



PEDİATRİDE GRANÜLOSİT TRANSFÜZYONU



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Pediyatrik Hematoloji-Onkoloji Bilim Dalı



Sunum Planı

- Kemoterapinin indüklediği veya indüklemediği nötroopenik hastalarda infeksiyon riski
- Granülosit tanımı
- Granülosit transfüzyonlarının tarihsel gelişimi
- Pediatrie granülosit transfüzyonlarının indikasyonları ve klinik etkinlik
- Donör hazırlanması
- Granülosit toplama, hazırlama ve kullanım
- Tedaviye yanıtın değerlendirilmesi
- Öneriler

Pediatric Cancers Distribution by Diagnosis



TPOG/TPHD Pediatric Cancer Registry: 2009-2012



Tumor Type	n	%
I Leukaemia	2355	29,34
II Lymphomas and Reticuloendothelial Neoplasm	1505	18,75
III CNS and Miscellaneous Intracranial and Intraspinial Neoplasm	1005	12,52
IV Sympathetic Nervous System Tumors	600	7,48
V Retinoblastom	217	2,70
VI Renal Tumors	400	4,98
VII Hepatic Tumors	116	1,45
VIII Malignant Bone Tumors	523	6,52
IX Soft-Tissue Sarcomas	588	7,33
X Germ Cell, Trophoblastic and Other Gonadal Neoplasm	460	5,73
XI Carcinomas and Other Malignant Epithelial Neoplasm	231	2,88
XII Other and Unspecified Malignant Neoplasm	26	0,32
Total	8026	100,0



- Antibiyotik tedavilerinde ilerlemelere rağmen
- Kemoterapi veya hematopoetik kök hücre nakli yapılan
- Nötropenik hastalarda (özellikle uzamış)
- Mortalite ve morbiditenin en önemli nedeni



İnfeksiyonlar

Nötropeni

Mutlak nötrofil sayısı (MNS) = Total lökosit sayısı
(hücre/mikrolitre) x (nötrofil yüzdesi+ band yüzdesi)
÷ 100

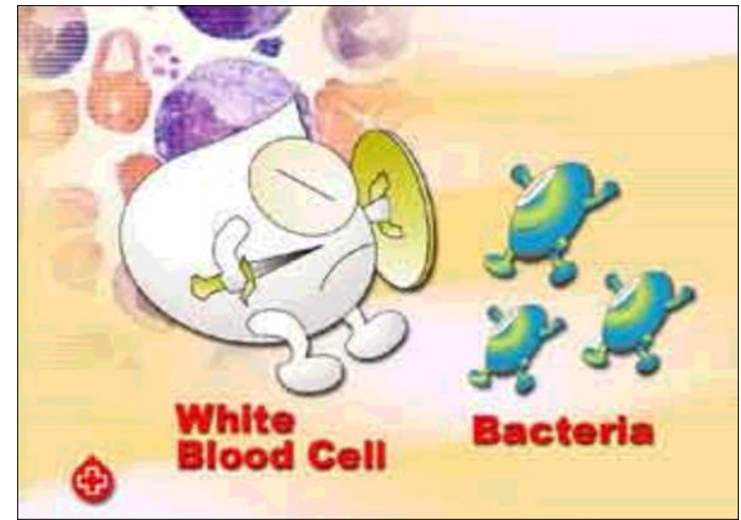
Hafif nötropeni– MNS 1000 to 1500/microL

Orta derecede nötropeni– MNS 500 to 1000/microL

Ağır nötropeni– MNS <500/microL

- Granülosit 500/mm³ olunca infeksiyon riskinde önemli artış!!!!

Nötropenik hastalarda infeksiyon spektrumu



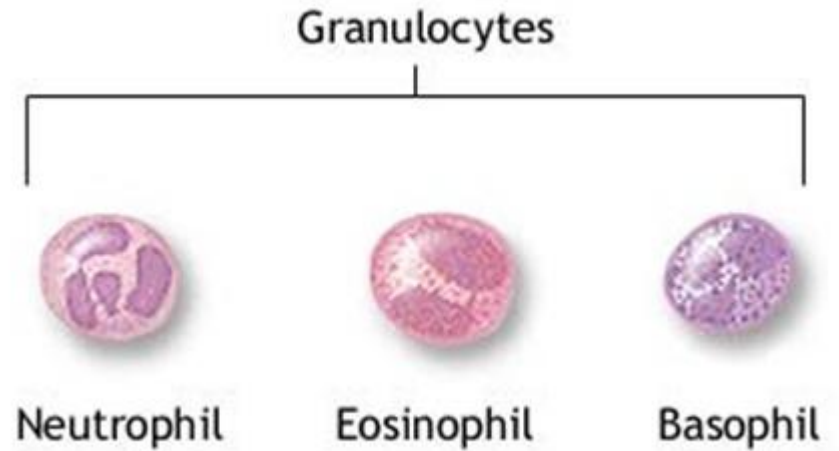
- Multidrug rezistan bakteriyel infeksiyonlar
- Fungal infeksiyonlar: Aspergillus, fusarium, zygomycetes

- Pediatrik onkoloji hastalarında iyileşme oranı son 30 yılda belirgin olarak artmış ve **%70'lere** ulaşmıştır.
- Maliniteli çocuklarda septik şok geliştiğinde mortalite %40
- Hatta KİT yapıp invaziv aspergillus enfeksiyonu olan hastalarda %85' lere kadar yükselmekte

Hallahan AR, Shaw PJ, Rowell G, O'Connell A, Schell D, Gillis J. Improved outcomes of children with malignancy admitted to a pediatric intensive care unit. Crit Care Med. 2000;28:3718–21.

Price TH. The current prospects for neutrophil transfusions for the treatment of granulocytopenic infected patients. Transfus Med Rev.2000;14:2–11.

Granülositler



- Normal kişilerde günlük granülosit üretimi 6×10^{10} /gün
- Yarılanma ömrü 6-7 saat
- Birkaç saatten fazla depolanamaz, hızla viabilitesini kaybederler.
- Granülositler toplanıp, günlük kullanılmalı

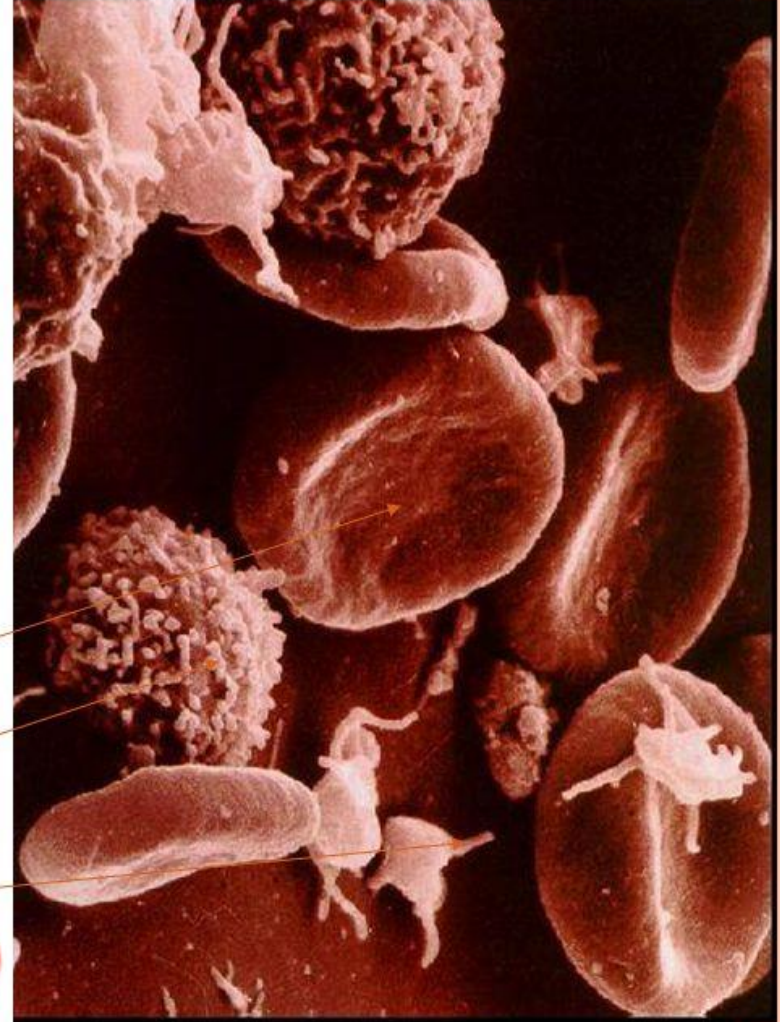


Kan Hücreleri

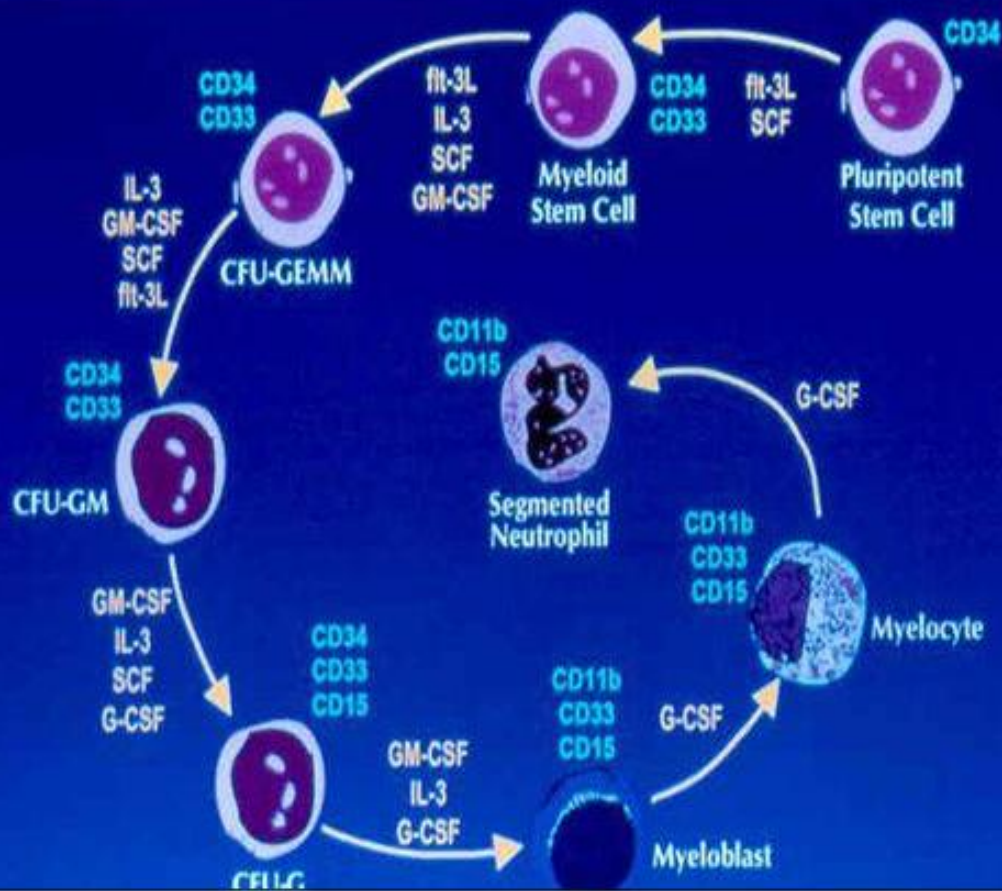
Eritrositler

Granülositler

Trombositler
(10.000 kat büyütme)



GRANULOCYTE DEVELOPMENT



Tarihçe



- Nötrofilik granülositlerin infüzyonu ile konağın direncini arttırma, 80 yıldan uzun süredir araştırılmakta.
- **1934** Strumia: Nötropenili hastalara intramuskuler lökosit krem enjeksiyonu, 9/10 hastada nötrofil sayısında artış
- **1953** Normal lökositlerin ilk transfüzyonu ➡ letal olarak ışınlanmış köpeklerle isogeneik lökositler verilmiş, doza bağlı olarak bakteriyel sepsisemiden hayvanları koruyabildiği gösterilmiş.

