
20.11.2015
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Gülsan Türkoz
Sucak
3.Ulusal
Klinik Mikrobiyoloji
17:26

Hematopoetik Kök Hücre Nakli Mikrobiyoloji Laboratuarından Beklentiler

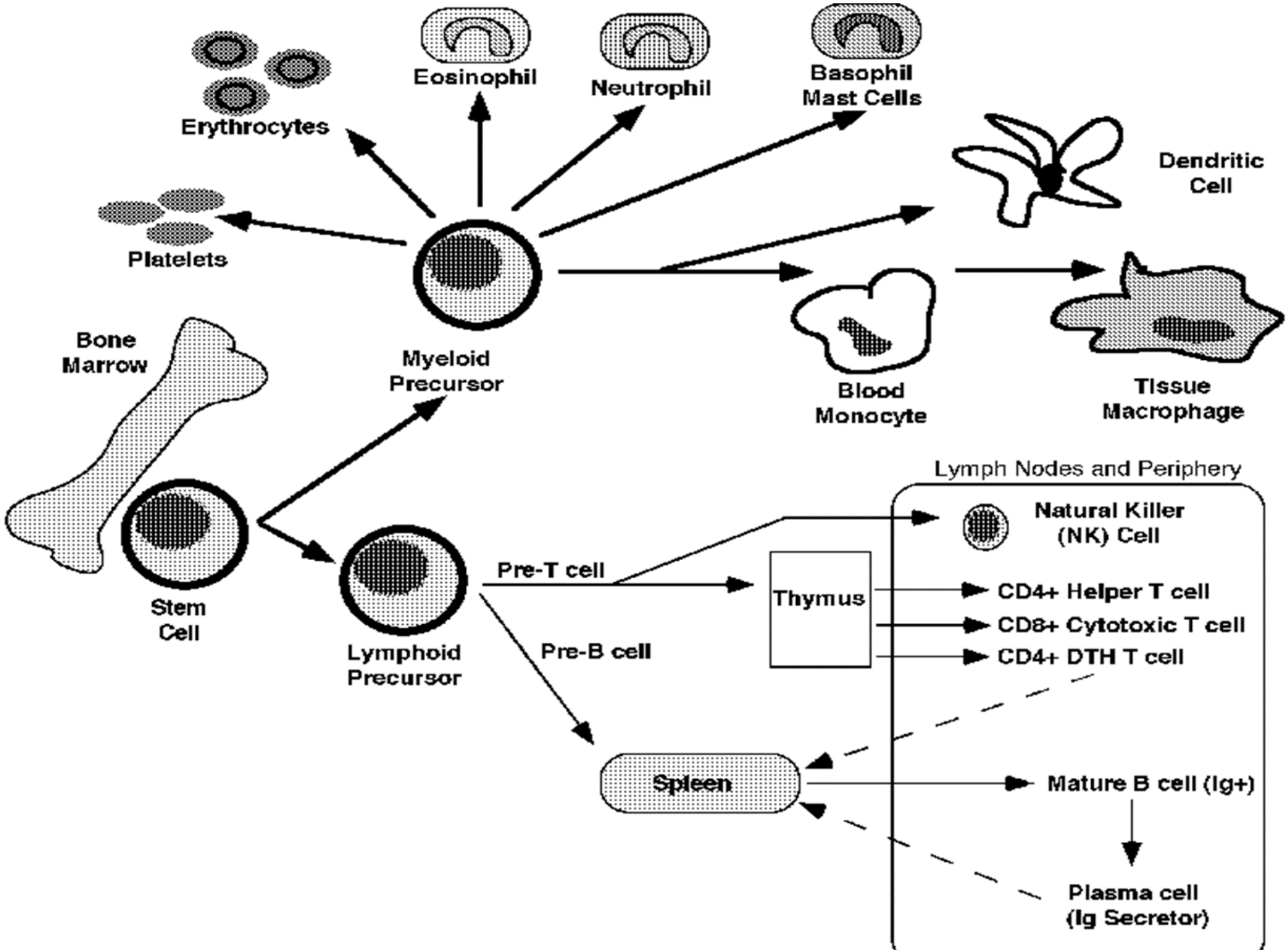
Dr. Gülsan Türköz SUCAK

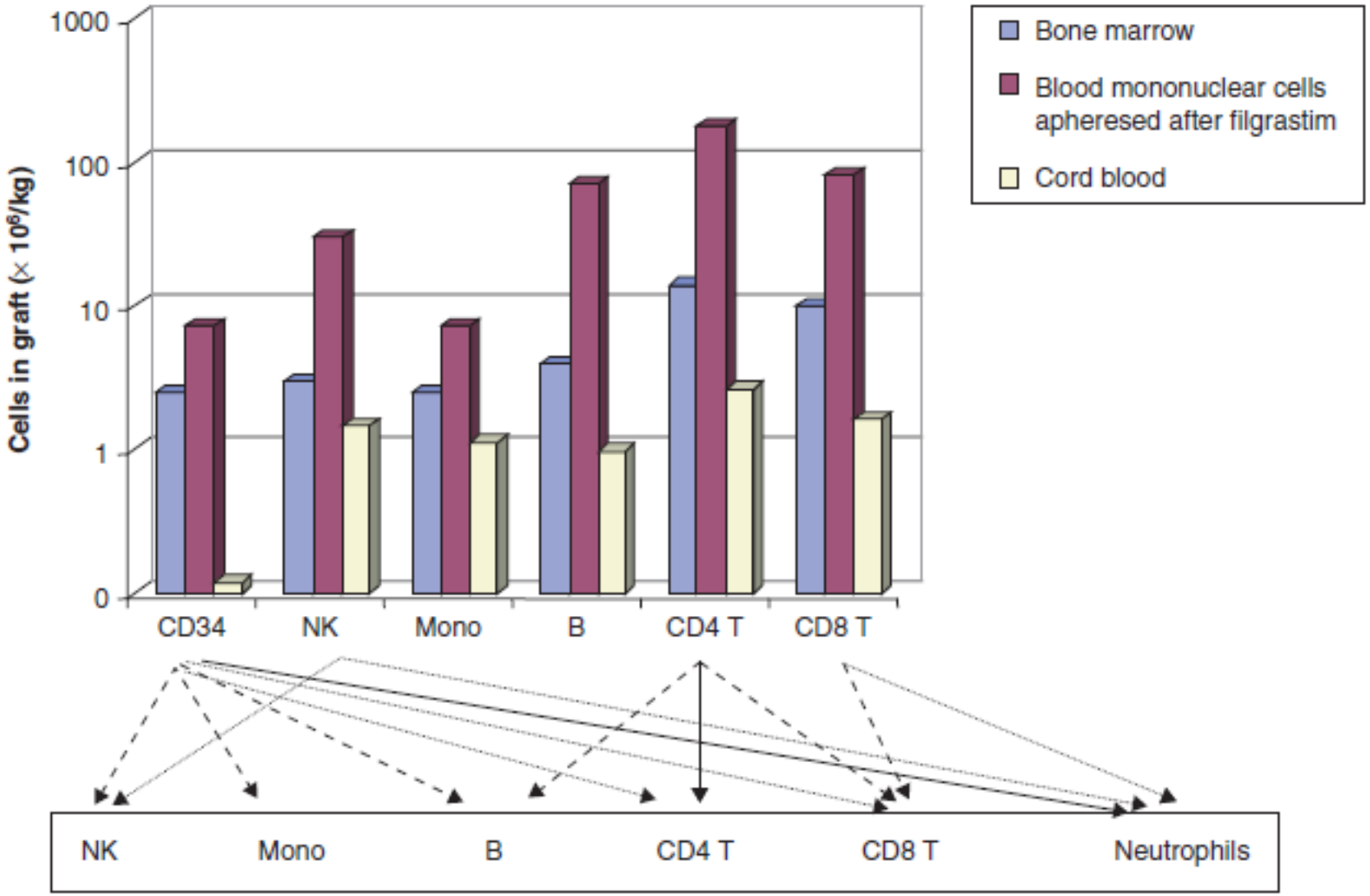
Allojeneik kök hücre nakli

- Lenfo-hematopoetik sistem kendini yineleme (self-renewal) kapasitesi olan tek organ sistemidir.
- Hematopoetik kök hücre bağışı solid organ nakillerinin aksine donör için kalıcı kayba yol açmayacak, bağışladığı hücrelerin yerine yenilerini koyacaktır.

