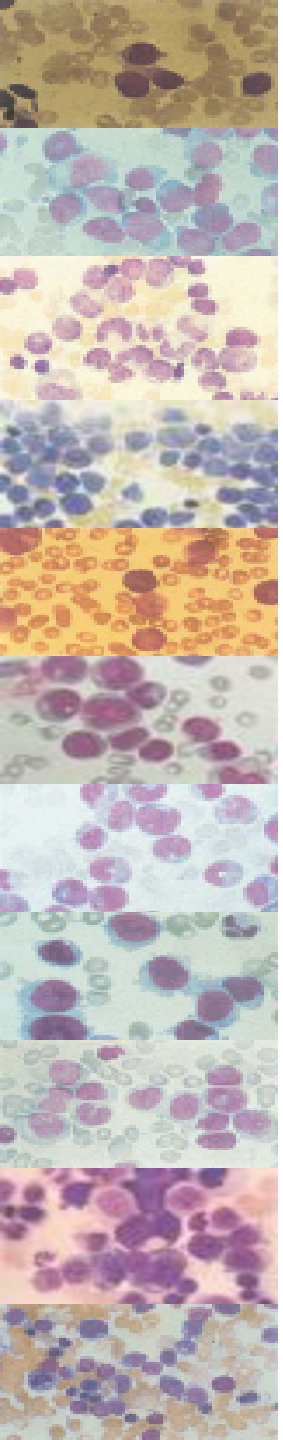
Chemotherapy Classes

- **Alkylating agents**
  - nitrogen mustards
  - thiotepa, busulfan
  - nitrosoureas, mitomycin
  - procarbazine, dacarbazine
- **Taxanes**
  - paclitaxel, docetaxel
  - nab-paclitaxel
- **Topoisomerase II inhibitors**
  - etoposide
- **Platinum Complexes**
  - cisplatin, carboplatin
  - oxaliplatin
- **Anthracyclines**
  - doxorubicin, daunorubicin
  - idarubicin, mitoxantrone
- **Antimetabolites**
  - methotrexate
  - purine antagonists
  - pyrimidine antagonists
- **Tubulin interactive agents**
  - vincristine, vinblastine
- **Miscellaneous agents**
  - bleomycin
  - asparaginase
  - hydroxyurea



Chemotherapy Toxicity

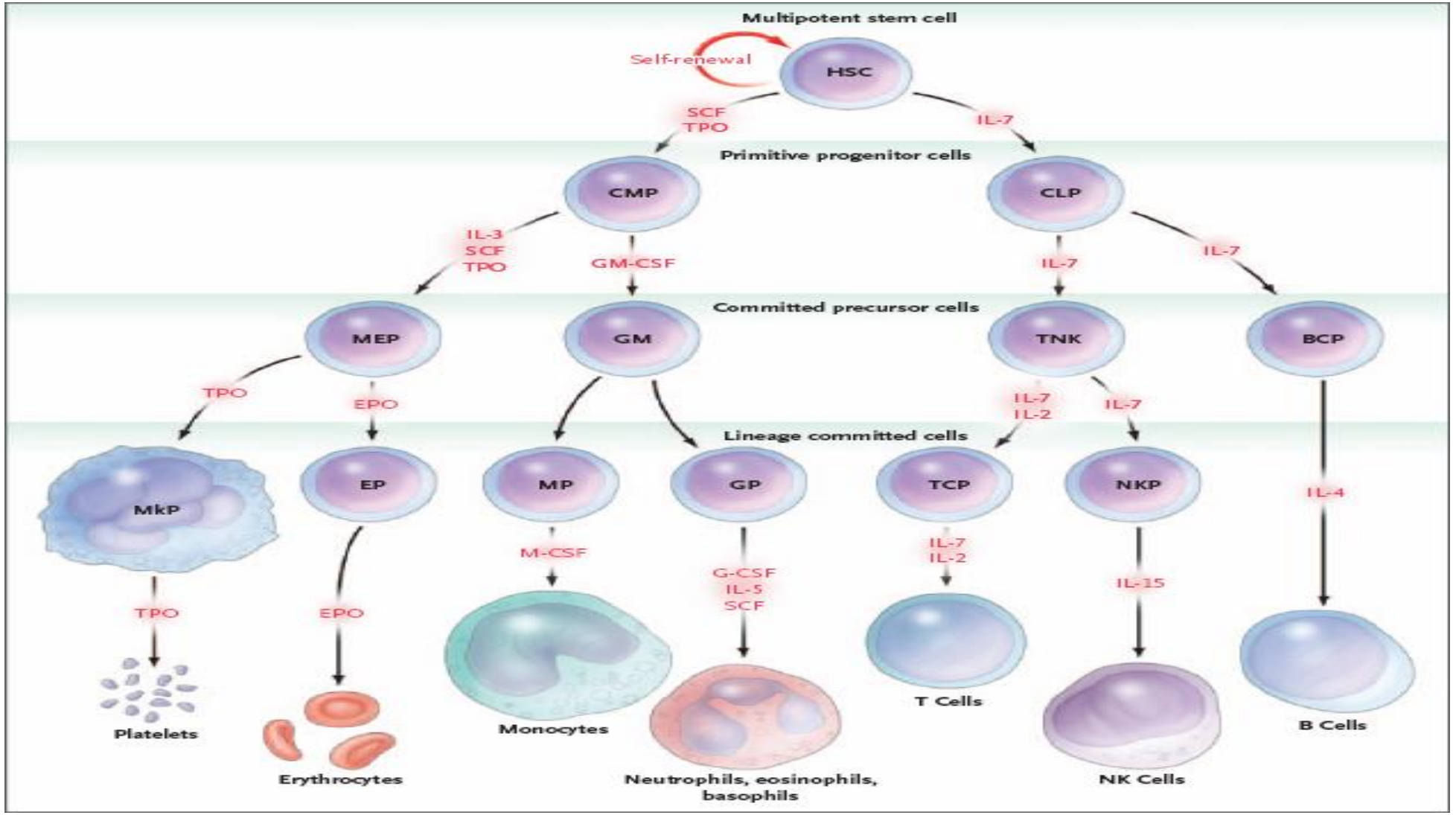
- Usually reflected by mechanism of action of drug
- Toxicity depends on many factors
  - Drug dosing and schedule (DLT)
  - Patient
  - Disease
- Toxicity not always a class effect
- Chemotherapy regimens usually combine drugs that have different toxicity profiles