- Strumia MM. The effect of leukocytic cream injections in the treatment of the neutropenias. Am J Med Sci 1934;187:527–44.
- Brecher G, Wilbur KM, Cronkite EP. Transfusions of separated leukocytes into irradiated dogs with aplastic marrows. Proc Soc Exp Biol Med 1953; 84:54–6.
- Brecher G, Cronkite EP, Bond VP, Dutcher TF. Problems of leukocyte transfusions. Acta Haematol (Kbh) 1958; 20:179–84.
- Brecher G, Wilbur KM, Cronkite EP. Transfusions of separated leukocytes into irradiated dogs with aplastic marrows. Proc Soc Exp Biol Med 1953; 84:54–6.



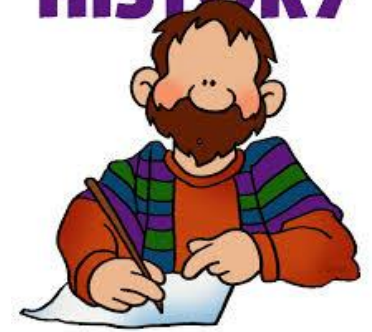
- **1958** Sıçan lökositlerinin farelere enjekte edildiğinde bazı fonksiyonlarını sürdürdüğünün gösterilmesi
- **1964** Granülositlerin tedavi edilmemiş KML'li hastalardan toplanma çabaları → Donör bulmaktaki zorluk, hücre engrafman olasılığı, potansiyel patojenlerin transmisyon riski → KML hastalarından granülosit toplanmasının başarısızlıkla sonuçlanmasına neden olması.

Brecher G, Cronkite EP, Bond VP, Dutcher TF. Problems of leukocyte transfusions. Acta Haematol (Kbh) 1958; 20:179–84.

Freireich EJ, Levin RH, Whang J, Carbone PP, Bronson W, Morse EE. The function and fate of transfused leukocytes from donors with chronic myelocytic leukemia in leukopenic recipients. Ann NY Acad Sci 1964; 113: 1081–90.

Strauss RG. Therapeutic granulocyte transfusions in 1993. Blood 1993; 81: 1675–8.

Schiffer CA, Aisner J, Dutcher JP, Wiernik PH. Sustained post-transfusion granulocyte count increments following transfusion of leukocytes obtained from donors with chronic myelogenous leukemia. Am J Hematol 1983; 15:65–74.



- **1970 li yıllar:** Filtrasyon lökoforezi ile granülosit toplama çabaları

Filtrelerin hücreleri travmatize ve aktive etmesi →


Granül salınım ve kompleman aktivasyonu →


Toplanan hücrelerin yaşam sürelerinin kısa olması,
pulmoner sekestrasyon olasılığı

McCullough J, Weiblen BJ, Deinard AR, Boen J, Fortuny IE, Quie PG. In vitro function and post transfusion survival of granulocytes collected by continuous-flow centrifugation and by filtration leukapheresis. Blood 1976; 48:315–26.

Hammerschmidt DE, Craddock PR, McCullough F, Kronenberg RS, Dalmasso AP, Jacob HS. Complement activation and pulmonary leukostasis during nylon fiber filtration leukapheresis. Blood 1978; 51:721–30.



- **1975: Sürekli akım santifigurasyon lökoforezi**
(Günümüzde de standart olan metod)
 - Periferik kanda lökosit sayısını yükseltmek için donörlere kortikosteroid verildi, eritrosit çöküşünü hızlandırmak için hidroksietil starch (HES) kullanıldı.
- 
- 10×10^9 - 30×10^9 sayıda (Günlük üretimin %10-30) nötrofil toplanması mümkün oldu.

- **1972-1982:** Birçok klinik çalışma, çelişkili sonuçlar
6 tanesinde iyi yanıt
- **1985-1995:** Antibiyotiklerin gelişimi, destek bakımda ilerlemeler, granülosit toplama ve transfüzyonda zorluklar
 Granülositlerin klinik kullanımdan çekilmesi
- **1990:** Aferez tekniklerinde gelişme
- **2000:** Donör granulosit yapımının G-CSF ve steroidle uyarılması

G-CSF stimulasyonundan sonra toplanan nötrofillerin kalitesi

- Transfüzyonda sonra daha uzun ömür (genç?)
- Apoptozda gecikme
- İnvitro fonksiyonlarda artma (örneğin, solunum patlaması, kemotaksis ve bakterisidal aktivite)

Joos K, Herzog R, Einsele H, et al. Characterization and functional analysis of granulocyte concentrates collected from donors after repeated G-CSF stimulation. Transfusion 2002; 42:603.

Leavey PJ, Thurman G, Ambruso DR. Functional characteristics of neutrophils collected and stored after administration of G-CSF. Transfusion 2000; 40:414.

Drewniak A, van Raam BJ, Geissler J, et al. Changes in gene expression of granulocytes during in vivo granulocyte colony-stimulating factor/dexamethasone mobilization for transfusion purposes. Blood 2009; 113:5979.

Granülosit Transfüzyonu-İndikasyonlar

- Kronik granülomatöz hastalık dışında MNS $<500/\text{mm}^3$ olması
- Bakteriyel veya fungal infeksiyon bulguları
(İnfeksiyonun klinik semptomları, pozitif kültürler, biyopsilerden patolojik tanılar, pnömoni radyografik bulguları)
- En az 48 saatlik antimikrobial tedaviye yanıt vermeme (Hayatı tehdit eden infeksiyon durumları hariç)

Granülosit Transfüzyonunun Tedavi Amaçlı Kullanılmaması Gereken Durumlar

- Kemik iliği yetersizliği olup, nötrofilin düzelmesi beklenmeyen ve daha fazla aktif tedavi planlanmayan hastalar
- Nötropeni veya bilinen nötrofil fonksiyon bozukluğunun eşlik etmediği sepsis
- Nedeni bilinmeyen ateş



- **Kemoterapi veya hematopoetik kök hücre nakli sonrası nötropeni** hala bu popülasyonda nadir kullanılmasına rağmen, granülosit süspansiyonlarının en yaygın kullanım alanıdır.
- Anemi ve trombositopeni ➡ Replasman tedavisi
- İnfeksiyonla ilişkili ağır nötropeni Kemik iliğinden granülosit üretimi için G-CSF
- Ancak bu gruptaki hastaların G-CSF yanıtı genellikle iyi değil

Sachs UJ, Reiter A, Walter T, et al. Safety and efficacy of therapeutic early onset granulocyte transfusions in pediatric patients with neutropenia and severe infections. Transfusion 2006; 46:1909.

Stanworth SJ, Massey E, Hyde C, et al. Granulocyte transfusions for treating infections in patients with neutropenia or neutrophil dysfunction. Cochrane Database Syst Rev 2005; :CD005339.

Díaz R, Soundar E, Hartman SK, et al. Granulocyte transfusions for children with infection and neutropenia or granulocyte dysfunction. Pediatr Hematol Oncol 2014; 31:425.

Donör Seçimi

- Donörden onam alınmalı, tıbbi değerlendirme ve virolojik taramadan geçirilmelidir. Donör olmak için gerekli minimum kriterleri taşımalıdır.
- Donörün alıcıyla ABO ve Rh uygunluğu olmalıdır.

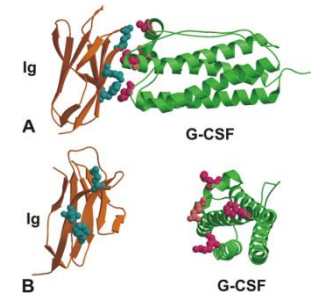
Table 1: Hierarchy for selection of granulocytes by ABO blood group

Recipient group	1st choice donation	2nd choice donation	3rd choice donation
O	O	N/A	N/A
A	A	O HT neg	N/A
B	B	O HT neg	N/A
AB	AB	A (or B) HTneg	O HT neg

- Granülosit donasyonunda, son 30 gün içinde yapılan, kan ile bulaşabilen infeksiyon testleri negatif olmalıdır.
- G-CSF kullanımı onaylanmadığı için hamile ve hemoglobinopatili kişiler donör olmamalı
- Donörün venöz girişime uygun iyi damar yatağı olmalı.
- Steroid ve nişasta allerjisi olmamalı.
- Steroid kullanımına kontrendike hipertansiyon, diyabet, gastrointestinal ülser, glokom, tüberkuloz veya fungal infeksiyon öyküsü olmamalı.

- CMV uyumluluđu araştırılmalıdır. Özellikle CMV (-) alıcıya CMV (-) donörden granülosit transfüzyonu önerilmektedir.
- Ancak bazı çalışmalarda CMV taranmamış GTX ile alıcıda daha fazla CMV reaktivasyonu ya da hastalığı olmadığı gösterildikten sonra bu tarama sorgulanmaya başlamıştır.
- HLA uygun donör tartışmalıdır. Klinisyenler kardeşinden KİT yapılması söz konusu hastalarda alloimmunizasyon olasılığına karşı aile içi donörlerden granülosit transfüzyonundan kaçınmalıdır.

Donör Hazırlanması



- Sağlıklı donörlere G-CSF uygulanmasının etik ve güvenilirlik yönü???
- Granülosit nötrofil kinetiğini ve fonksiyonlarını aktive edici rolü yanında, G-CSF monosit ve lenfosit sayı ve/veya fonksiyonları etkileyebilir.
- Invivo çalışmalarda, G-CSF düzeylerinin, periferik kanda, G-CSF uygulamasından 4 saat sonra maksimuma ulaştığı, 2 günde normal düzeylere döndüğü gösterilmiş.

Anderlini P. Effects and safety of granulocyte colony-stimulating factor in healthy volunteers. *Curr Opin Hematol.* 2009;16:35–40.

Shaw BE, Confer DL, Hwang W, Pulsipher MA. A review of the genetic and long-term effects of G-CSF injections in healthy donors: a reassuring lack of evidence for the development of haematological malignancies. *Bone Marrow Transpl.* 2015;50(3):334–40.

Avalos BR, Lazaryan A, Copelan EA. Can G-CSF cause leukemia in hematopoietic stem cell donors? *Biol Blood Marrow Transplant.* 2011;17:1739–46.

- Elde bulunan mevcut klinik veriler ile, G-CSF ün, normal hematopoetik kök hücrelerde transformasyon yaptığına dair net veri yok.

Geç yan etkilerde muhtemel mekanizmalar mevcut.

- Sitogenetik anormallikler
- Adrenerjik Reseptörler
- DNTM aktivasyonu ve DNA Metilasyonu
- STAT fosforilasyonu
- MLL
- Hox genlerinin deregülasyonu BCL-2 yi regüle etmekte.

Sitogenetik anormallikler

- Birkaç aya kadar devam eden allel replikasyonunda asenkroni
- 268 güne kadar sebat eden aneuploidi
- Birkaç aya kadar devam eden DNA destabilizasyon
- Replikasyon asenkronisi
- Aneuploidi

Adrenerjik Reseptörler

- İnsan CD34+ stem hücrelerinden daha primitif olan CD34+/CD38- hücreler katekolaminerjik reseptör taşır. G-CSF bu reseptör ifadelerini arttırır
- Adrenerjik reseptörler motilite, homing ve proliferasyon ile ilgilidir.
Adrenerjik etkiler leukemia gelişimi ile ilişkili gibi görülmektedir

Nagler, Exp Hematol 2004; Shapira, Am J Hematol 2013; Hirsh, Blood 2011

Lapidot, Hematology 2010; Hanoun, Cell Stem Cell 2014

DNTM aktivasyonu ve DNA Metilasyonu

Sağlıklı stem hücre donörlerinde geçici olarak rHu G-CSF etkisi ile DNMT aktivitesi artmaktadır.