Hematopoetik kök hücre nakli

- Kemik iliği ve/veya immun sistemi doğuştan veya tümör, kemoterapi radyoterapi gibi nedenlerle hasar görmüş kişilerde hematopoetik sistemin restorasyonunu sağlamak amacıyla pluripotent kök hücrelerin (CD34 + hücreler) alıcıya transfer edilmesidir.


Erythrocytes
Eosinophil
Neutrophil
Basophil
Mast Cells
Dendritic
Cell
Platelets
Myeloid
Precursor
Blood
Monocyte
Tissue
Macrophage
Bone
Marrow
Stem
Cell
Lymphoid
Precursor
Pre-T cell
Pre-B cell
Thymus
Lymph Nodes and Periphery
Natural Killer
(NK) Cell
CD4+ Helper T cell
CD8+ Cytotoxic T cell
CD4+ DTH T cell
Spleen
Mature B cell (Ig+)
Plasma cell
(Ig Secretor)


1000
100
10
1
0
Cells in graft (× 10⁶/kg)
CD34
NK
Mono
B
CD4 T
CD8 T
Bone marrow
Blood mononuclear cells apheresed after filgrastim
Cord blood
NK
Mono
B
CD4 T
CD8 T
Neutrophils

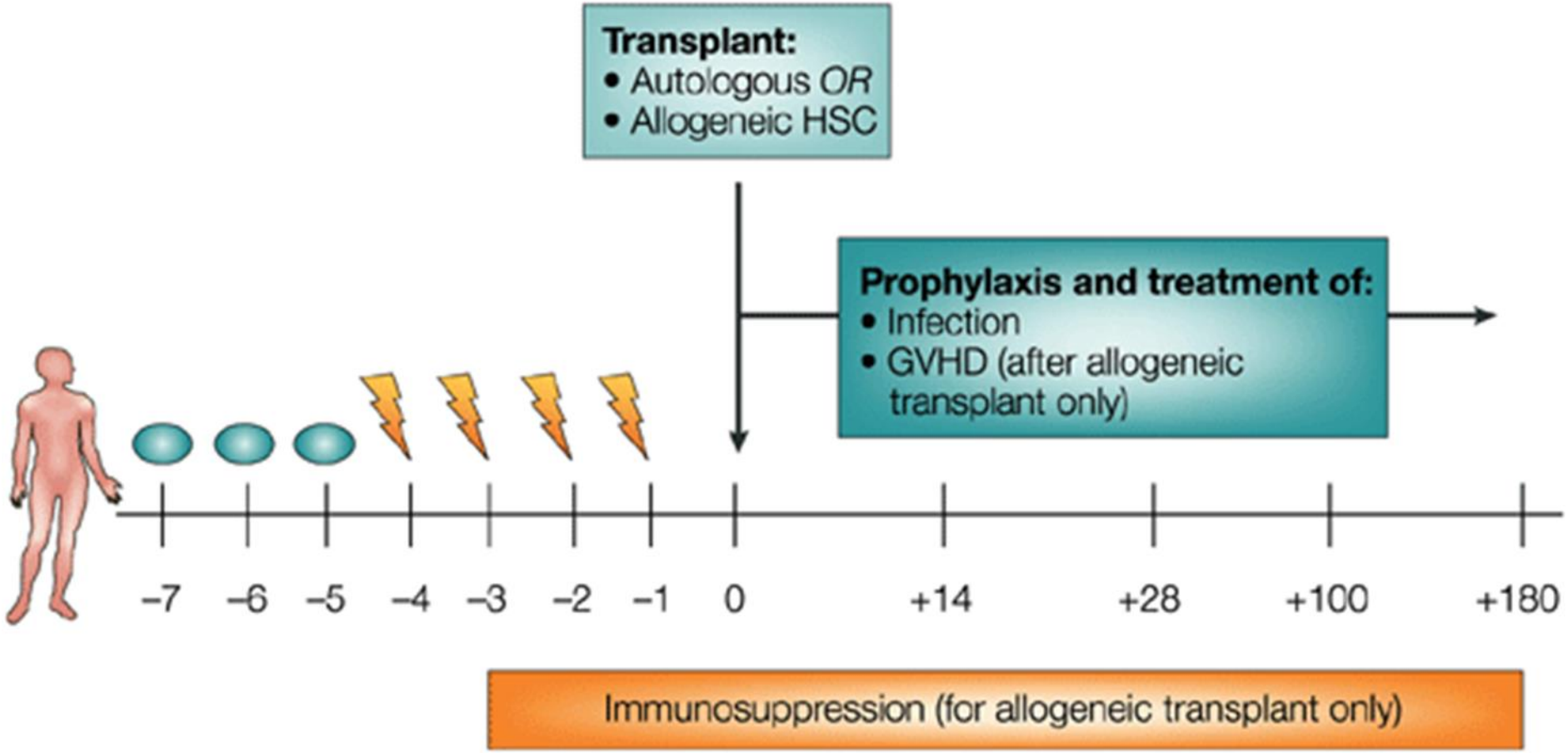