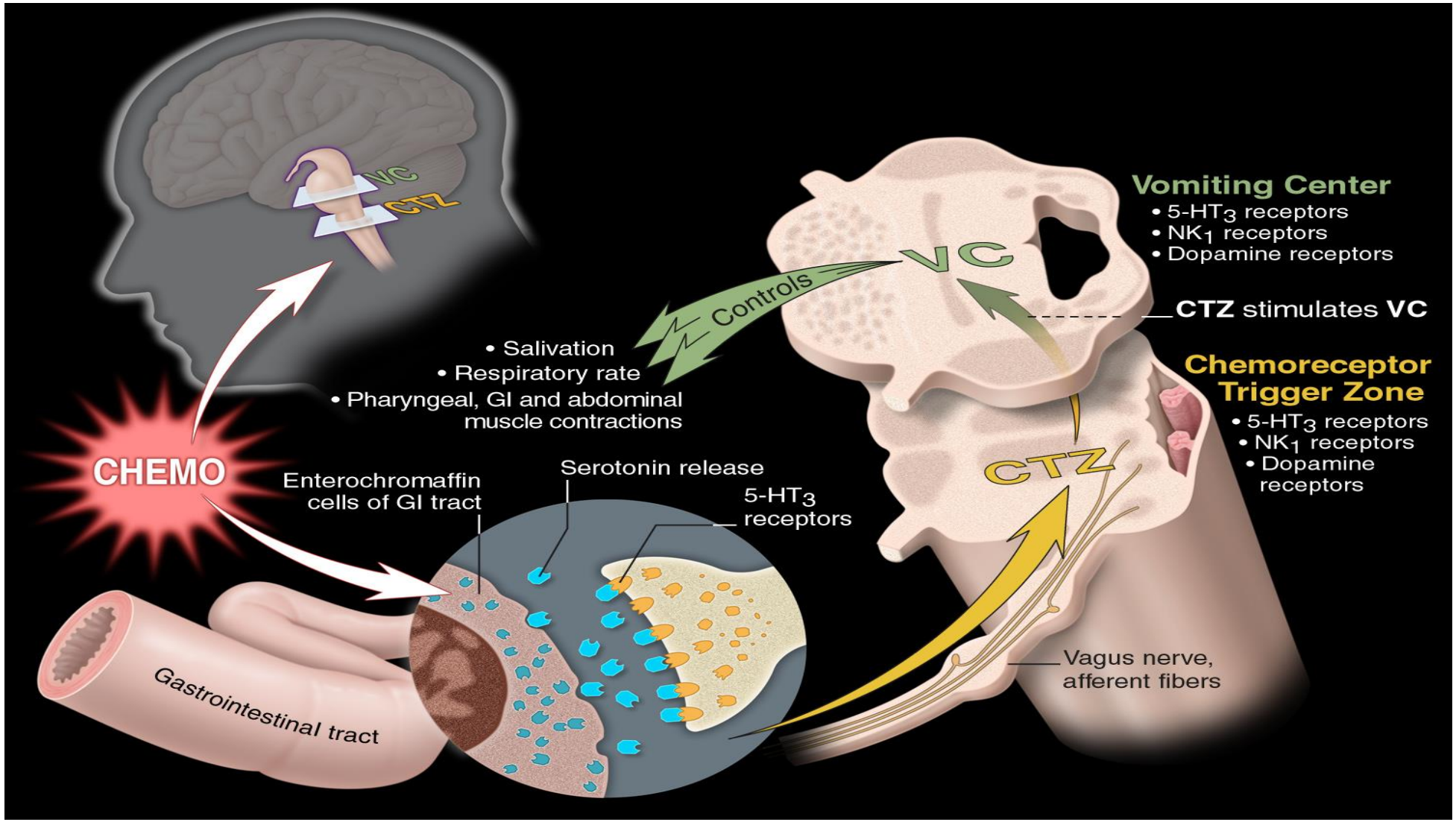
Common Toxicities

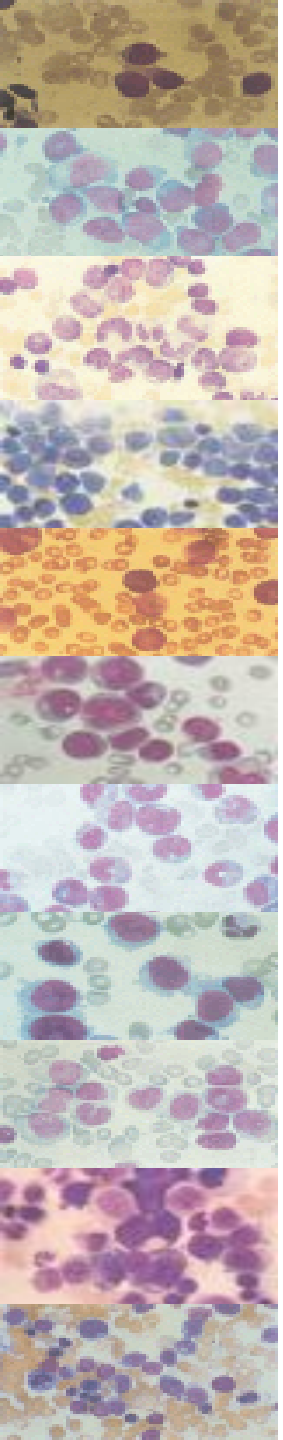
- Most chemotherapy drugs are active in cells that are rapidly multiplying
  - Chemotherapy may not be very active in indolent or slow growing tumors
- Because of cytotoxic action on rapidly dividing cells they are toxic to normal cells that are actively multiplying
  - Bone marrow, GI tract, hair follicles are all rapidly multiplying
- Thus common toxicity of chemo agents are -