DNMT ifadesinin kanseri olan hastalarda arttığı bilinmektedir

Haematological malignancies developing in previously healthy individuals who received haematopoietic growth factors: report from the Research on Adverse Drug Events and Reports (RADAR) project

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¹VA Midwest Center for Health Services and Policy Research, the Jesse Brown VA Medical Center, ²Divisions of Hematology and Oncology of the Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, ³Washington University School of Medicine, Saint Louis, MO, ⁴University of Nebraska School of Medicine, Omaha, NE, and ⁵Harvard Medical School, Boston, MA, USA

Received 30 June 2006; accepted for publication 3 August 2006

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Summary

Pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) and granulocyte colony-stimulating factor (G-CSF) promote haematopoietic progenitor cell maturation. We reviewed the findings for healthy volunteers/donors who developed haematological malignancies following PEG-rHuMGDF or G-CSF administration. Information was reviewed for three of 538 volunteers who received PEG-rHuMGDF in clinical trials and two of 200 donors who underwent G-CSF mobilised stem cell harvesting procedures for sibling stem cell transplants. Mantle cell, diffuse large B-cell lymphoma and chronic lymphocytic leukaemia were diagnosed 1–5 years after PEG-rHuMGDF exposure among three volunteers. For one patient, thrombocytopenia due to autoantibodies to PEG-rHuMGDF developed shortly after PEG-rHuMGDF administration and persisted until chemotherapy was administered. All three achieved complete remission, although one patient relapsed. Acute myeloid leukaemia was diagnosed 4 and 5 years after G-CSF mobilisation in two donors who underwent peripheral blood stem cell donation for sibling allogeneic haematopoietic stem cell transplantation. Following intensive chemotherapy, one died from acute leukaemia and the second is in complete remission. Controversy exists over the appropriateness of administering haematopoietic growth factors to healthy individuals. While a causal relationship with haematological malignancies cannot be demonstrated, long-term follow-up among healthy individuals who receive haematopoietic growth factors is needed.

Keywords: haematopoietic growth factors, megakaryocyte growth and development factor, granulocyte colony-stimulating factor, Research on Adverse Drug Events and Reports.

Benneth 2006; 538 donör arasında 1-5 yıl sonra, 3 kişide mantle cell, DLBCL ve KLL

200 donör arasında ise 2 AML rapor etti.

Sebe-sonuç ilişkisi kanıtlanmasa da, uzun süreli donör takibinin gerekliliğine işaret etti.

Table 1. Long-term evaluation of leukaemia development among G-CSF treated blood stem cell donors and persons with chronic neutropenia, myelodysplasia or cancer.

Study Type	Population	No. of patients	Median duration of follow-up	Evidence related to leukaemogenesis
Healthy Donors				
Case report (This study)	Leukaemia in healthy donors after PBSC collection	2	6.7 years	Case reports of leukaemia
Case report (Makita <i>et al.</i> 2004)	Leukaemia in a healthy donor after PBSC collection	1	1.2 years	Case report of leukaemia
Retrospective survey (Cavallano <i>et al.</i> 2000)	Healthy PBSC or Granulocyte donor	101	3.6 years	None
Prospective survey (Tasá <i>et al.</i> 2005)	Healthy PBSC donors	90	2.8 years	None
Retrospective survey (Andersson <i>et al.</i> 2002)	Healthy PBSC donors	281	3.3 years	None
Retrospective examination (Sakamaki <i>et al.</i> 1995)	Bone marrow of healthy PBSC donors	3	5 years	None
Retrospective study (Hosowitz & Carter, 2005)	Haematopoietic stem cell donors	28 134	Not stated	None
Retrospective study (Palapghar <i>et al.</i> 2006)	Normal paediatric haematopoietic cell donors	60 000 sibling donors, 3000 unrelated donors	Not stated	None
Breast cancer patients				
Review (Smith <i>et al.</i> 2003)	NSABP experience in breast cancer studies	8563	7.4 years	5.0-fold increase in AML/MDS compared with patients who did not receive G-CSF (101% vs. 02%).
Review (Hardenman <i>et al.</i> 2006)	Surveillance Epidemiology End Results-Medicare experience with older women with breast cancer	5515	4 years	1.8-fold increase in AML/MDS risk compared with patients who did not receive G-CSF (18 vs. 07%).
Severe chronic neutropenia or Schwachman Diamond syndrome				
Prospective review (Donaldson <i>et al.</i> 2005)	Patients with severe congenital neutropenia followed by the French Severe Chronic Neutropenia Study Group	101	>10 years	11% cumulative incidence of MDS/AML/ALL at 20 years.
Prospective review (Donaldson <i>et al.</i> 2005)	Patients with Schwachman Diamond syndrome followed by the French Severe Chronic Neutropenia Study Group	55	>10 years	19% cumulative incidence of MDS/AML/ALL at 20 years.
Prospective review (Rowenbong <i>et al.</i> 2006)	Patients with severe congenital neutropenia followed by the Chronic Neutropenia International Registry	374	>10 years	21% cumulative incidence for MDS/AML after 10 years of G-CSF therapy and 36% after 12 years. Higher rates among patients who were less responsive to G-CSF.
Prospective review (Rowenbong <i>et al.</i> 2006)	Patients with Schwachman Diamond syndrome followed by the Chronic Neutropenia International Registry	29	>10 year	Two cases (1 month and 2.2 years after initiation of G-CSF). Incidence estimate could not be derived because of small sample size.

Safety of Living Donation of Hematopoietic Stem Cells.

Szer J¹, Elmoazzen H, Fechter M, Hwang W, Korhonen M, Miller J, Mengling T, Shaw B, Stein J.

Author information

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Abstract

More than 12 000 volunteer unrelated donors have been established an expert committee to evaluate the safety of living donation as a necessary part of World Marrow Donor Program. A confidential process designed to alert donors to potential risks to the committee for imputability (causal link between donation and registry. In 2014, there were 50 reports of adverse events in donors including 3 hematologic malignancies, 4 autoimmune phenomena in donors all of which were gastrointestinal, 2 infections, 2 pulmonary, and 6 thought to be less likely causal. The safety of living hematopoietic stem cell donation is a topic of ongoing disorders. A decade of detailed examination

15 ülkeden 50 rapor

16 malignensi gelişimi, 3 ü hematolojik malignensi

14 ünde donasyondan bir yıldan daha sonra

4 ünde otoimmün olay

Geri kalan 30 unda, allerjik, kardiyak, gastrointestinal, infeksiyon ve diğerleri

Granülosit Toplanması

- Aferez yöntemi ile
- Granülositlerin alınıp, eritrosit ve plazmanın donöre geri dönmesi
- Süre 150-180 dakika
- 7-10 lt kan
- Antikoagulan sitrat
- Granülositlerin eritrositlerden ayrımı için donör kanına HES ilavesi
- Donörün vital bulgular açısından izlemi



Toplanan Ürün

- Hacim: 200-250ml
- İçerik 1×10^{10} granülosit

Doz

- < 10 kg: $1-2 \times 10^9/\text{kg}$ nötrofil / granülosit solüsyonu
- >10 kg: 1×10^{10} nötrofil / granülosit solüsyonu
- Adolesan: $5-8 \times 10^{10}$ nötrofil / granülosit solüsyonu
- İstenilen nötrofil düzeyi: Birkaç gün süreyle $1.0 \times 10^9/\text{L}$

Granülosit Saklanması



- Saklamak için uygun değildir, toplandıktan sonra en kısa süre içinde (maksimum 24 saat) transfüze edilmelidir.
- Hemen kullanılamadığı durumlarda, $22 \pm 2^{\circ}\text{C}$ de, ideal olarak çalkalama yapmadan saklanır.
- Eğer granülositler yanlılıkla çalkalanırsa, bu durum transfüzyona engel değildir. Çalkalamanın fonksiyonlarını etkilediğine dair sınırlı delil vardır.
- Seidel MG, Peters C, Wacker A, Northoff H, Moog R, Boehme A, Silling G, Grimminger W, Einsele H. Randomized phase III study of granulocyte transfusions in neutropenic patients. Bone Marrow Transplantation. Advance online publication 11 August 2008; doi: 10.1038/bmt.2008.237
Sasakawa S and Miyamoto M. Studies on granulocyte preservation III. Effect of agitation on granulocyte concentrates (1987). Transfusion 27(2): 165-6

Granülosit Transfüzyonu

Nasıl Yapılır?



- Transfüzyon reaksiyonu riski yüksek olduğundan öncesinde asetaminofen ve difenhidramin ile **premedikasyon**
- Transfüzyon sırasında por büyüklüğü **170 mikron** olan filtreleri içeren standart kan setleri kullanılmalı, yatak başı lökosit filtreleri asla kullanılmamalı
- Çocuk dozu 30 kg altı çocuklara 10-20 ml/kg
- **Yavaş** 2 ml/dak olarak başlatılmalı, yakın vital bulgu, O2 satürasyonu, komplikasyonlar açısından izlenmeli, transfüzyon reaksiyonu yoksa infüzyon hızı, hasta tolere edinceye kadar arttırılmalı
- Ürün **2 saat içinde** transfüze edilmeli
- Transfüzyon reaksiyonu gelişirse, infüzyon hemen durdurulmalı, SF verilmeli
- Ürün hemen imha edilmemeli, kan bankasına bilgi verilmeli, hasta tekrar değerlendirilmeli, bulgular düzeldiyse infüzyona devam edilmeli
- Granülosit imha kararı mutlaka doktor tarafından verilmeli

Tedaviye Yanıtın Değerlendirilmesi



- Günlük mutlak nötrofil, lökosit sayısı izlemi
- **5.1×10^{10}** granülosit içeren transfüzyon yapıldığında MNS sayısında **1000/microL** artış, **1-1.5 gün**
- Hastaların infeksiyon belirti ve bulguları, mikrobiyolojik kültür ve görüntüleme yöntemleri ile izlenmesi
- Günlük granülosit transfüzyonu, ağır nötroopenik hastalarda, nötrofil sayısını yükseltme yanında, bakterisidal, fungisidal, kemotaktik aktivitenin artmasını, ekstrasvasküler alana lokalize infeksiyon alanına nötrofil migrasyonunu sağlar.

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Vij R, DiPersio JF, Venkatraman P, et al. Donor CMV serostatus has no impact on CMV viremia or disease when prophylactic granulocyte transfusions are given following allogeneic peripheral blood stem cell transplantation. *Blood* 2003; 101:2067.

Ein-Gal S, Pepkowitz SH, Hurvitz CH, Goldfinger D. Dramatic tissue response after a single granulocyte transfusion. *Transfusion* 2007; 47:2185.

Tedavi Sonlandırma Kriterleri



- Klinik belirti ve bulgularla ve laboratuvar, radyolojik bulgularla enfeksiyonun gerilemesi
- Granülosit transfüzyonu almadan, kemik iliği recovery bulgularından olan MNS'nin 3 gün 500/ mm³ üzerinde olması
- Granülosit transfüzyonuna kötü yanıtın göstergesi olarak hastanın klinik durumunun kötüleşmesi (Tedavi planı ailden onay alınarak palyatif bakım olarak yapılır.) Granülosit transfüzyonu, palyatif bakımın bir bölümü olarak düşünülmemektedir.

Süre: Hastanın klinik durumu, tedavi planı, tedaviye yanıt ve donör bulabilme durumuna göre 3 gün-aylar

Yanıtın Değerlendirilmesi

The Resolving Infection in Neutropenia with Granulocytes (RING)



Blood. 2015 Oct 29; 126(18): 2153–2161.