Endikasyonlar

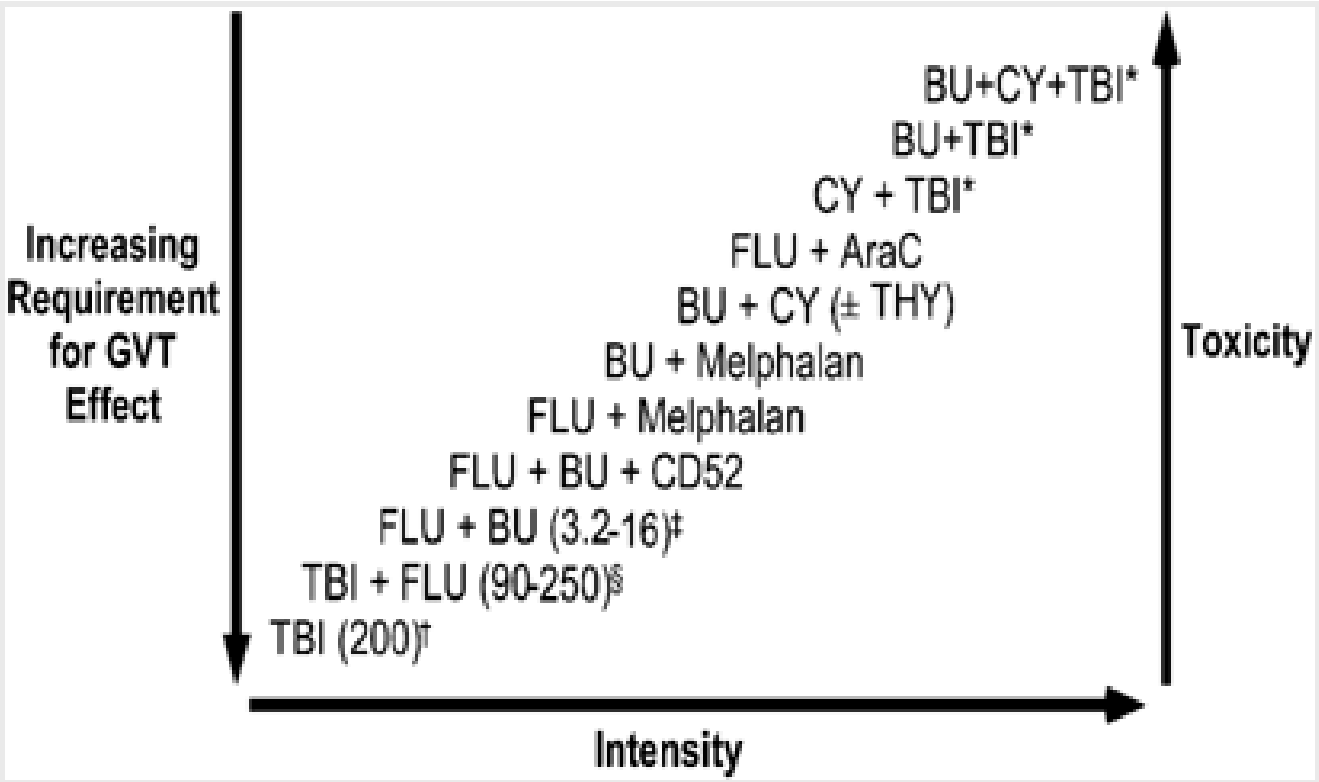
Malign Hastalıklar	Benign Hastalıklar
Hematolojik Hastalıklar	**Kazanılmış Hastalıklar**
Akut Lösemiler	Aplastik Anemi, Saf eritroid hücre aplazisi
Kronik Lösemiler	Paroksismal Noktürnal hemoglobinüri
Myelodisplastik Sendromlar	Otoimmun hastalıklar (Multiple Skleroz, SLE, Romatoid Artrit)
Lenfomalar	**Konjenital Hastalıklar**
Plazma hücre hastalıkları	İmmun yetmezlikler (SCID)
Akut Lösemiler	Hemoglobinopatiler
Solid Tümörler	Konjenital Anemiler (Fankoni Anemisi)
Renal hücreli karsinom	Depo Hastalıkları (Mukopolisakkaridozlar)
Ewing Sarkomu	Kemik iliği yetmezliği sendromları (Diskeratozis Konjenita)
Nöroblastoma	Osteopetrozis
Meme, Kolon, Over, pankreas tümörleri (deneysel)	

Hazırlık Rejimi

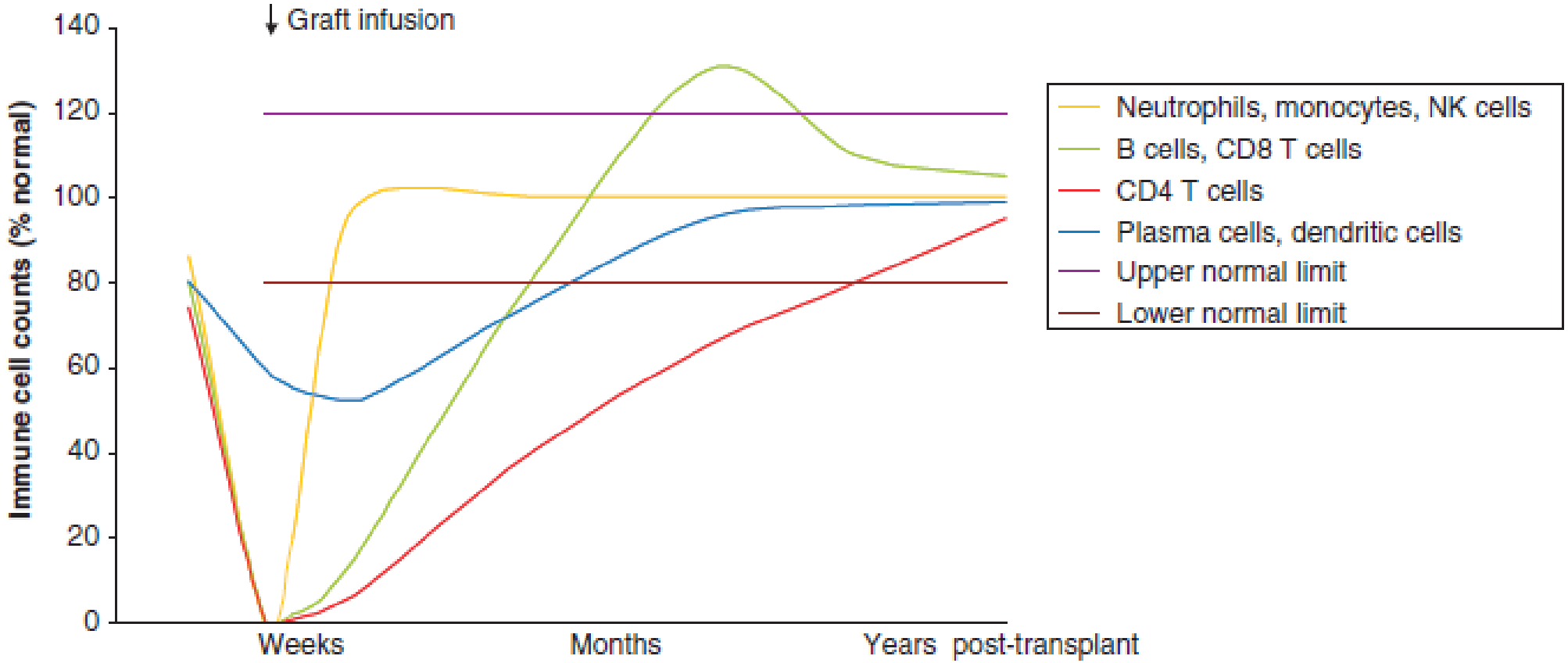
1. Altta yatan hastalığı eradike etmek (Ablasyon)