  - Neutropenia, anemia, and thrombocytopenia (collectively called myelosuppression or bone marrow suppression)
  - Mucositis, diarrhea (GI toxicity)
  - Nausea and vomiting
  - Alopecia
  - Sterility/Infertility (especially sterility in males)
- Common Toxicity Criteria Grading System (CTC)
  - Grade 0 – 4

Myelosuppression



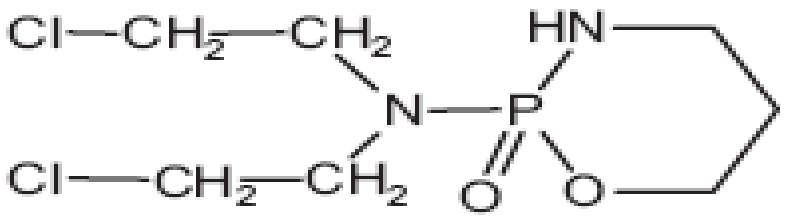
Nausea and Vomiting



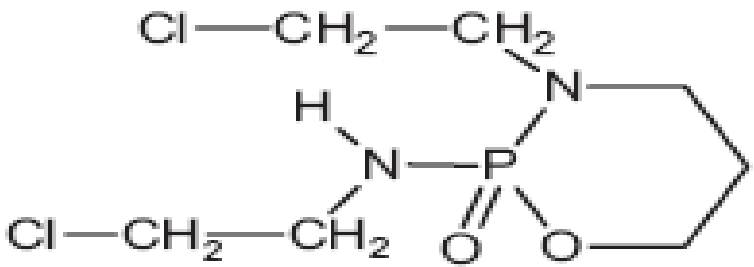


Alkylating Agents

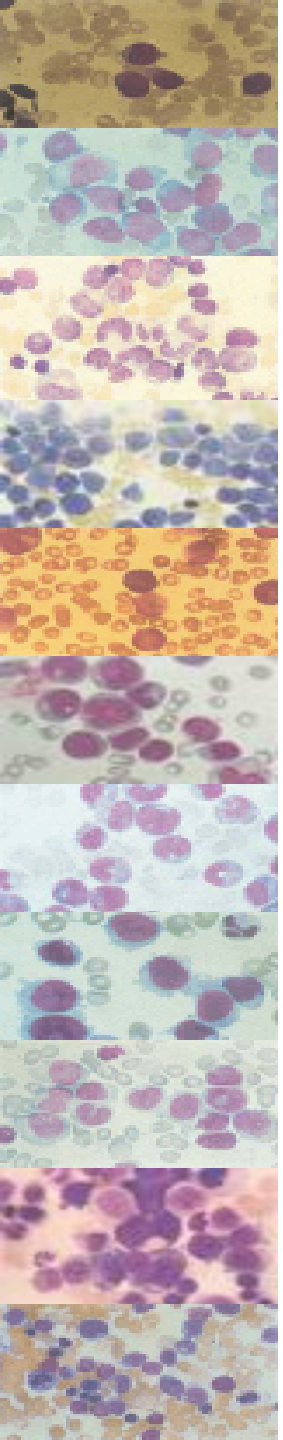
- **Main effect is on DNA synthesis with most cytotoxicity to rapidly proliferating cells**