PMCID: PMC4626256

Republished online 2015 Sep 2. doi: [10.1182/blood-2015-05-645988](https://doi.org/10.1182/blood-2015-05-645988)

Efficacy of transfusion with granulocytes from G-CSF/dexamethasone–treated donors in neutropenic patients with infection

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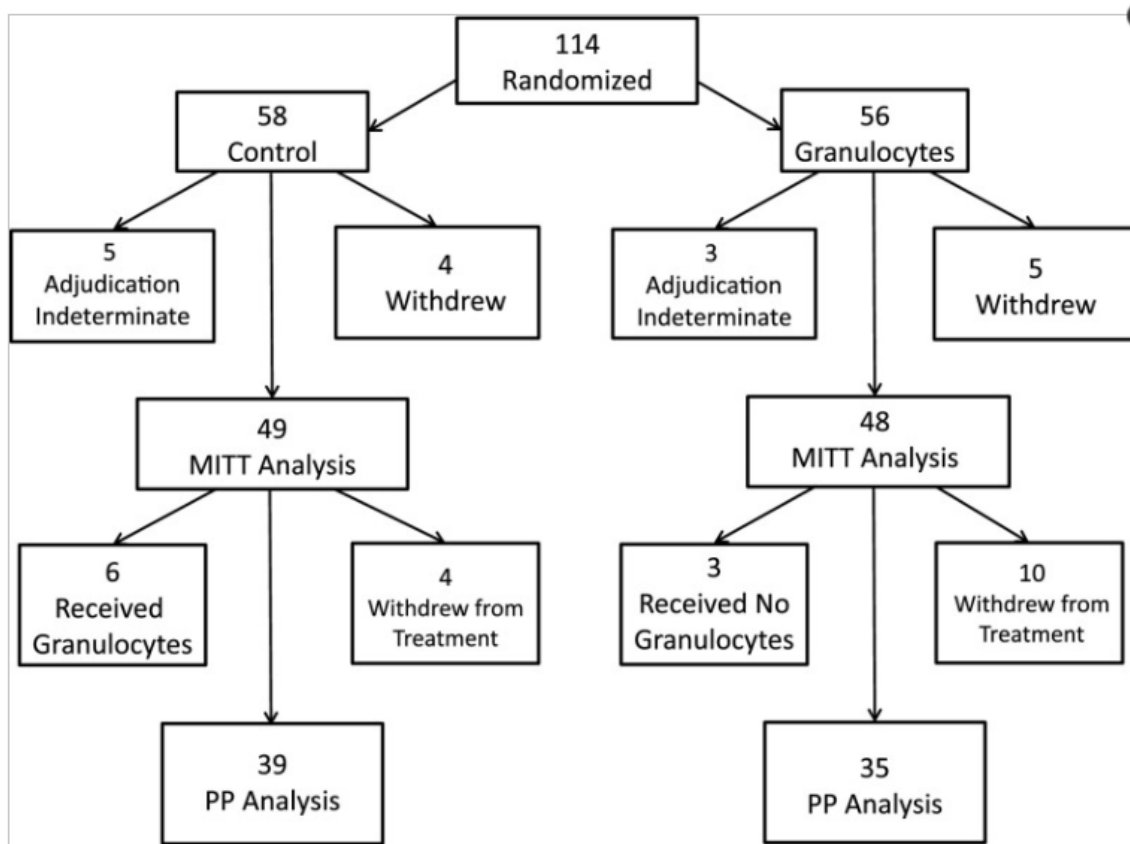
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Randomize Granülosit Çalışması



- Kesin veya olası tanı
- Bakteriyel/fungal infeksiyon
- G-CSF ile mobilizasyon
- 114 hasta
- Kemoterapi/HSCT
- Nötrofil < 500 mm³
- 97 hasta çalışmayı tamamladı

Flow diagram of the study. A total of 114 patients were randomized, 56 to the granulocytes group and 58 to the control group. Nine subjects withdrew from the study, and an additional 14 subjects withdrew from treatment.

Baseline characteristics for modified intention-to-treat subjects (N = 97)

	Treatment arm		<i>P</i> [*]
	Control, n = 49	Granulocytes, n = 48	
Age, y	46.9 ± 20.2	54.9 ± 17.1	.04
<18, n (%)	6 (12)	4 (8)	.24
18-64, n (%)	33 (67)	27 (56)	
>65, n (%)	10 (20)	17 (35)	
Male sex, n (%)	27 (55)	28 (58)	.84
Race, n (%)			.18
White	31 (63)	37 (77)	
Asian	4 (8)	1 (2)	
Black/African American	1 (2)	3 (6)	

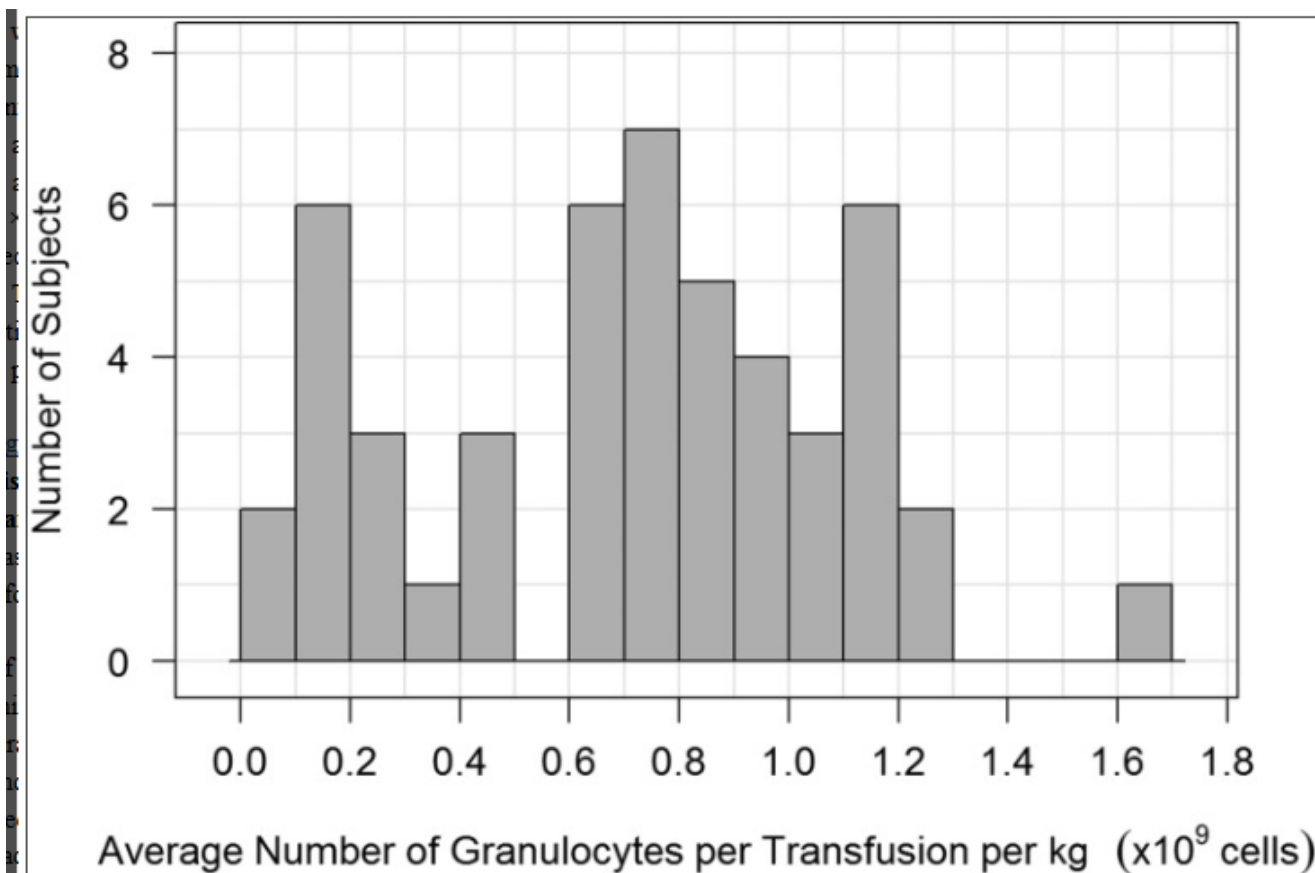
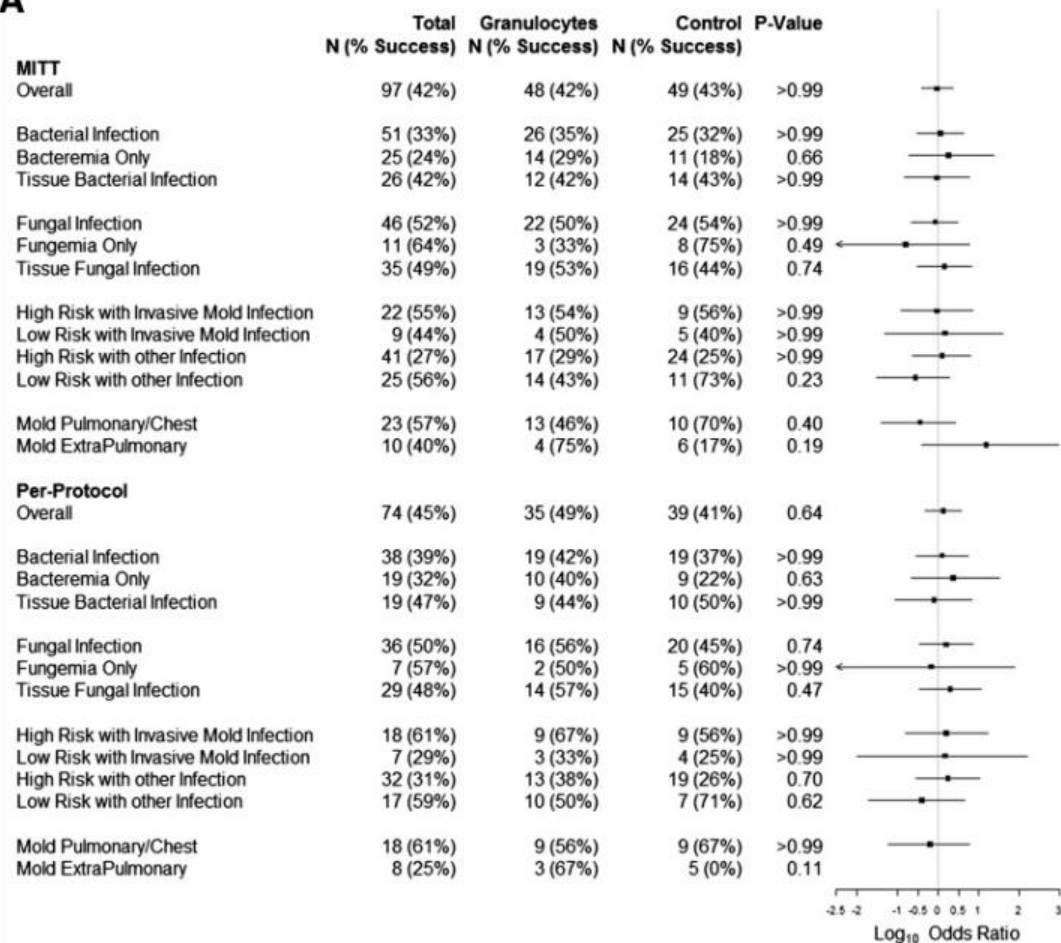


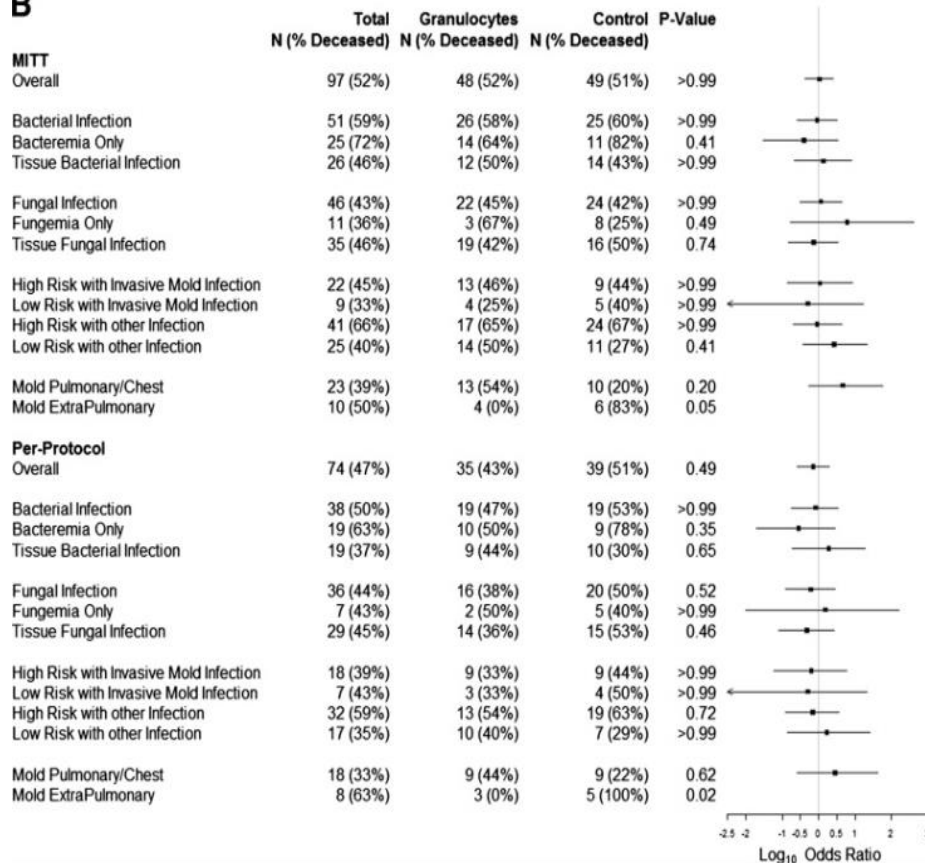
Figure 2

Distribution of the average number of granulocytes per transfusion per kilogram ($\times 10^9$). Forty-nine subjects received at least 1 G-CSF-stimulated granulocyte transfusion with sufficient information to calculate dose.