2. Hastanın immun sistemini baskılayarak graft reddini engellemek

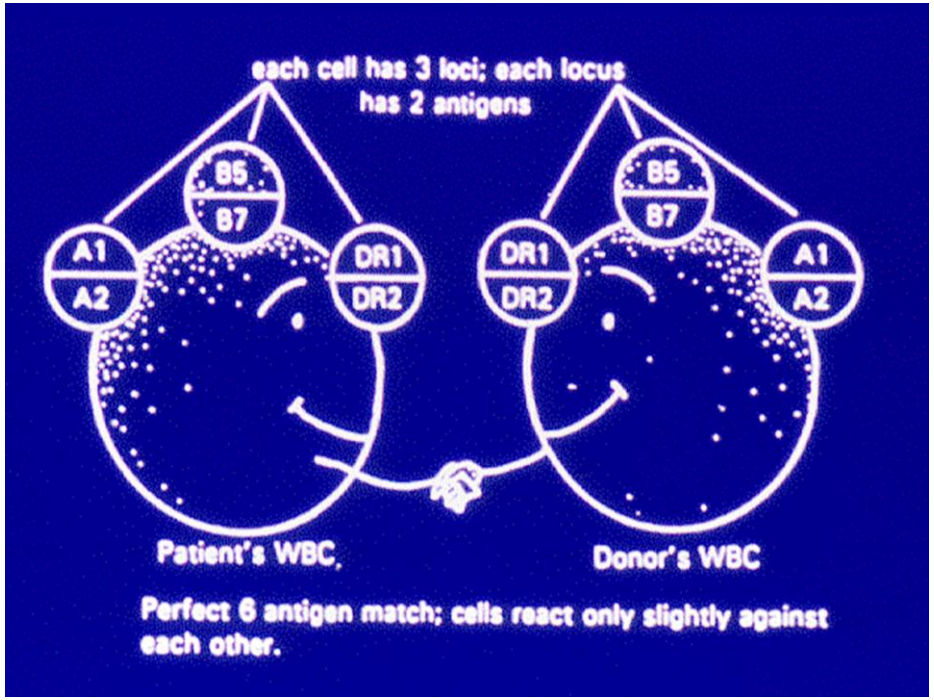

Transplant:
• Autologous OR
• Allogeneic HSC
Prophylaxis and treatment of:
• Infection
• GVHD (after allogeneic transplant only)
−7
−6
−5
−4
−3
−2
−1
0
+14
+28
+100
+180
Immunosuppression (for allogeneic transplant only)
Transplant outcome:
• Age and fitness of patient
• Response of tumour to chemotherapy, radiotherapy and GVL effect (after allogeneic transplant only)
Chemotherapy
Radiation

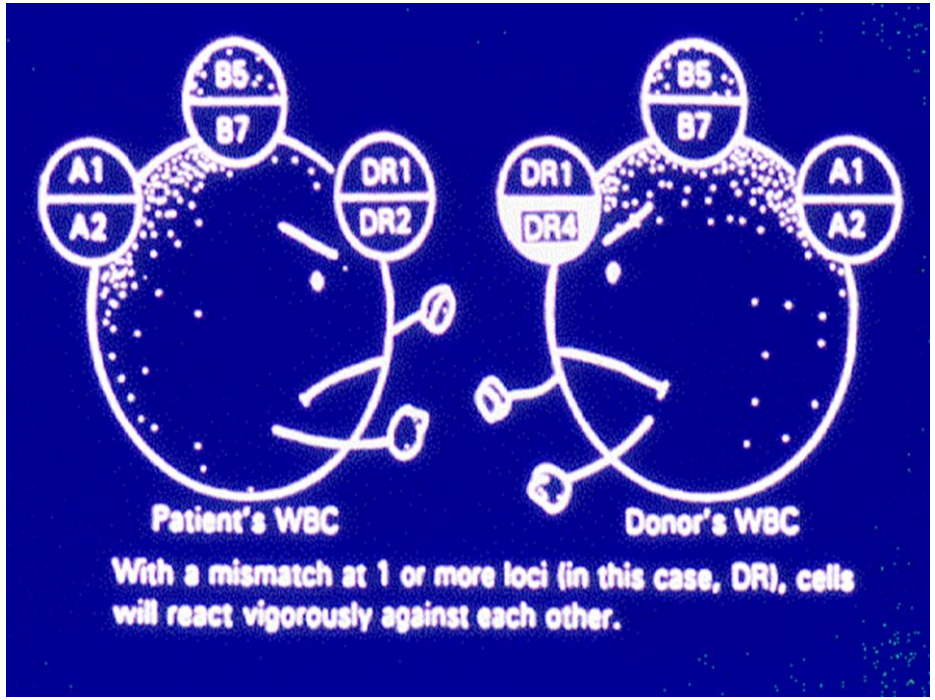

Increasing Requirement for GVT Effect
BU+CY+TBI*
BU+TBI*
CY + TBI*
FLU + AraC
BU + CY (± THY)
BU + Melphalan
FLU + Melphalan
FLU + BU + CD52
FLU + BU (3.2-16)‡
TBI + FLU (90-250)§
TBI (200)†
Toxicity
Intensity

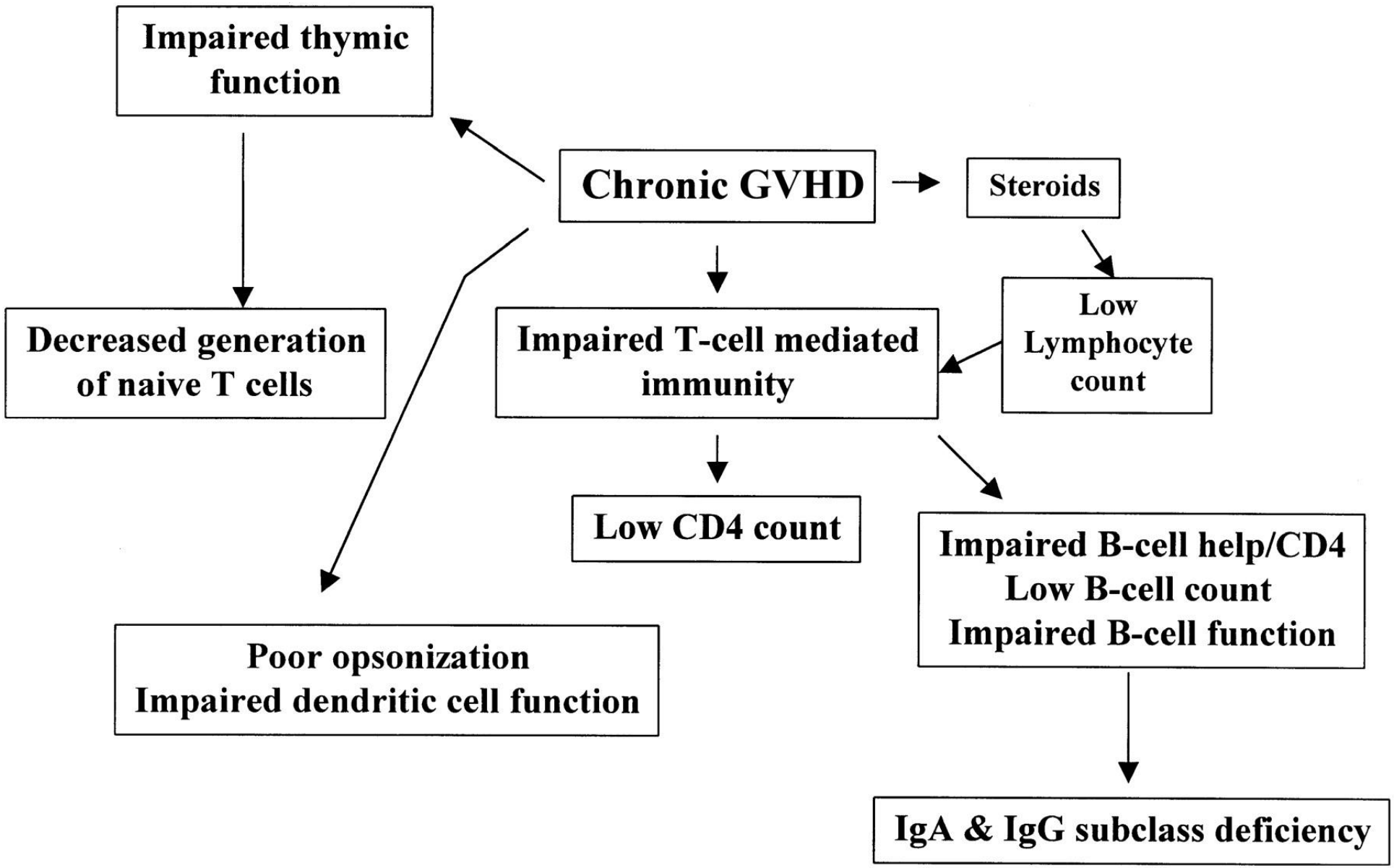
KHN GEÇ KOMPLİKASYONLAR
Kronik graft versus host hastalığı
Enfeksiyonlar
Akciğer ve hava yolu hastalıkları (Bronchiolitis obliterans)
Otoimmun disfonksiyon
Büyüme ve gelişme geriliği
Endokrin disfonksiyon
Sterilite
Katarakt
Diş problemleri
Osteopeni ve Osteoporoz
Aseptik kemik nekrozu
Yeni maliniteler
Psikososyal sorunlar