Cyclophosphamide

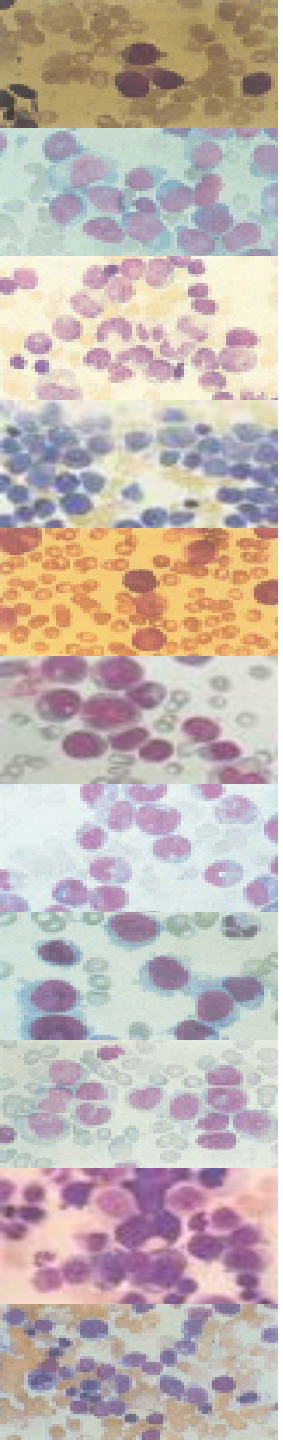


Ifosfamide



Alkylating Agents

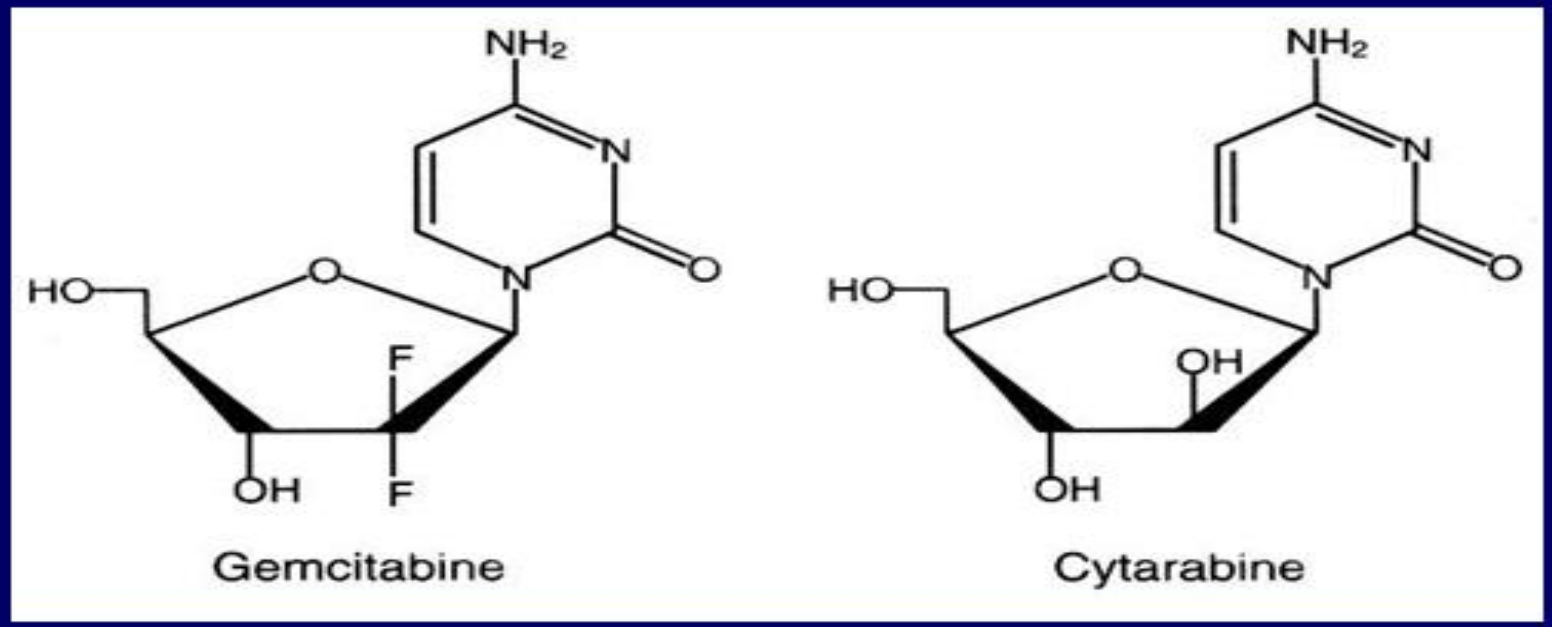
- Mechanism of action
  - act as bifunctional alkylating agents following metabolic activation and formation of mustards
    - mustards react with the N7 atom of purine bases (guanine)
    - these DNA adducts go on to form cross-links through reaction of the second arm of the mustard
  - prevent cell division by cross-linking DNA strands
    - intra- and interstrand cross-links
    - cell continues to synthesize other cell constituents, such as RNA and protein, and an imbalance occurs and the cell dies
    - if these modifications in the nucleic acid structure are compatible with cell life (after DNA repair), mutagenesis and carcinogenesis result

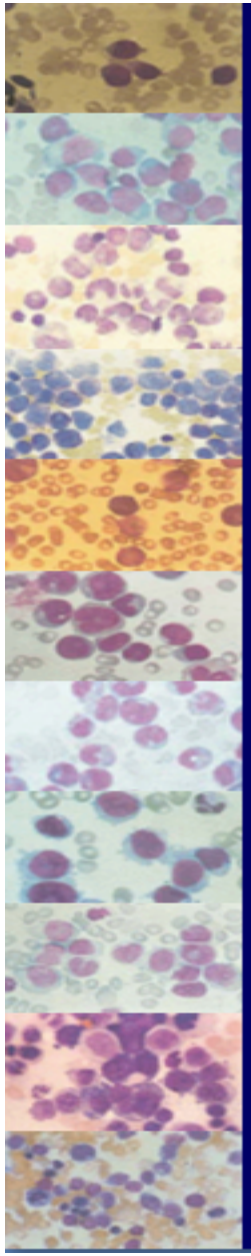


Cyclophosphamide and Toxicity

- Myelosuppression
  - principle dose-limiting toxicity
  - primarily leukopenia
- Hemorrhagic cystitis
  - acrolein metabolite
  - associated with high-dose therapy
  - more common in poorly hydrated or renally compromised patients
  - onset may be delayed from 24 hours to several weeks
  - manifests as gross hematuria
  - aggressive hydration required with high dose therapy
  - mesna administration
  - management: increase IVF, mesna, total bladder irrigation