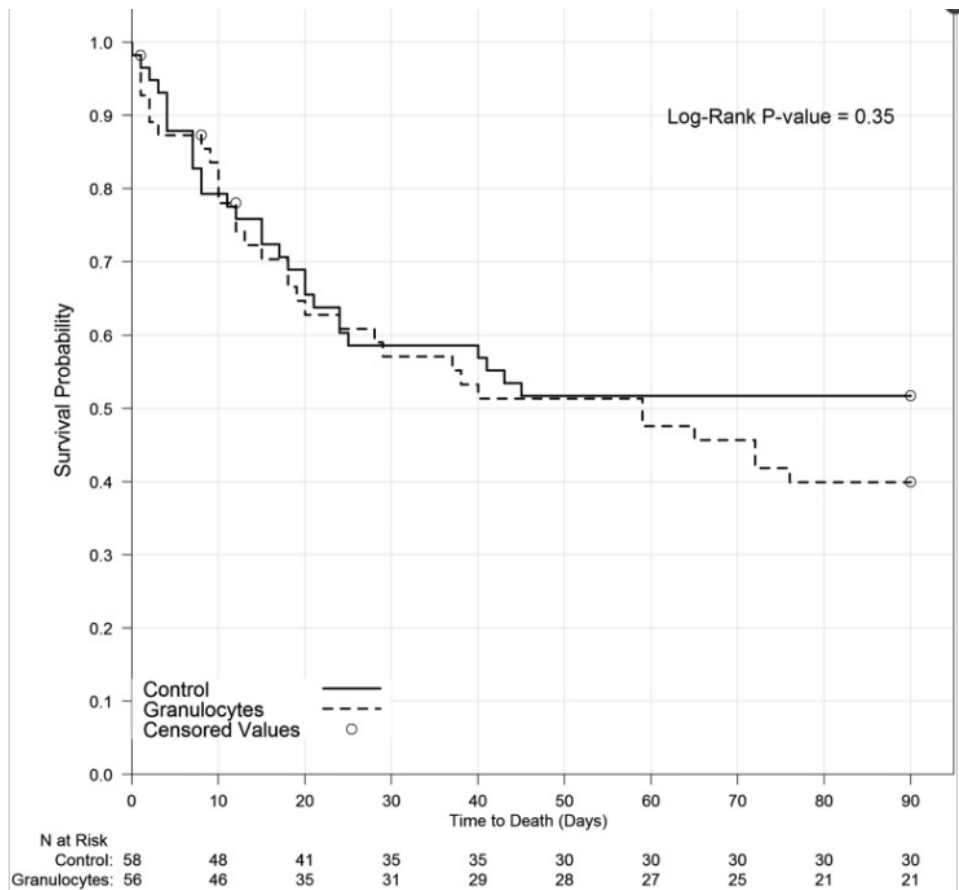
A



B

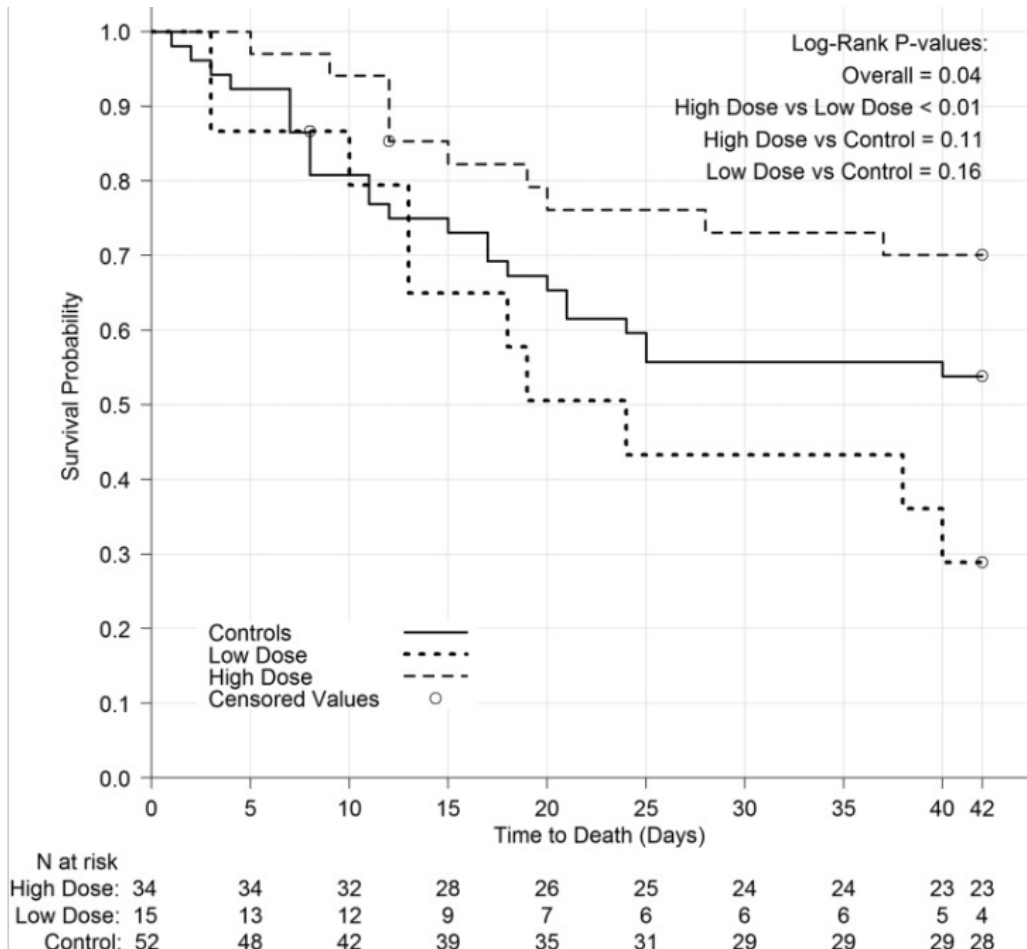


- Primer sonuç:
Survival+Mikrobiyal yanıt
- Randomizasyonun 42. gününde değerlendirme
- Granülosit grubunda 20/48 (%42)
- Kontrol grubunda 21/49 (%43)



Survival to 90 days by treatment arm. Analyzed using Kaplan-Meier methodology. Three subjects were censored prior to day 90 due to missing information.

Aldıkları Granülosit Dozuna Göre Sağkalım



Pediatric Granulocyte Transfusions

Table 2 Clinical trials in children

# of pts	Clinical trial	Indications for GTX	Remarks/outcome	Reference(s)
27	Prospective, phase II	Severe neutropenia and infections	Donor mobilization: 75 µg/kg G-CSF; resolution of infection in 92.6 % of patients; 81.5 % OS on day +30; early administration after a median infection period of 6 days	[41]
49	Prospective	Neutropenia and invasive bacterial or fungal infection	Donor mobilization with 5 µg/kg G-CSF + 50 mg PDN. Mixed cohort, including 10 adults; 72 % OS on day +28 and 52 % OS on day +100	[42]
13	Prospective phase VII	Neutropenia and severe infection	Donor mobilization with 5–10 µg/kg G-CSF; Collection through the bag method: 69 % OS on day +30	[90]
3	Prospective	CGD and invasive aspergillosis	Donor's mobilization with 450 µg G-CSF + 8 mg DXM; one patient died for ARDS, one was lost at follow-up and died 1 year after discharge, one is alive	[49]
35	Retrospective	Febrile neutropenia or defective granulocyte function	Donor mobilization with 480 µg G-CSF + 8 mg DXM; OS 77.1 and 65.7 %, respectively, on day +30 and +60; 82.4 % infection-related OS	[40]
32	Retrospective	Sepsis and neutropenia	Donor mobilization with single-dose lenograstim + DXM 8 mg; 59 % OS (8/32 pts died for the underlying infection and 8/32 pts for non-infectious causes)	[39]
16	Retrospective	Severe neutropenia and documented bacterial and/or fungal infections in HSCT recipients	Donor mobilization with 8 mg DXM after 2007; unstimulated donors before 2007: 50 % OS on day +30	[37]
10	Retrospective	High risk febrile neutropenia with/without microbiologically documented severe infection	Donor mobilization with 5 µg/kg G-CSF + 8 mg DXM; Clinical response rate 62.9 %, 40 % infection-related mortality, 40 OS %	[91]
13	Retrospective	Febrile neutropenia	Resolution of the documented infection in 9/12 (75 %) pts; good early survival (12/14 courses of GTX, 86 %); poor long-term survival (5/13 pts, 39 %)	[47]
13	Retrospective	Severe infections and neutropenia	Donor mobilization with G-CSF 300 µg from day -3; complete or partial recovery in 6 and 3 of the 15 courses of GTX (40 and 20 % respectively)	[43]
13	Retrospective	Granulocyte dysfunction or severe neutropenia and acute life-threatening infections	Donor mobilization with 600 µg G-CSF + 8 mg DXM; complete or partial clinical response in 12/13 pts (92 %); 15 % infection-related mortality and 42 % OS	[38]
3	Retrospective	Secondary prophylaxis of invasive fungal infections during neutropenic episodes	Donor mobilization with G-CSF; concomitant combination antifungal therapy; no infection-related mortality	[39]
3	Prospective	Prophylaxis in HSC recipients with chronic infections	Donor mobilization with 480 µg G-CSF + 7.5 mg DXM; after transplant, no flares of the infections (active <i>S. aureus</i> liver abscesses, chronic pulmonary aspergillosis, soft tissue mucormycosis)	[50]
20	Prospective	Proven fungal or bacterial infection, unresponsive to anti-microbial therapy (n = 16). Poor control of fungal infection prior to allogeneic HSCT (n = 4)	In the curative group, infection was controlled in 11 out of 16 children. All patients treated pre-emptively survived the HSCT procedure	[24]
10	Prospective	CGD with severe infections	Resolution of infection in 9 out of 10 patients, despite the fact that 8 patients were alloimmunized and had poor recovery of transfused granulocytes	[65]

Completed and ongoing clinical trials of therapeutic granulocyte transfusions in children are summarized

HSCT hematopoietic stem cell transplantation, DXM dexamethasone, OS overall survival, GTX granulocyte transfusions, CGD chronic granulomatous disease



REVIEW

Open Access



Granulocyte transfusions in children and adults with hematological malignancies: benefits and controversies

Chiara Cugno^{1,2}, Sara Deola^{1,3}, Perla Filippini⁴, David F. Stroncek⁵ and Sergio Rutella^{1*}

Abstract

Bacterial and fungal infections continue to pose a major clinical challenge in patients with prolonged severe neutropenia after chemotherapy or hematopoietic stem cell transplantation (HSCT). With the advent of granulocyte colony-stimulating factor (G-CSF) to mobilize neutrophils in healthy donors, granulocyte transfusions have been broadly used to prevent and/or treat life-threatening infections in patients with severe febrile neutropenia and/or neutrophil dysfunction. Although the results of randomized controlled trials are inconclusive, there are suggestions from pilot and retrospective studies that granulocyte transfusions may benefit selected categories of patients. We will critically appraise the evidence related to the use of therapeutic granulocyte transfusions in children and adults, highlighting current controversies in the field and discussing complementary approaches to modulate phagocyte function in the host.