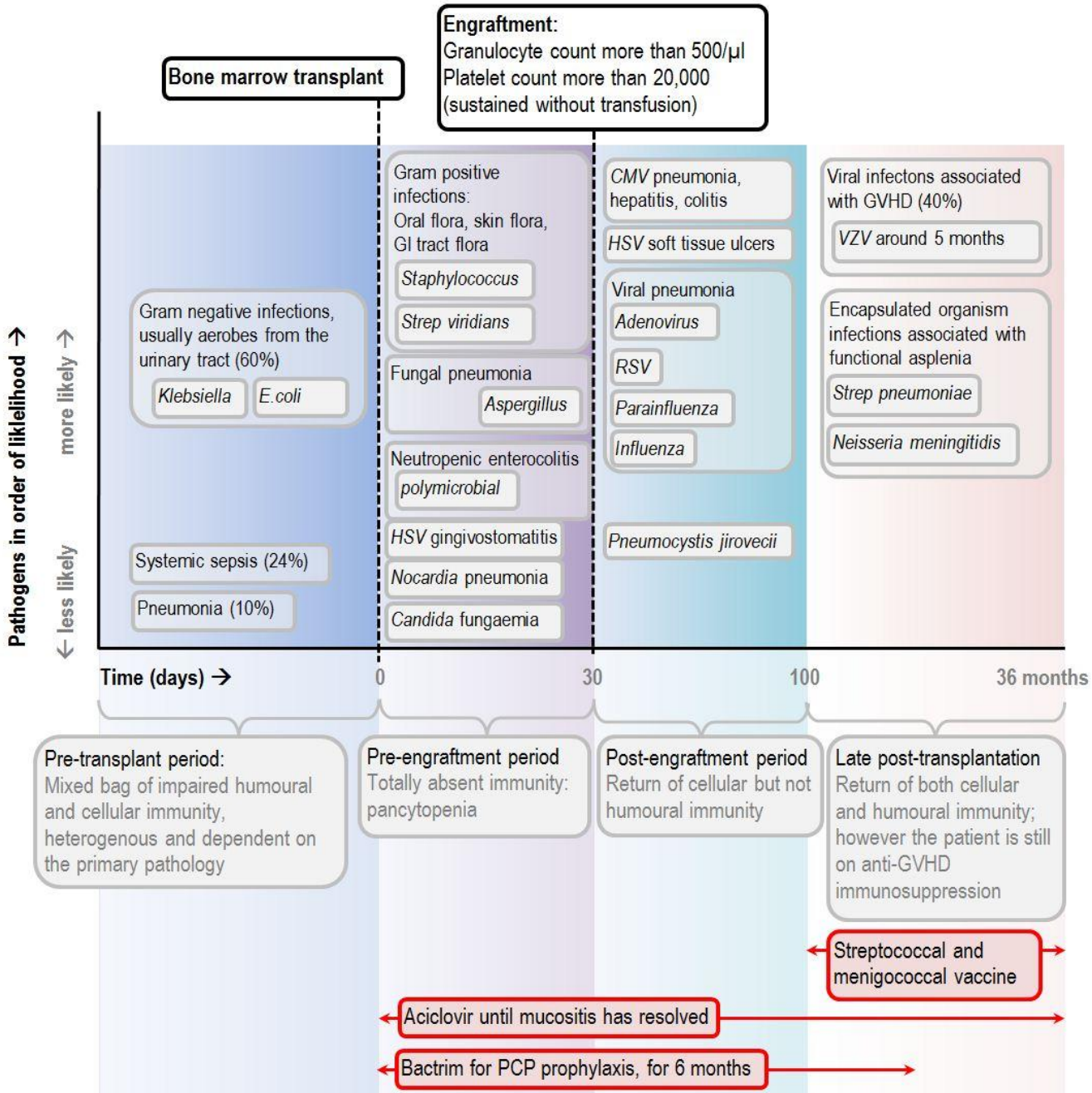

Graft infusion
Immune cell counts (% normal)
140
120
100
80
60
40
20
0
Weeks
Months
Years post-transplant
Neutrophils, monocytes, NK cells
B cells, CD8 T cells
CD4 T cells
Plasma cells, dendritic cells
Upper normal limit
Lower normal limit


HOST
GRAFT
V.S.
GRAFT
HOST


each cell has 3 loci; each locus has 2 antigens
B5
B7
A1
A2
DR1
DR2
Patient's WBC
Donor's WBC
Perfect 6 antigen match; cells react only slightly against each other.


B5
B7
A1
A2
DR1
DR2
DR4
Patient's WBC
Donor's WBC
With a mismatch at 1 or more loci (in this case, DR), cells will react vigorously against each other.


Impaired thymic function
Chronic GVHD
Steroids
Decreased generation of naive T cells
Impaired T-cell mediated immunity
Low Lymphocyte count
Low CD4 count
Impaired B-cell help/CD4
Low B-cell count
Impaired B-cell function
Poor opsonization
Impaired dendritic cell function
IgA & IgG subclass deficiency


Engraftment:
Granulocyte count more than 500/µl
Platelet count more than 20,000
(sustained without transfusion)
Bone marrow transplant
Pathogens in order of liklelihood →
more likely →
← less likely
Gram negative infections, usually aerobes from the urinary tract (60%)
Klebsiella
E.coli
Systemic sepsis (24%)
Pneumonia (10%)
Gram positive infections: Oral flora, skin flora, GI tract flora
Staphylococcus
Strep viridians
Fungal pneumonia
Aspergillus
Neutropenic enterocolitis
polymicrobial
HSV gingivostomatitis
Nocardia pneumonia
Candida fungaemia
CMV pneumonia, hepatitis, colitis
HSV soft tissue ulcers
Viral pneumonia
Adenovirus
RSV
Parainfluenza
Influenza
Pneumocystis jirovecii
Viral infectons associated with GVHD (40%)
VZV around 5 months
Encapsulated organism infections associated with functional asplenia
Strep pneumoniae
Neisseria meningitidis
Time (days) →
0
30
100
36 months
Pre-transplant period:
Mixed bag of impaired humoural and cellular immunity, heterogenous and dependent on the primary pathology
Pre-engraftment period
Totally absent immunity: pancytopenia
Post-engraftment period
Return of cellular but not humoural immunity
Late post-transplantation
Return of both cellular and humoural immunity; however the patient is still on anti-GVHD immunosuppression
Streptococcal and menigococcal vaccine
Aciclovir until mucositis has resolved
Bactrim for PCP prophylaxis, for 6 months