Cytidine Analogs

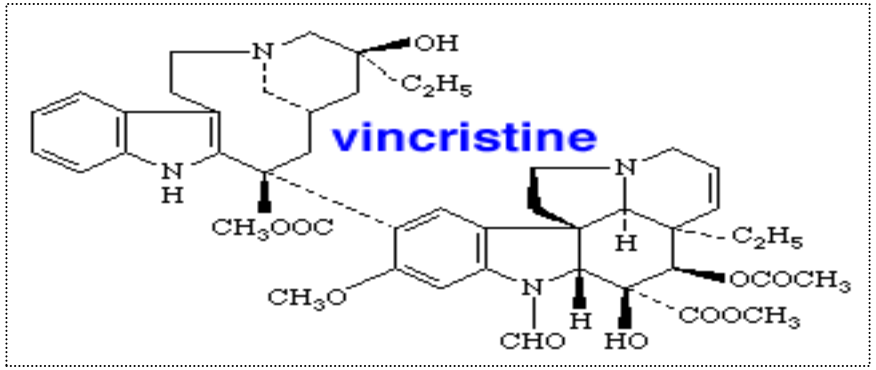


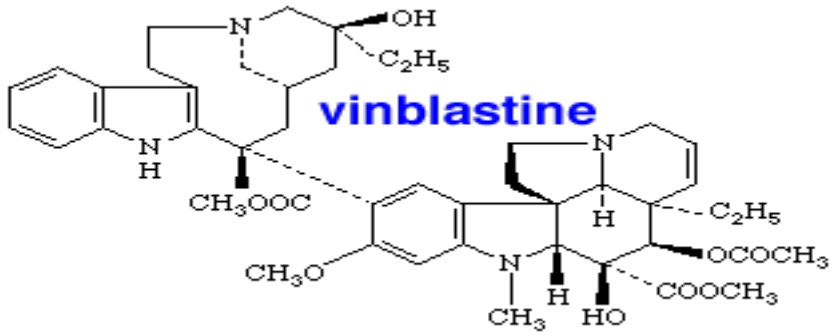


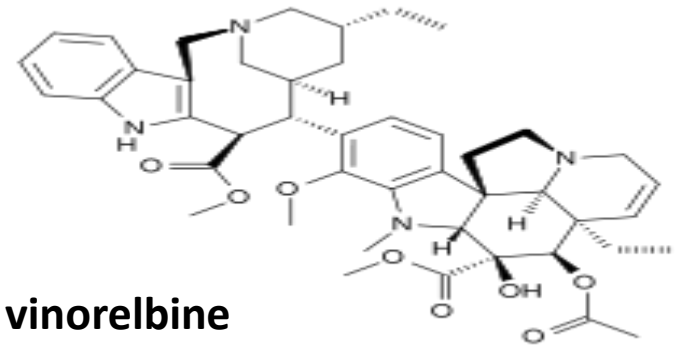
Cytarabine

- Mechanism of action
  - Cell cycle phase specific
  - undergoes phosphorylation to form arabinosylcytosine triphosphate (ara-CTP), which competes with the normal substrate deoxycytidine 5'-triphosphate (dCTP), in the inhibition of DNA polymerase α
- Pharmacokinetics
  - ara-C degraded to ara-U by cytidine deaminase and ara-CMP to inactive ara-UMP by dCMP deaminase
  - CSF levels are about 40 – 50% of the plasma level (lack of cytidine deaminase activity in CSF)
  - Distributes widely into total body water, also distributes to tear fluid and crosses into CNS

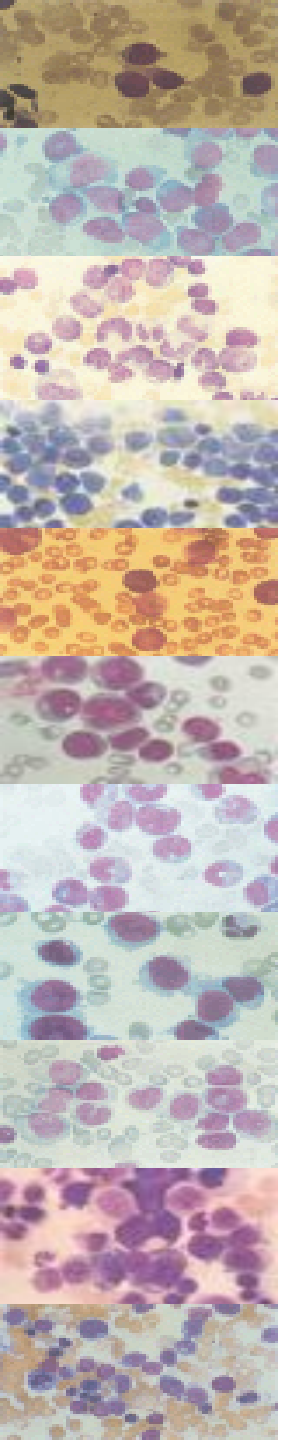
e Vinca Alkaloids







vinorelbine



Vinca Alkaloids

- Mechanism of action
  - Bind to tubulin
  - Prevent polymerization of tubulin thus preventing microtubule formation
  - Chromosomes remain lined up in middle
  - Apoptosis
- Small differences in structure changes toxicity and activity
  - vincristine active in leukemia and is neurotoxic
  - vinblastine active in lymphomas and testicular cancer and is myelosuppressive
  - vinorelbine active in lung cancer and is neurotoxic and myelosuppressive