Keywords: Granulocyte transfusion, G-CSF, Dexamethasone, Hematopoietic stem cell transplantation, Febrile neutropenia, Infection

TRANSFUSION PRACTICE

Safety and efficacy of therapeutic early onset granulocyte transfusions in pediatric patients with neutropenia and severe infections

Ulrich J.H. Sachs, Alfred Reiter, Tobias Walter, Gregor Bein, and Wilhelm Woessmann

BACKGROUND: Bacterial and fungal infections in profound neutropenia after chemotherapy are associated with high mortality despite appropriate antibacterial and antifungal treatment. Granulocyte transfusions are used as a therapeutic addendum, but concern regarding pulmonary reactions often results in delayed use in clinical practice. Accordingly, many patients are already at advanced stages of their infectious disease once granulocytes are transfused. Thus, a prospective Phase II trial was conducted to test the safety and efficacy of therapeutic early-onset granulocyte transfusions in immunocompromised children with neutropenia and severe infections.

STUDY DESIGN AND METHODS: Twenty-seven children with hematologic disorder or malignancy and severe neutropenia with clinically and/or microbiologically documented severe infection unresponsive to standard treatment were included. They received granulocyte colony-stimulating factor (G-CSF)-elicited, crossmatched granulocyte concentrates every other day until complete recovery from infection was documented.

RESULTS: A median of two granulocyte transfusions with a median of 8×10^8 granulocytes per kilogram of body weight were administered. All transfusions were well tolerated, and no pulmonary symptoms were observed. A total of 92.6 percent of our patients were able to clear their initial infection, and 81.5 percent were alive and without signs or symptoms of their infection 1 month later. All six children with aspergillosis cleared their infection.

CONCLUSIONS: G-CSF-elicited, crossmatched granulocyte concentrates are a safe and efficient therapeutic addendum in immunocompromised children with prolonged neutropenia and severe infections. Early transfusion of granulocyte concentrates can lead to an overall response rate of 92.6 percent without adverse events. Randomized clinical trials with an early-onset design are required to determine appropriate clinical applications.

Despite the use of antibacterial and antifungal agents, infections still represent the major cause of morbidity and mortality in patients with prolonged neutropenia after intensive chemotherapy or hematopoietic peripheral blood progenitor cell (PBPC) transplantation.¹⁻³ In many patients, control of infection can be achieved upon recovery from neutropenia, but not before, indicating that neutrophil counts are of critical importance for pathogen elimination. Accordingly, granulocyte transfusions (GTxs) have been used as both a supportive measure to bridge the interval until hematopoietic regeneration and therapeutic addendum.

Analysis of previous trials on administration of granulocytes showed that, besides donor-recipient HLA-HNA match, severity of neutropenia, and patient's immunodeficiency status, the dose of cells delivered was crucial.⁴ In contrast to previously used glucocorticoids, administration of recombinant human granulocyte colony-stimulating factor (rHuG-CSF) to donors produces a

ABBREVIATIONS: ANC(s) = absolute neutrophil count(s); CRP = C reactive protein; FUO = fever of unknown origin; GTX(s) = granulocyte transfusion(s).

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This study was supported by grants from the German Society for Transfusion Medicine and Immunohematology (DGTI), Chugai Pharma, Frankfurt/Main, and Amgen, Munich, Germany. UJHS is a fellow of the German Foundation for Hemotherapeutic Research (Bonn, Germany).

Received for publication February 3, 2006; revision received April 24, 2006, and accepted April 24, 2006.

doi: 10.1111/j.1537-2996.2006.00996.x

TRANSFUSION 2006;46:1909-1914.

Prospektif, faz II çalışma
33 hasta
G-CSF 7.5 µg/kg ile
mobilizasyon
İnfeksiyonun rezolüsyonu
%92.6
+30. günde GS %81.5
Erken uygulama, medyan
infeksiyonun 6. gününde

Granulocyte Transfusions in Children and Young Adults Does the Dose Matter?

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Ulrike Pötschger, MSc,* Nina Worel, MD,† Gerda Leitner, MD,† Jan Stary, MD,†
Helmut Gadner, MD,* and Christina Peters, MD*

Background: Granulocyte transfusions (GTs) may increase the absolute neutrophil count (ANC) before hematopoietic regeneration in neutropenic patients after chemotherapy or hematopoietic stem cell transplantation and support anti-infective immunity.

Procedure: We assessed efficacy and tolerability of 778 GTs in 70 treatment episodes of 49 children and 10 young adults [median age 6.28 y (range: 0.13 to 17.7 y) and 21 y (18.0 to 28.0), respectively] suffering from bacterial ($n = 35$) and/or fungal ($n = 31$) infections during neutropenia owing to conventional chemotherapy ($n = 14$), hematopoietic stem cell transplantation conditioning ($n = 44$), or the underlying disease ($n = 1$). We analyzed the impact of body weight, organ dysfunction, neutrophil dose on ANC increment, infection elimination, and survival.

Results: The median day-5 ANC increment was 1460/ μ L, correlating to the administered dose. However, 28-day survival did not correlate to the neutrophil dose nor to the ANC increment, potentially owing to the high number of neutrophils transfused to all patients (median $> 6 \times 10^9$ /kg within 5 d). The 28-day survival probability of the total patient cohort was 0.72 ± 0.06 and the 100-day survival was 0.52 ± 0.07 . Adverse reactions were rare, including fever (\leq World Health Organization grade III, 14%), chills (7%), and mild pulmonary complications (1%).

Conclusion: These data corroborate the empirical evidence that GT with sufficient cell doses and rapid availability are a feasible, well-tolerated supplemental means to fight severe infections in neutropenic patients.

Key Words: febrile neutropenia, invasive aspergillosis, granulocyte transfusions, infectious complications, stem cell transplantation, high-dose chemotherapy

(*J Pediatr Hematol Oncol* 2009;31:166–172)

Granulocyte transfusion (GT) therapy as means to shorten neutropenia and combat tissue pathogens in neutropenic patients has recently drawn new attention

owing to the availability of new granulocyte mobilization and apheresis methods (reviewed in Refs. 1, 2). For pediatric patients, GT with sufficient cell numbers can be harvested from both granulocyte colony-stimulating factor (G-CSF) and prednisolone-primed donors, whereas for adult patients only G-CSF-stimulated GTs are sufficient.^{3,4} Being practiced in many centers based on empirical evidence and results of earlier controlled studies,^{10,11} randomized trials are still needed to definitively prove the efficacy of GT and particularly, whether sustained increment of the neutrophil counts results in improved survival.¹²

In this investigation, we analyzed the impact of granulocyte dose (per kilogram recipient's body weight), dose intensity of GT (cumulative dose within the first 5 d of GT treatment), presence of sepsis-related organ dysfunction on side effects, ANC increment, infection elimination, and survival. As a prospective clinical study, this analysis aimed to define response parameters and risk factors of adverse reactions of GT treatment and to identify a target patient population most likely to benefit from this still rarely used and controversially discussed therapeutic option.

PATIENTS AND METHODS

Patients: Between 1995 and 2005, 59 immunocompromised neutropenic children and young adults with severe infections were included in this trial. Data collected from the first 30 trial patients were published in part previously.⁷ After the initial publication, another 29 patients were included in the prospective study, thus forming a total cohort of 59 patients, treated with a total of 778 GTs for 70 infection episodes. The median age of the total cohort was 7.0 years (range: 0.1 to 28.0). To facilitate detection of dose-dependent effects the population was divided into 2 groups, namely, patients < 18 years and ≥ 18 years, reflecting a division into individuals below and above 50 kg bodyweight (Table 1). Fifteen patients had various degrees of treatment-related comorbidity with most frequent diagnoses such as toxic cardiomyopathy, hepatopathy, and neurologic and endocrinologic disorders. Sepsis-related organ dysfunction was separately analyzed (Table 2). The study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was obtained from all patients and all related and unrelated donors.

Inclusion criteria: (1) diagnosis of a hematologic disorder or malignancy (Table 1); (2) invasive bacterial or fungal infection (Table 2) with insufficient response to standard antibacterial and antifungal therapy; (3) ANC $< 0.2 \times 10^9$ /L ($< 200/\mu$ L) after conventional chemotherapy ($n = 14$), conditioning for autologous ($n = 4$) or allogeneic ($n = 40$) stem cell transplantation, or owing

Prospektif, miks kohort çalışma
49 çocuk, 10 erişkin hasta
G-CSF 5 μ g/kg ve 50 mg
prednizolon ile mobilizasyon
28. Günde **GS %72**
100.Günde **GS %52**

Received for publication June 17, 2008; accepted November 4, 2008.
From the *St. Anna Children's Hospital Medical University Vienna, Clinic for Blood Group Serology and Transfusion Medicine, Vienna, Austria; and †Department of Pediatric Hematology-Oncology, University Hospital Praha-Motol, Prague, Czech Republic.

Markus G. Seidel and Milen Minkov have contributed equally.
No conflict of interest in funding to disclose.
Milen Minkov, Helmut Gadner, and Christina Peters designed the study. Ulrike Pötschger carried out statistical analysis. Milen Minkov, Volker Witt, Susanne Matthes-Martin, Nina Worel, Gerda Leitner, and Jan Stary contributed patient and donor data and helped to evaluate results. Milen Minkov and Markus G. Seidel analyzed the data and drafted the manuscript.
Reprints: Christina Peters, MD, Associate Professor of Pediatrics, St. Anna Children's Hospital, A-1000 Vienna, Austria (e-mail: christina.peters@stanna.at).
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Therapeutic transfusions of granulocytes collected by simple bag method for children with cancer and neutropenic infections: results of a single-centre pilot study

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Vox Sanguinis

Background and Objectives Granulocyte transfusion therapy (GTX) can be effective for life-threatening infections unresponsive to conventional antimicrobial therapies in severely neutropenic children with cancer. We developed a new granulocyte collection method, named the 'bag method', in which apheresis, hydroxyethyl starch (HES) or dexamethasone are not used. We undertook a pilot study to determine the feasibility and the safety of GTX collected by the bag method for children with cancer and life-threatening infections.

Materials and Methods A total of 25 GTX were administered to 13 patients (median age 3 years, range: 0–3–17; median weight 10.6 kg, range: 4.5–49.8) with neutropenia-related infections. Thirteen blood-related donors received granulocyte colony-stimulating factor (G-CSF) (5–10 µg/kg), subcutaneously, 14 h before collection. Major end-points were granulocyte yields, post-transfusion absolute neutrophil counts (ANC) in patients, donor and patient safety, and clinical outcome on day 30.

Results The median yield of ANC per 400 ml of processed whole blood was 6.2×10^9 (range: 2.5 – 15.0×10^9). Patients received a mean of $6.4 \pm 0.8 \times 10^8$ granulocytes per kg of body weight per transfusion. The 1-h and 24-h post-transfusion ANC rose to $607 \pm 124/\mu\text{l}$ and $704 \pm 300/\mu\text{l}$, respectively, from the baseline of $21/\mu\text{l}$ before the first GTX. Adverse reactions were observed in five of 13 donors (bone pain, headache, vasovagal reaction; all \leq grade 2) and in two of 25 transfusions of 13 patients (transient hypoxia; grade 3). Ten patients had favourable responses, and infection resolved in nine patients.

Conclusions The bag method without apheresis relieves the physical load of donors and enables patients with a low body weight to provide an adequate dose of granulocytes.

Key words: bag method, cancer, granulocyte transfusion, infection, neutropenia.

Received: 31 October 2005,
revised 30 January 2006,
accepted 1 March 2006,
published online 5 April 2006

Introduction

Severe bacterial and fungal infections are major complications in neutropenic patients undergoing haematopoietic stem cell transplantation (HSCT) and intensive chemotherapy for

malignant diseases, and are related to increased morbidity and mortality [1,2]. Despite modern antibiotics and the use of haematopoietic growth factors to reduce the duration of post-treatment neutropenia, infection remains a major cause of mortality [3].