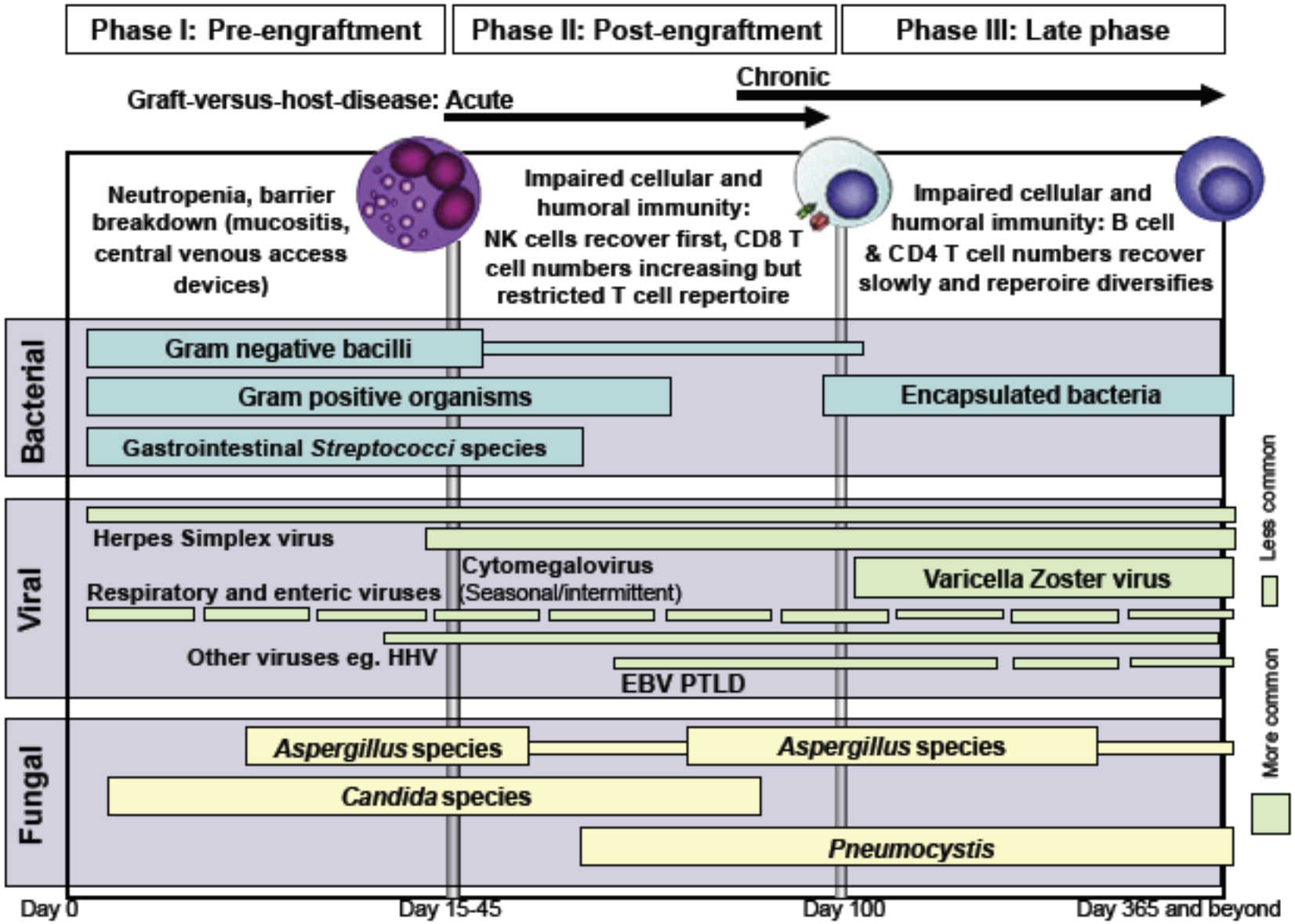


Figure 1: Phases of opportunistic infections among allogeneic HSCT recipients

Kedia S, Acharya PS, Mohammad F, Nguyen H, Asti D, et al. (2013)
J Stem Cell Res Ther S3:002. doi:10.4172/2157-7633.S3-002

İmmun sistemi Baskılanmış Konak

- Hazırlık rejimi
- Graft versus host hastalığı profilaksisi ve tedavisi
- Graft versus Host hastalığının kendisi

İlk 30 gün

- Hazırlık rejimi, bakteriemi, mukozit, kateter ilişkili enfeksiyonlar ağırlıktadır. Temel faktör Nötropeni ve doku hasarıdır.

Cord Koliti

- Yeni tanımlanmış bir bakteriel enfeksiyon tipi
- Kilo kaybı persistan diare, ateş
- Abdominal BT de fokal veya difüz kolon duvarı kalınlaşması
- Kolonoskopide eritemli bir mukoza
- Tanı kolon biyopsisi ile
- Granülomlarla seyreden kronik aktif kolit (GVHD de apoptoz hakim)
- **Bradyrhizobium enteritis**

30-80 gün

- Klasik fırsatçı enfeksiyonlar söz konusudur.
- Sitomegalovirus
- PCP pnömonisi
- Toksoplazmosis
- Nocardia
- İnvaziv aspergilloz
- Diğer küf mantarı enfeksiyonları

> +180 gün

- Enkapsüle mikroorganizmalar
- Varicella Zoster Virüsü
- PCP pnömonisi

Profilaksi uygulamaları

- Tüberküloz profilaksisi → ppd, TB-Gold
- Anti-bakteriyel profilaksi
- Anti-fungal profilaksi

Pre-emptif tedaviler

- Sitomegalovirüs enfeksiyonlarına karşı uygulanmaktadır
- Hepatit??

Viral enfeksiyonlar

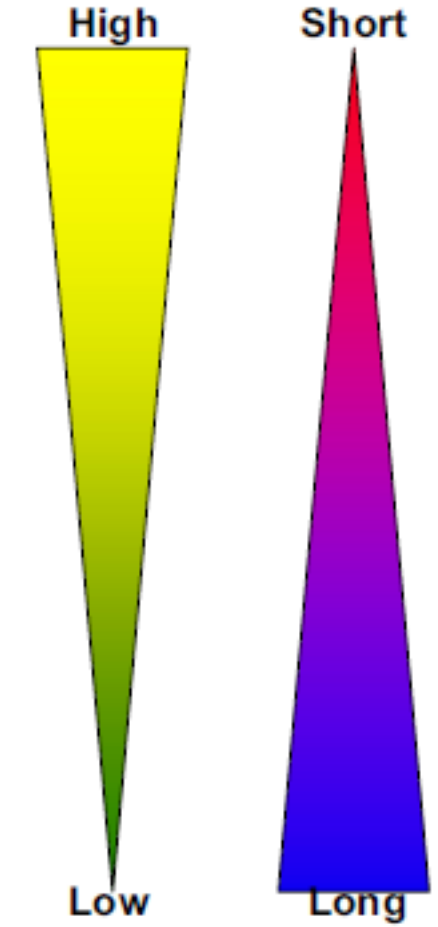
- CMV
- HSV
- VZV
- Adenovirus
- Epstein-Barr Virüsü (EBV)
- Human Herpes Virüs-6 (HHV-6)
- Solunum Yolu Virüsleri (İnfluenza, parainfluenza Tip III, RSV)
- Hepatitler