Tretman na pacienti so AML < 60 godini

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Acute Myeloid Leukemia

CLASSIFICATION			TREATMENT INDUCTION[mm,nn]
AML[kk,ll]	Age <60 y	→	Clinical trial (preferred) or Standard-dose cytarabine 100-200 mg/m² continuous infusion x 7 days with idarubicin 12 mg/m² or daunorubicin 90 mg/m² x 3 days[oo,pp] (category 1) or Standard-dose cytarabine 200 mg/m² continuous infusion x 7 days with daunorubicin 60 mg/m² x 3 days and cladribine 5 mg/m² x 5 days (category 1)[qq] or High-dose cytarabine (HiDAC)[pp,rr] 2 g/m² every 12 hours x 6 days[ss] or 3 g/m² every 12 h x 4 days[tt] with idarubicin 12 mg/m² or daunorubicin 60 mg/m² x 3 days (1 cycle) (category 2B)
	Age ≥60 y	→ See Treatment Induction (AML-11)	

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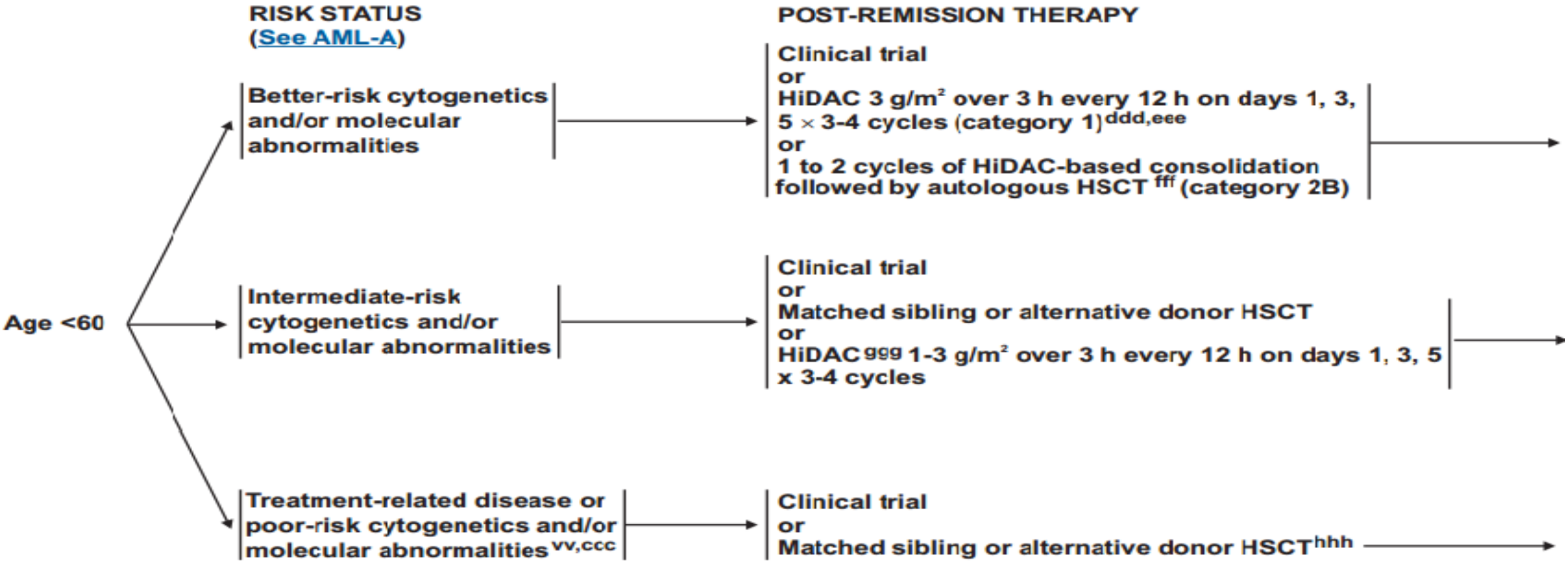
Acute Myeloid Leukemia



Tretman na pacienti so AML ≥ 60 godini

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Acute Myeloid Leukemia

AML[kk,iii] ≥60y

TREATMENT INDUCTION[mm,jjj]

PS 0-2

- **Non-adverse cytogenetic/ molecular markers without prior MDS/therapy-related AML** →
  - Clinical trial
  - or
  - Standard-dose cytarabine (100-200 mg/m² continuous infusion x 7 days) with idarubicin[kkk] 12 mg/m² (preferred) or daunorubicin[lll] 45-90 mg/m² x 3 days or mitoxantrone 12 mg/m² x 3 days
  - or
  - Low-intensity therapy (subcutaneous cytarabine, 5-azacytidine, decitabine)[mmm] (may be more appropriate for elderly patients or relatively unfit patients with comorbidities)
- **Therapy-related AML/prior MDS or unfavorable cytogenetic/ molecular markers** →
  - Clinical trial
  - or
  - Low-intensity therapy (5-azacytidine, decitabine)[mmm]
  - or
  - Standard-dose cytarabine (100-200 mg/m² continuous infusion x 7 days) with idarubicin[kkk] 12 mg/m² (preferred) or daunorubicin 45-60 mg/m² x 3 days or mitoxantrone 12 mg/m² x 3 days (may be more appropriate for fit patients who are candidates for subsequent HSCT)