Granulocyte transfusion therapy (GTX) was advocated enthusiastically in the 1970s; however, interest in it declined rapidly, for several reasons, including insufficient efficacy, the introduction of new antimicrobial agents and recombinant haematopoietic growth factors [4,5]. Recently, there has been renewed interest in GTX following several reports of the

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Prospektif, faz I/II çalışma
33 hasta
G-CSF 5-10 µg/kg ile
mobilizasyon
Bag metodu
30. Günde **GS %69**

Granulocyte Transfusions in Children With Chronic Granulomatous Disease and Invasive Aspergillosis

Aydan İkinciogulları,^{1,2} Figen Doğru,^{1,2} Nuri Solaz,³ İsmail Reisli,^{1,2} Sabri Kemahlı,^{1,3}
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Abstract: The transfusion of granulocytes to restore host defenses in severely granulocytopenic patients or in patients with defective granulocyte functions has been studied for more than 60 years. However, inadequate dosage of cells and inconsistent efficacy has limited the usage of these transfusions. Recently, the use of mobilizing agents such as granulocyte colony stimulating factors and dexamethasone has renewed interest in these treatment modalities. The present study is conducted to determine an appropriate method of enriched granulocyte collection with Fresenius AS.TEC.204 cell separator (Fresenius, Bad Homburg, Germany) and to evaluate the preliminary clinical results of granulocyte transfusion therapy in patients with chronic granulomatous disease and invasive Aspergillosis in parallel with in vitro granulocyte function. Three patients who have been treated for chronic granulomatous disease and invasive Aspergillosis received a total of 20 granulocyte transfusions. To mobilize granulocytes,

healthy donors were given 450 µg of granulocyte colony-stimulating factor (G-CSF) subcutaneously and 8 mg of dexamethasone orally approximately 12 h before collection. Five µg/kg/day of G-CSF was also subcutaneously administered prior to granulocyte transfusions. The first patient received 4; the second, 14 and the third, 2 transfusions. The granulocyte count given to these patients ranged between 0.4 and 3.0 × 10⁹/kg. Most transfusions were well tolerated. The nitroblue tetrazolium (NBT) tests that were done 16–24 h after the transfusion showed 14–46% dye reduction. Two of the three patients survived the infection. Granulocyte transfusions from G-CSF and dexamethasone stimulated donors could be a choice of treatment in chronic granulomatous disease patients, especially with disseminated invasive Aspergillosis. **Key Words:** Chronic granulomatous disease, G-CSF, Granulocyte transfusion, Invasive Aspergillosis.

Prospektif çalışma

3 hasta

G-CSF 450 µg ve 8 mg
DXM ile mobilizasyon

1 hasta ARDS ile öldü
1 hasta takipten çıkıp 1
yıl sonra öldü

1 hasta yaşıyor

Effect and Safety of Granulocyte Transfusions in Pediatric Patients With Febrile Neutropenia or Defective Granulocyte Functions

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Sema Anak, MD,† and Omer Devecioglu, MD†

Background: Despite the introduction of new broad-spectrum antibiotics and antifungal therapies over the past decade, infections remains the most frequent cause of death in patients with neutropenia. The aim of this study is to assess the effect and safety of granulocyte transfusions (GTX) for the treatment of severe life-threatening infections in pediatric patients with febrile neutropenia or defective granulocyte functions.

Methods: In this study, 35 pediatric patients with high-risk febrile neutropenia or defective granulocyte functions, who received 111 GTX, were included. GTX were used for 3 consecutive days during infections not responding to antimicrobial therapy.

Results: The mean granulocyte content per concentrate was 27.4×10^9 (min: 4.2×10^9 to max: 68.4×10^9) depending on donor's white blood cell count before harvest. GTX were well tolerated in all patients. The infection-related survival rate was 82.4% and overall survival rate was 77.1% at day 30. The overall survival rate was 65.7% and 52% at 3 and 48 months, respectively.

Conclusions: GTX is safe and effective in controlling the life-threatening infections. Further randomized controlled studies with long-term follow-up are needed to assess the exact role of GTX in the outcome of patients with neutropenia and patients with defective granulocyte functions.

Key Words: granulocyte transfusion, pediatric hematology-oncology patients, severe infection

(*J Pediatr Hematol Oncol* 2011;33:e220–e225)

Published reviews have suggested that the efficacy of GTX in patients with neutropenia is proportional to the dose of granulocytes transfused, with an optimal level being at least 10^{10} granulocytes or at least 10^{10} granulocytes per meter squared of recipient body surface area per transfusion.^{5,6} Improvement in leukapheresis technology and the combined use of granulocyte colony stimulating factor (G-CSF) and glucocorticosteroid treatment for donor stimulation, now allow granulocyte doses within the therapeutic range to be routinely collected.

The objective of this study was to determine the effect and safety of GTX therapy in severe life-threatening infections. Our study is based on data collected from 35 pediatric patients who had received 111 GTX retrospectively. We report our results of using transfusion of granulocytes from unrelated donors for the treatment of severe infections in pediatric patients with different oncohematologic diseases.

MATERIALS AND METHODS

Neutrophil Recipients

Thirty-five pediatric patients who received 111 GTX were reviewed retrospectively. The criteria for patient selection were; patients with oncohematologic malignancy and prolonged neutropenia ($<0.5 \times 10^9/L$ for at least 5 days and expected not to resolve from neutropenia within the next 5 days) or defective granulocyte functions in severe

Retrospektif çalışma

35 hasta

Febril nötropeni ve nötrofil fonksiyon bozukluğu

G-CSF 480µg ve 8 mg

DXM ile mobilizasyon

30. Günde GS %77.1, 60.

günde GS %65.7,

İnfeksiyon ilişkili sağkalım

%82.4

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Andreas Beilken
Hansjoerg Schmid
P. Kirschner
Karl-Walter Sykora
Christin Linderkamp
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Secondary prophylaxis of invasive fungal infections with combination antifungal therapy and G-CSF-mobilized granulocyte transfusions in three children with hematological malignancies

Received: 9 August 2005
Accepted: 26 October 2005
Published online: 16 February 2006
© Springer-Verlag 2006

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Abstract Fungal infections represent a life-threatening complication for patients receiving chemotherapy or undergoing hematopoietic stem cell transplantation. Historically, antifungal monotherapy is associated with a poor outcome. We treated three children with hematological malignancies and proven fungal infections (one cerebral mold infection, one disseminated *Candida* infection, one nasopharyngeal mucor infection) with combination antifungal therapy plus granulocyte-colony-stimulation-factor-mobilized granulocyte transfusions as secondary prophylaxis during subsequent neutropenic episodes. With this approach, the fungal infection was effectively treated, and the anticancer therapy was completed without major delay. All children survived the fungal infection and the underlying malignancy. These experiences illustrate the feasibility of this approach using more than one antifungal agent together with immunotherapy in high-risk patients.

With this approach, the fungal infection was effectively treated, and the anticancer therapy was completed without major delay. All children survived the fungal infection and the underlying malignancy. These experiences illustrate the feasibility of this approach using more than one antifungal agent together with immunotherapy in high-risk patients.

Keywords Fungal infection · Childhood · Cancer · Combination therapy · Granulocyte transfusion

Retrospektif çalışma
32 hasta
Tek doz lenograstim +
DXM 8 mg ile donör
mobilizasyonu
Genel sağkalım **%59**
8/32 hasta infeksiyon,
8/32 hasta infeksiyon dışı
nedenlerle kaybediliyor

Granulocyte Transfusion Therapy in Pediatric Patients After Hematopoietic Stem Cell Transplantation: A 5-Year Single Tertiary Care Center Experience

Huy P. Pham, MD,* Kim Rogoza, CPNP,† Brie Stotler, MD,* Deirdre Duffy, BS,‡
Sylvia Parker-Jones, MT(ASCP)BB,* Yelena Ginzburg, MD,§ Monica Bhatia, MD,†
Mitchell Cairo, MD,‡ and Joseph Schwartz, MD*

Background: Granulocyte transfusion (GTx) has been used in neutropenic patients to treat infections; however, there are few studies that document its efficacy, especially in pediatric patients after hematopoietic stem cell transplantation (HSCT). We, therefore, reviewed the use of GTx in these patients.

Materials and Methods: A retrospective observational analysis was performed on all pediatric HSCT patients between January 2005 and January 2010 who met our institution's criteria for GTx and received more than 1 GTx. Unstimulated granulocyte donors were used until June 2007, followed by dexamethasone-stimulated donors thereafter. Outcomes were infection clearance, safety profile of GTx, and 30-day survival.

Results: One hundred fifty-three GTxs were administered to 16 pediatric HSCT patients. Indications for GTx: bacterial (69%), fungal (19%), and combined infection (12%). Concurrent infections, mostly bacterial, developed in 60% patients. One adverse reaction (pulmonary toxicity) was reported. The absolute neutrophil count of the stimulated products was significantly higher compared with the unstimulated products; however, neither the average number of granulocytes transfused by weight nor outcomes difference was noticed between these groups.

Conclusions: GTx is safe in neutropenic and infected pediatric patients after HSCT. However, no difference in the outcomes was noticed between the group that received stimulated products and the group that received unstimulated products.

Key Words: granulocytes, granulocyte transfusion, pediatric hematopoietic stem cell transplant patients

(*J Pediatr Hematol Oncol* 2012;34:e332-e336)

pediatric oncology patients with febrile neutropenia, and in patients after HSCT, the mortality has been reported up to 40%.² Duration of neutropenia has been associated with a poor prognosis in these patients.³ It has been documented that in HSCT patients with invasive *Aspergillus*, mortality rates are as high as 85%.⁴ Furthermore, adequate blood and tissue neutrophils have been shown to be the strongest predictor of recovery from invasive fungal infections.⁵ These observations led to the use of daily granulocyte transfusion (GTx) from either unstimulated donors or donors stimulated with corticosteroids, granulocyte colony-stimulating factor (G-CSF), or both, for the purpose of bridging the gap between bone marrow suppression and neutrophil recovery. However, the data regarding the efficacy of this treatment are limited and the results are inconclusive.⁶ Moreover, no study has been conducted to study the efficacy of GTx in the specific group of pediatric patients after HSCT. Therefore, a retrospective analysis reviewing the efficacy of GTx and the effect of stimulated versus unstimulated products on the patient outcome was conducted.

MATERIALS AND METHODS

Study Design

This is a retrospective observational review of the use of GTx in neutropenic and infected pediatric patients after HSCT from January 1, 2005 to January 15, 2010 at the Morgan Stanley Children's Hospital of New York-Presbyterian, Columbia University Medical Center (CUMC).

Retrospektif çalışma
HSCT yapılan bakteriyel
ve fungal infeksiyonlu
16 hasta

Donor mobilization 8 mg
DXM, 2007 den sonra;
stimulasyonsuz 2007
den önce;
+30. günde GS %50



Contents lists available at SciVerse ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci



Granulocyte transfusion therapy in paediatric patients with severe neutropenic infection

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ARTICLE INFO

Keywords:

Children
Febrile neutropenia
Granulocyte transfusions
Hematologic disorder

ABSTRACT

The data of 10 children who developed 13 high-risk febrile neutropenia with/without microbiologically documented severe infection, while being treated for a hematologic disorder were investigated retrospectively. The 24th hour post-transfusion neutrophil and platelet counts increased significantly, compared to the baseline values ($p = 0.034$, $p = 0.025$). Except three granulocyte transfusions (GTs) after which oliguria and/or mild respiratory distress developed, the transfusions were well tolerated. The clinical response, hematologic response and infection related mortality rates were 69.2%, 53.8% and 30.8%, respectively. Although our study includes limited number of patients, we can conclude that GT seems beneficial for children with severe sepsis during neutropenia.

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Retrospektif çalışma
G-CSF 480µg ve 8 mg
DXM ile mobilizasyon
Klinik yanıt **%69.2**,
hematolojik yanıt **%53.8**,
enfeksiyon ilişkili mortalite
%30.8

Revisiting the Use of Granulocyte Transfusions in Pediatric Oncology Patients

Alan S. Graham, MD,* Thomas H. Price, MD,†‡ and Thomas V. Brogan, MD§

Objective: To describe the clinical course of neutropenic pediatric oncology patients undergoing granulocyte transfusions (GTF).

Design: Retrospective chart review including all children receiving GTFs between March, 1998 and June, 2000.

Setting: Tertiary Children's Hospital and Regional Medical Center.

Patients: Thirteen pediatric oncology patients (age, 9 mo to 16 y) with neutropenia and proven or suspected serious infection.

Interventions: These 13 patients received a total of 14 courses of GTFs (number of transfusions per course ranged from 1 to 43, median = 4.5).

Measurements and Main Results: Twelve of the patients had documented infections before GTF. Ten of the 14 courses (71%) were followed by survival to hospital discharge. All 5 patients who were intubated before GTF were extubated afterward. Two early deaths occurred due to invasive *Aspergillus*. No significant differences in monitoring laboratory results were found. Ultimately, 8 of 13 (62%) patients in this group died.