Sitomegalovirüs Enfeksiyonları

- Transplant sonrası 2-6 aylar arası en riskli dönem
- Tüm adaylar nakil öncesi CMV immunitesi açısından tetkik edilmeli
- CMV geçirmiş ve «CMV naive» donörden graft alanlar özel risk altındadır

Sitomegalovirüs Enfeksiyonları

- Graft versus host hastalığı riski belirgin ölçüde arttırır
- T hücre ayıklanmış graftler
- Düşük CD 4 sayısı
- Kordon kanından yapılan nakiller de artmış risk taşır



Immuno-suppression	CMV doubling time	Risk Groups	CMV Plasma DNA Level to Start PET at FHCRC*	CMV Whole Blood DNA Level to Start PET at Karolinska Institute**
High	Short	Cord blood	Any level	1000 copies
		Allograft - High-dose steroids+ - T cell depletion - Anti-T cell antibodies - CD34 selection	> 100 copies/mL	1000 copies
		Allograft - Low dose steroids - No T cell depletion or anti T cell antibodies	> 500 copies/mL > or 5-fold ⇑ †	1000 copies
Low	Long	Allograft - after day 100	> 1000 copies/mL > or 5-fold ⇑ †	1000 copies if GVHD Other individual assessment based on ⇑

* Assays performed weekly or twice weekly (highest risk); limit of detection 25 copies/mL
+ 1 mg per kg of prednisone or higher
† If initial level is less than threshold
** Assays performed weekly, limit of detection 50 copies/mL

(Blood. 2009;113:5711-5719)

Figure 1. CMV viral load to start preemptive therapy (PET) used at the FHCRC in Seattle, WA, and the Karolinska Institute, Stockholm, Sweden.

Sitomegalovirüs Enfeksiyonları

- İlk 100 gün Gansiklovir/Valagansiklovir profilaksisi
- Veya ilk 100 gün veya immusupresyon devam ettiği sürece pre-emptif tedavi, lökosit filtresi, CMV (-) kan ürünleri
- Haftalık CMV takibi ile tedavi planı yapılır

Sitomegalovirüs Enfeksiyonları

- Pnömoni
- Hepatit
- Gastroenterit
- Retinit
- Ensefalit

Factors Associated with Cytomegalovirus Reactivation Following Allogeneic Hematopoietic Stem Cell Transplantation: Human Leukocyte Antigens Might Be Among the Risk Factors

Allojeneik Kök Hücre Nakli Sonrası Sitomegalovirus Reaktivasyonu ile İlişkili Faktörler: İnsan Lökosit Antijenleri Risk Faktörleri Arasında Olabilir

Kadir Acar[1], Şahika Zeynep Akı[1], Zübeyde Nur Özkurt[1], Gülendam Bozdayı[2], Seyyal Rota[2], Gülsan Türköz Sucak[1]

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Abstract:

Objective: Cytomegalovirus (CMV) is a significant cause of morbidity and mortality in allogeneic hematopoietic stem cell transplantation (AHSCT) recipients. Current practice includes prophylactic and preemptive treatment modalities, which have risks, side effects, and costs of their own. There is no established risk scoring system that applies to all patients. We aimed to investigate the risk factors for CMV reactivation in AHSCT recipients.

Materials and Methods: We retrospectively analyzed the risk factors for CMV reactivation in 185 consequent AHSCT recipients transplanted between September 2003 and December 2009 at the Stem Cell Transplantation Unit of Gazi University. Besides the standard transplant-related parameters, HLA antigens were also included among the variables analyzed.

Results: Despite the very high rate of donor (94.6%) and recipient (100%) seropositivity, which are the so-called major risk factors in previous reports, our reactivation rate was much lower, with a frequency of 24.9%. The underlying disease, sex, conditioning regimen, and presence of antithymocyte globulin or fludarabine in the conditioning regimen had no impact on reactivation rate. CMV reactivation was significantly more frequent in recipients with graft-versus-host disease (GVHD) compared to those without GVHD ($p<0.0001$). CMV reactivation was significantly more frequent ($p<0.05$) in patients with HLA-B14, HLA-DRB1*01, and HLA-DRB1*13 antigens and less frequent in recipients with HLA-A11 and HLA-DRB1*04 antigens ($p<0.05$).

Conclusion: Universal risk factors/scores that apply to all transplant recipients are required for tailored prophylaxis and/or treatment strategies for CMV reactivation. Uncovering the role of genetic factors, including HLA antigens, as possible risk factors might lead the way to risk-adaptive strategies for adoptive cellular therapy and/or vaccination.

Key Words: Cytomegalovirus reactivation, Human leukocyte antigens, Allogeneic stem cell transplantation, Graft-versus-host disease, Prognosis, CMV scoring index

Direnç ???

Herpes enfeksiyonları

- Profilaksi esastır, 1 yıla kadar veya immunsupresyon devam ettiği sürece, Herpes simplex → mukozit ile ilişkili olabilir, Direnç ???
- Buna karşın enfeksiyon gelişirse tedavi edilir.
- Varicella Zoster ile temas olursa tedavi düşünülür

Epstein B virus

- Bir çeşit lenfomaya yol açar
- Ekstranodal bölgeleri tutma eğilimindedir
- T hücre ayıklanması ve Kordon kanı nakilleri özel risk gruplarıdır.
- Risk yüksek ise EBV-PCR ile takip önerilir

HHV-6 Virus (HHV-7, HHV-8…)

- Pansitopeni
- Pnömonitis
- Ensefalit (özellikle kordon kanı nakillerde, %1-2)

Solunum Yolu Virüsleri

- Adenovirus,
- Respiratuar Sinsityal Virus
- Human Metapneumovirüs
- İnfluenza
- Hafif hastalıktan-Fulminan dissemine enfeksiyona kadar değişen tablolar

RSV

- Pnömoniye progrese olan üst solunum yolu enfeksiyonu
- Geç hava yolu obstrüksiyonu
- İnsidans %10 lara kadar çıkabiliyor
- Olguların %80-90 ında pnömoniye ilerliyor. İleri yaş ve lenfopeni önemli bir risk faktörü…
- ÖLÜMCÜL!!!!
- %30 ilk 7 gün, erken tanı önemli

Human Metapneumovirus

- Fatal seyredebilen alt solunum yolu enfeksiyonları
- İnsidans % 5
- Mortalite % 43 lerde..
- Hızla ilerleyen akciğer infiltratları, Hipotansiyon, septik Şok

Parainfluenza Virüsleri

- Olguların % 90'ından tip 3 sorumlu
- ÜSYE ile başlıyor
- Pnömoniye progresyon RSV ye göre daha az
- Geç hava yolu obstrüksiyonuna yol açabiliyor
- Steroid ve lenfopeni önemli risk faktörleri
- %50 olguda pulmoner kopatojenler söz konusu***
- BRONKOSKOPİ yapılmalı