PS >2 or PS 0-3 with significant comorbidities →
- Clinical trial
- or
- Low-intensity therapy ([5-azacytidine, decitabine],[mmm] subcutaneous cytarabine)
- or
- Best supportive care (hydroxyurea, transfusion support)

Citogenetska stratifikacija spored grupi na rizik za tretman na bolnite so AL

RISK STATUS BASED ON VALIDATED CYTOGENETICS AND MOLECULAR ABNORMALITIES[1]

RISK STATUS	CYTOGENETICS	MOLECULAR ABNORMALITIES
Better-risk	inv(16)[2,3] or t(16;16)[2] t(8;21)[2] t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined	t(8;21), inv(16), t(16;16): with c-KIT[5] mutation
Poor-risk	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[4]	Normal cytogenetics: with FLT3-ITD mutation[6]

Tretman na pacienti so Multipen mielom

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NCCN Guidelines Version 2.2014
Multiple Myeloma

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Multiple Myeloma Table of Contents
Discussion

MYELOMA THERAPY[1-3]

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compl

ACTIVE (SYMPTOMATIC) MYELOMA		FOLLOW-UP/SURVEILLANCE
Prim Tran (Ass 2 cy	Response after primary therapy[f] → Autologous[k,l] stem cell transplant (category 1) OR Allogeneic[i,j] stem cell transplant in clinical trial OR Continue myeloma therapy until best response[f]	• Quantitative immunoglobulins + quantitation of M protein at least every 3 mo • CBC, differential, platelet count • BUN, creatinine, calcium • Bone survey annually or for symptoms • Bone marrow aspirate and biopsy as clinically indicated • Serum FLC assay as clinically indicated • MRI as clinically indicated • PET/CT scan as clinically indicated → Monitor as above and/or maintenance therapy[g]
Prim Non (Ass 2 cy		
		• Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)
Maintenance Therapy	• Bortezomib • Lenalidomide[5] (category 1) • Thalidomide (category 1)	• Bortezomib + prednisone (category 2B) • Bortezomib + thalidomide (category 2B) • Interferon (category 2B) • Steroids (category 2B) • Thalidomide + prednisone (category 2B)

Tretman na pacienti so Hodgkin –ova bolest

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NCCN Guidelines Version 2.2013
Hodgkin Lymphoma

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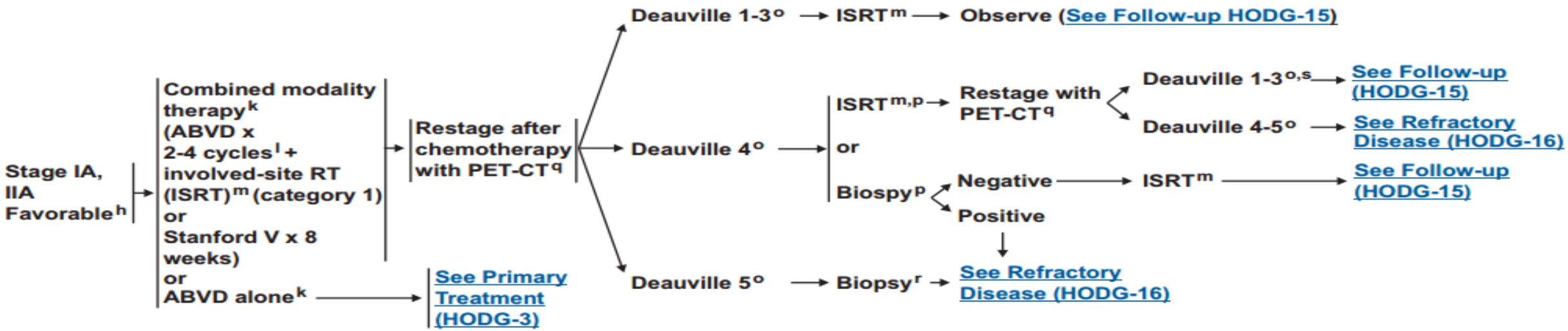
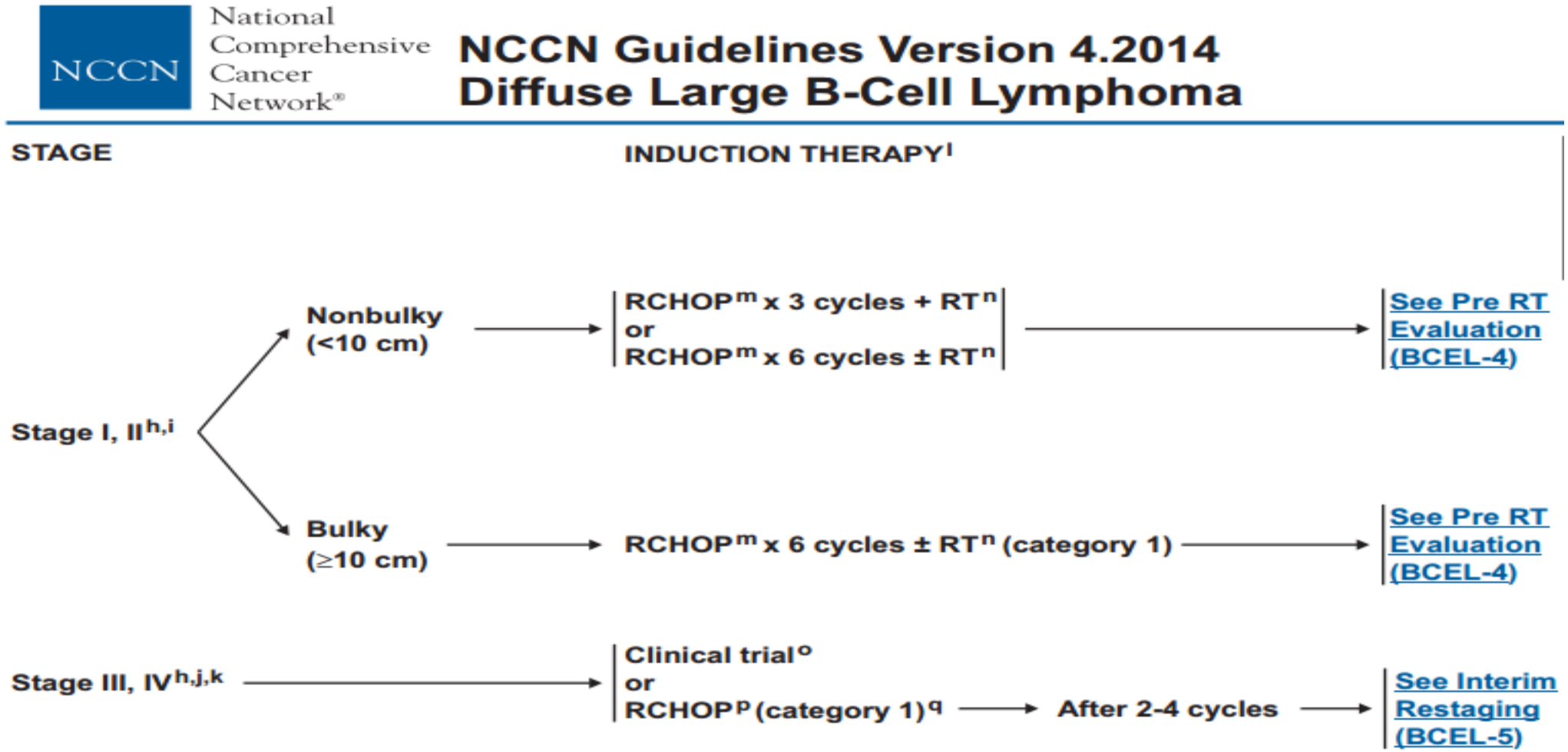
CLINICAL PRESENTATION:
Classical Hodgkin lymphoma[f]
Stage IA, IIA Favorable