İnfluenza virüsleri

- En sık tip A görülür
- Sağlık çalışanlarının aşılanması önlenmesinde son derece önemli
- Pnömoniye progresyon görece daha az
- Steroid bir risk faktörü değil
- Prodromal belirtiler görülmez
- Profilaksi mümkündür

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Short communication

H1N1 infection in a cohort of hematopoietic stem cell transplant recipients: prompt antiviral therapy might be life saving

E. Suyani, Z. Aki, Ö. Güzel, Ş. Altindal, E. Şenol, G. Sucak. H1N1 infection in a cohort of hematopoietic stem cell transplant recipients: prompt antiviral therapy might be life saving.
Transpl Infect Dis 2011: 13: 208–212. All rights reserved

E. Suyani[1], Z. Aki[1], Ö. Güzel[2], Ş. Altindal[1], E. Şenol[2], G. Sucak[1]

Departments of [1]Hematology and [2]Infectious Disease, Faculty of Medicine, Gazi University, Ankara, Turkey

E. Suyani, Z. Aki, O. Güzel, Ş. Altindal, E. Şenol, G. Sucak. H1N1 infection in a cohort of hematopoietic stem cell transplant recipients: prompt antiviral therapy might be life saving.
Transpl Infect Dis 2011: **13**: 208–212.

Abstract: Influenza A H1N1 virus, causing a pandemic since spring 2009, has been an important cause of morbidity and mortality worldwide. Patients with hematological malignancies and hematopoietic stem cell transplant (HCT) recipients are in a high-risk group and might require hospitalization more commonly because of H1N1 infection. Early demonstration of H1N1 influenza virus and commencing antiviral therapy promptly can be life saving particularly in immunosuppressed patients. We retrospectively reviewed the data of 10 HCT recipients who were diagnosed with influenza H1N1 infection at the Stem Cell Transplantation Unit of Gazi University Hospital in Turkey, from October through December 2009. All patients, except 1, were started empirically on oseltamivir on admission, after nasopharyngeal and oropharyngeal sampling for H1N1 virus. Four of the patients, 2 of whom developed pneumonia, required hospitalization. One of the patients with pneumonia died of respiratory failure caused by bacterial co-infection. The course of the remaining patients was uneventful. In conclusion, HCT recipients infected with H1N1 during the influenza H1N1 pandemic did not necessarily have an adverse prognosis, particularly with prompt administration of the appropriate antiviral therapy.

Outcome of pandemic H1N1 infections in hematopoietic stem cell transplant recipients

Per Ljungman,[1] Rafael de la Camara,[2] Lena Perez-Bercoff,[1] Manuel Abecasis,[3] Jose Bartolo Nieto Campuzano,[4] M. Jimena Cannata-Ortiz,[2] Catherine Cordonnier,[5] Hermann Einsele,[6] Marta Gonzalez-Vicent,[7] Ildefonso Espigado,[8] Jörg Halter,[9] Rodrigo Martino,[10] Bilal Mohty,[11] Gülsan Sucak,[12] Andrew J Ullmann,[13] Lourdes Vázquez,[14] Katherine N. Ward,[15] and Dan Engelhard[16] for the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT) and the Infectious Complications Subcommittee of the Spanish Group of

ABSTRACT

During 2009, a new strain of A/H1N1 influenza appeared and became pandemic. A prospective study was performed to collect data regarding risk factors and outcome of A/H1N1 in hematopoietic stem cell transplant recipients. Only verified pandemic A/H1N1 influenza strains were included: 286 patients were reported, 222 allogeneic and 64 autologous recipients. The median age was 38.3 years and the median time from transplant was 19.4 months. Oseltamivir was administered to 267 patients and 15 patients received zanamivir. One hundred and twenty-five patients (43.7%) were hospitalized. Ninety-three patients (32.5%) developed lower respiratory tract disease. In multivariate analysis, risk factors were age (OR 1.025; 1.01-1.04; P=0.002) and lymphopenia (OR 2.49; 1.33-4.67; P<0.001). Thirty-three patients (11.5%) required mechanical ventilation. Eighteen patients (6.3%) died from A/H1N1 infection or its complications. Neutropenia (P=0.03) and patient age (P=0.04) were significant risk factors for death. The 2009 A/H1N1 influenza pandemic caused severe complications in stem cell transplant recipients.

Key words: H1N1, influenza, pandemic, HSCT.

Citation: Ljungman P, de la Camara R, Perez-Bercoff L, Abecasis M, Nieto Campuzano JB, Cannata-Ortiz MJ, Cordonnier C, Einsele H, Gonzalez-Vicent M, Espigado I, Halter J, Martino R, Mohty B, Sucak G, Ullmann AJ, Vázquez L, Ward KN, and Engelhard D for the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT) and the Infectious Complications Subcommittee of the Spanish Group of Haematopoietic Stem-cell Transplantation (GETH). Outcome of pandemic H1N1 infections in hematopoietic stem cell transplant recipients. Haematologica 2011;96(8):1231-1235. doi:10.3324/haematol.2011.041913

Diğer solunum yolu virüsleri

- Human Rhinovirüs, enterovirüs
- Human Coronavirüs
- Human Bocavirus
- WU/KU polyoma virüs

Adenovirüsler

- Transplant alıcılarında sık görülür
- Pnömoni, gastrointestinal hastalık, hepatit, nefrit, sistit ve göz enfeksiyonları yapar
- TBI, Genç yaş, T hücre ayıklanması, TBI, GVHD, UCB risk faktörleri
- % 30-50 FATAL !!!!!

BK Polyomavirus

- Transplant alıcılarının %5inde
- Engrafman sonrası hemorajik sistit tablosu ile ilişkilidir
- Nefritis ve pnömonitis de yapabilir, Plasma viremisi önemlidir
- Özellikle viral yük 10 000 kopyayı geçince etken olması muhtemeldir
- İdrarda virüsün anlamı tartışmalı…

TABLE 4. Post-Transplantation Immunization Schedule

Organism	Vaccine	Time Post-HSCT to Initiate Vaccine	Dose and Route	Comments
Inactivated Vaccines				
Pneumococcal	PCV7/ PPSV23	3–6 months	0.5 ml IM or SQ	Can be given six months post-transplantation
Pertussis, tetanus, diptheria	DTAP	6–12 months	0.5 m. IM	Can be given six months post-transplantation
Haemophilus influenzae type B	HIB	6–12 months	0.5 ml IM	Can be given six months post-transplantation
Hepatitis B	–	6–12 months	1 ml IM	Administer to patients who are hepatitis B virus negative.
Meningococcus	–	6–12 months	0.5 ml SQ	Recommended in areas with an increase in meningococcus
Influenza	–	4–6 months	0.5 ml IM (the nasal version is live and, therefore, not recommended)	Give annually as available in the autumn months. May administer four months post-transplantation; however, two doses of the vaccine are suggested.
Live Virus Vaccines				
Measles, mumps, and rubella	MMR	24 months	0.5 ml SQ	MMR should not be given if the patient is immunosuppressed.
Varicella zoster virus (shingles)	Zoster vaccine	Not currently recommended. Clinical trials are ongoing.	–	Not currently recommended; inactivated version is under investigation. Prevention with antiviral medication is recommended.

HSCT—hematopoietic stem cell transplantation; IM—intramuscular; SQ—subcutaneous

Note. Based on information from Cordonnier et al., 2010; Kroger et al., 2011; Ljungman et al., 2009; Tomblyn et al., 2009.

Teşekkürler…….