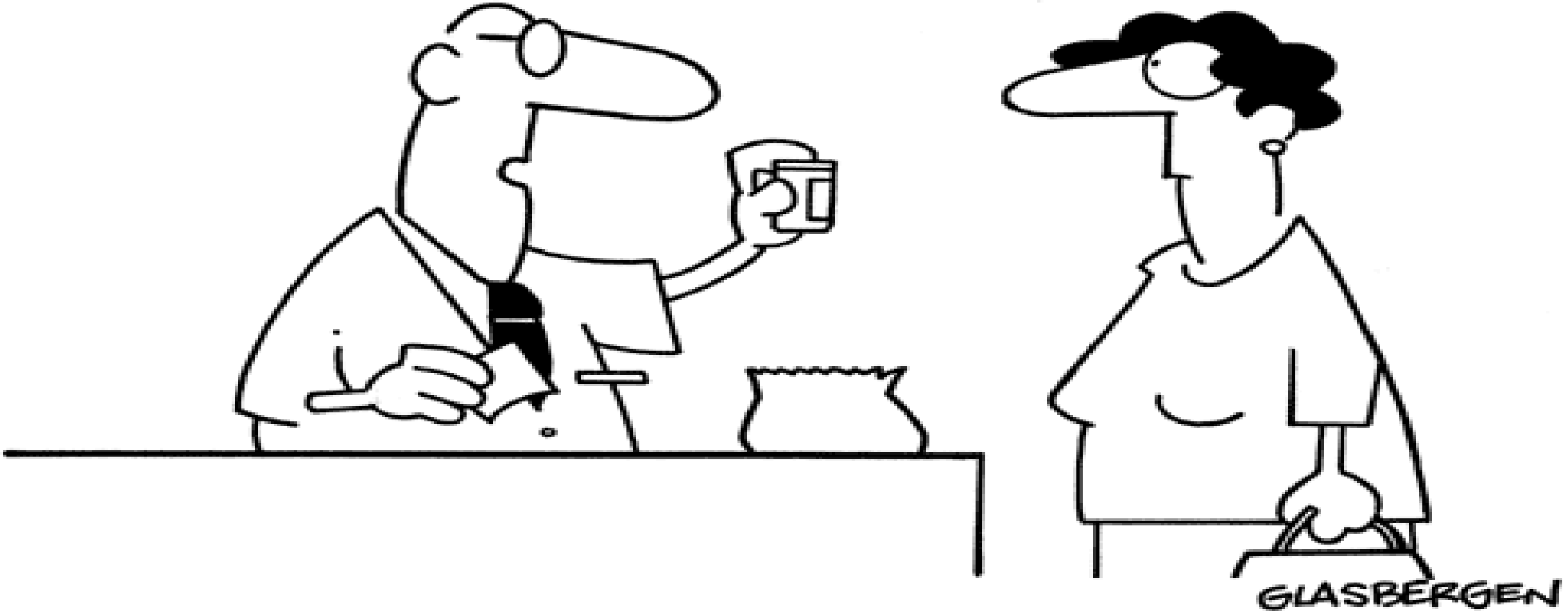
PRIMARY TREATMENT[j]



Tretman na pacienti so NHL



PRESCRIPTIONS



**"This is one of those new miracle drugs.
If you can afford it, it's a miracle."**