Conclusions: This case series documents the course of 13 septic neutropenic pediatric oncology patients who underwent a total of 14 GTF courses. GTFs were generally well tolerated with little decline in respiratory status or organ function. Short-term survival in this population was good whereas long-term outcome remains more difficult.

Key Words: cancer, granulocyte, infections, neutropenia, transfusion

(*J Pediatr Hematol Oncol* 2009;31:161–165)

penia. Initially, enthusiasm led some physicians in the 1970s to declare that withholding GTF from such patients was unethical.⁵ Later, concerns from reports of adverse pulmonary reactions and questions about appropriate dosing, saw GTF fall from favor. With the advent of improved collection methods and more efficacious doses, GTF has seen a cautious resurgence internationally in both children and adults.^{6,7} Data for efficacy and complications in children remains limited. The objective of this study is to document response to, and complications following, GTF in a series of neutropenic pediatric oncology patients at a regional medical center.

METHODS

The charts of all pediatric patients with fever and neutropenia who received GTF at Children's Hospital and Regional Medical Center (CHRM) in Seattle between March 1, 1998 and December 1, 2000 were reviewed retrospectively. This study period was chosen because it appeared to be a representative time period for the review of children undergoing GTF and also represented the time period that all authors were available to perform the review. Criteria for GTF were prolonged absolute neutropenia (absolute neutrophil count < 200) and evidence of overwhelming or disseminated life-threatening infection. Criteria for discontinuing GTF were a return of absolute neutrophil count > 500 to 1000 for at least 24 hours after the last GTF. CHRM is a regional referral hospital for pediatric care serving 5 states in the Western United States.

Retrospektif
çalışma, 13 hasta,
dökümanite
infeksiyon iyileşme
oranı **%75**, erken
dönem sağkalım
%86, geç dönem
sağkalım **%39**

Granulocyte-colony-stimulating factor-stimulated healthy donors and leukaemia riskS. Cesaro,¹ P. Marson² & C. Messina¹¹Pediatric Hematology-Oncology Clinic, Department of Paediatrics, University of Padova, Padova, Italy²Blood Transfusion Service and Apheresis Unit, University Hospital of Padova, Padova, Italy

Received: 15 April 2003; accepted: 10 May 2003

The question of whether leukaemia may derive from stimulating healthy donors with granulocyte-colony-stimulating factor (G-CSF) receptors of haematopoietic stem cells is still debated. The problem has, to date, been under-investigated, but published data argue against any risk after 4–5 days of exposure to G-CSF [1], at least in the mid-term (3–5 years). Recently, Anderlini *et al.* reported that none of 281 sibling or blood-relative healthy adult donors, who underwent G-CSF stimulation prior to collection of peripheral blood progenitor cells, developed acute or chronic leukaemia after a median of 39 months (range: 7–80) from donation [2]. Another application of G-CSF-stimulated healthy donors is granulocyte transfusion (GTX), where donors are stimulated differently, with a less intensive but longer schedule.

From 1994 to 2002, we performed a study on GTX for severe infection in neutropenic paediatric patients. Permission to undertake the study was granted by the local ethical committee. Twenty infectious episodes in 15 severely neutropenic (granulocytes $< 0.1 \times 10^9/l$) patients, unresponsive to broad-spectrum antibiotic and antifungal treatment for ≥ 7 days, received a median of three GTX (range 1–11). Granulocyte donors were selected among parents or blood relatives after the suitability for blood donation (on the basis of aptitude tests required by Italian law) was confirmed and informed consent was obtained. Twenty donors were stimulated daily with filgrastim, 300 µg, subcutaneously, starting 2 or 3 days before the first granulocyte collection and continuing until the end of the treatment, for a median 6 days (range 3–14). Leukapheresis for granulocyte collection was performed by centrifugal cell separators (DIDECO-Vivacell, Mirandola, Italy or COBE-Spectra, Gambro/Cobe BCT, Inc., Lakewood, CO, USA), daily or on alternate days, without any significant side-effect.

Stimulation with filgrastim was well tolerated, the most common side-effects being bone pain, malaise and paresthesia. All of these symptoms were mild and no G-CSF withdrawal or medication were ever necessary; all the symptoms regressed

when the treatment was stopped. All donors are alive and well, after a median of 5 years (range 0–7–9) since donation.

Concern regarding the long-term safety of colony-stimulating factors has limited their more widespread use in unrelated donors of haematopoietic stem cells or blood for transplantation and GTX, respectively. On the other hand, the G-CSF stimulation of the donor enables, or is advisable for, haploidentical haematopoietic stem cell transplantation, mini-allo, and T-depleted haematopoietic stem cell transplantation, as well as for GTX in severe infections [3–5].

In this light, our retrospective survey may add some reassuring data to the issue of the long-term safety of G-CSF. We believe that greater efforts should be made, in years to come, by national and international blood donor registries, to collect data prospectively on the long-term haematological safety of G-CSF priming in donors. This would enable us to clarify whether administering G-CSF to healthy donors can induce any morbidity and mortality caused by haematological malignancies.

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Retrospektif çalışma
13 hasta
300µg G-CSF ile -3. günde
donör mobilizasyonu.
Komplet ve parsiyel yanıt
%40 ve %20

ORIGINAL ARTICLE
Supportive Care

Granulocyte Transfusions for Children with Infection and Neutropenia or Granulocyte Dysfunction

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Transfusions of granulocytes can be used as an adjunct therapy to antimicrobials in patients with infection and neutropenia or granulocyte dysfunction. However, there is a lack of strong clinical evidence to support the use of this treatment strategy, particularly in children. We retrospectively reviewed the medical records of children who received granulocytes at our institution from April 2009 to October 2012, with emphasis on primary indication for the transfusion and clinical outcome in terms of infection. The patients had granulocyte dysfunction or severe neutropenia, defined as absolute neutrophil count (ANC) < 500 cells/mm³ due to chemotherapy or hematopoietic stem cell transplant (HSCT), and reasonable hope for bone marrow recovery or engraftment. Eighteen children received granulocytes during 20 distinct episodes: 62% ($n = 13$) for acute infection, 29% ($n = 5$) for unresolved chronic infection during the time of HSCT, and 9% ($n = 2$) for other clinical conditions such as typhilitis and appendectomy. Overall, 92% ($n = 12$) of the episodes of acute infection had complete or partial resolution, as determined by review of vital signs, physical exam findings and discontinuation of antimicrobials. A substantial number (46%) of children who received granulocytes for acute infection developed respiratory adverse events, but all of these recovered. We conclude that granulocyte transfusions continue to be primarily used in neutropenic patients with acute infections, and that its use in this group of patients is reasonable. However, a prospective randomized clinical trial is needed to evaluate safety and whether the use of granulocytes is superior to antimicrobial-only therapy.

Keywords: bone marrow transplant, infections, neutropenia, supportive care, transfusion

Retrospektif çalışma
13 hasta
G-CSF 600µg ve 8 mg
DXM ile mobilizasyon
Parsiyel ve tam klinik yanıt
12/13 (%92)
İnfeksiyon ilişkili mortalite
%15
Genel sağkalım %42



NIH Public Access

Author Manuscript

Transfusion. Author manuscript; available in PMC 2012 August 17.

Published in final edited form as:

Transfusion. 2011 June ; 51(6): 1154–1162. doi:10.1111/j.1537-2995.2010.02993.x.

The relationship between alloimmunization and posttransfusion granulocyte survival: experience in a chronic granulomatous disease cohort

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Abstract

BACKGROUND—The efficacy of granulocyte transfusions in patients with HLA alloimmunization is uncertain. A flow cytometric assay using dihydrorhodamine 123 (DHR), a marker for cellular NADPH oxidase activity, was used to monitor the differential survival of transfused oxidase-positive granulocytes in alloimmunized patients with chronic granulomatous disease (CGD).

STUDY DESIGN AND METHODS—Ten patients with CGD and serious infections were treated with daily granulocyte transfusions derived from steroid and granulocyte–colony-stimulating factor–stimulated donors. The proportion of neutrophils with intact oxidase activity was quantitated by DHR fluorescence on samples drawn before and 1 hour after transfusion. The incidence of acute transfusion reactions was correlated with the results of DHR fluorescence and biweekly HLA serologic screening assays.

RESULTS—Eight of 10 patients experienced acute adverse reactions in association with granulocyte transfusions. Four had only chills and/or fever, and four experienced respiratory compromise; all eight exhibited HLA alloimmunization. Mean (\pm SD) oxidase-positive cell recovery was $19.7 \pm 17.4\%$ ($n = 15$ transfusions) versus $0.95 \pm 1.59\%$ ($n = 16$) in the absence and presence of HLA allosensitization, respectively ($p < 0.01$). Greater than 1% in vivo recovery of DHR-enhancing donor granulocytes was strongly correlated with lack of HLA alloimmunization.

CONCLUSION—The ability to detect DHR-positive donor granulocytes by flow cytometry is strongly correlated with absence of HLA alloimmunization and lack of acute reactions to granulocyte transfusions in patients with CGD. If HLA antibodies are present and the survival of donor granulocytes is low by DHR analysis, transfusions should be discontinued, avoiding a therapy associated with high risk and unclear benefit.

Prospektif çalışma
10 hasta
9/10 hastada hastalık
bulgularında iyileşme
8 hasta alloimmünize,
Bu hastaların granülosit
sayısında yeterli yükselme
yok

Granülosit Profilaktik kullanımı

Published in final edited form as:

Cochrane Database Syst Rev. ; 6: CD005341. doi:10.1002/14651858.CD005341.pub3.

Granulocyte transfusions for preventing infections in people with neutropenia or neutrophil dysfunction

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Abstract

Background—Despite modern antimicrobials and supportive therapy, bacterial and fungal infections are still major complications in people with prolonged disease-related or therapy-related neutropenia. Since the late 1990s there has been increasing demand for donated granulocyte transfusions to treat or prevent severe infections in people who lack their own functional granulocytes. This is an update of a Cochrane review first published in 2009.

Objectives—To determine the effectiveness and safety of prophylactic granulocyte transfusions compared with a control population not receiving this intervention for preventing all-cause mortality, mortality due to infection, and evidence of infection due to infection or due to any other cause in people with neutropenia or disorders of neutrophil function.

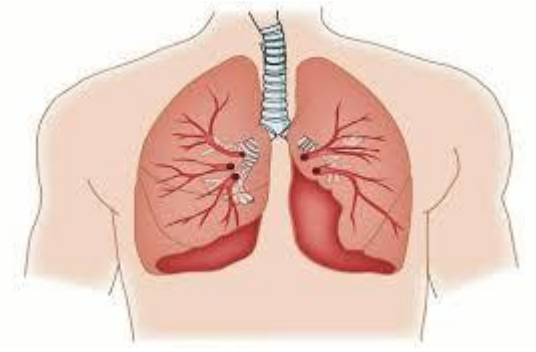
Search methods—We searched for randomised controlled trials (RCTs) and quasi-RCTs in the Cochrane Central Register of Controlled Trials (*Cochrane Library* 2015, Issue 3), MEDLINE

2015 Cochrane metaanaliz
11 randomize çalışma
653 nötropenili hasta
30. Günde mortalite ve
infeksiyon oranı farklı değil
Bakteriyemi ve fungemi
riskinde azalma
10x10¹⁰ granülosit/gün yeterli

Komplikasyonlar

- ES replasmanına göre transfüzyon reaksiyon riski daha fazla
 - %25-50 hafif-orta reaksiyonlar
 - Ağır komplikasyon riski %1
 - En fazla karşılaşılan reaksiyon ateş ve titreme.
 - Granülosit konsantrasyonunun yavaş infüzyonu ve öncesinde premedikasyon yapılması yan etkilerin sıklığını ve şiddetini azaltıyor.
- Pulmoner yan etkiler
- Transfüzyon ilişkili graft versus host hastalığı
- HLA alloimmünizasyon
- Transfüzyonla bulaşan infeksiyonlar

Granülosit transfüzyonu- Pulmoner komplikasyonlar



- Orta-ağır şiddette pulmoner yan etkiler
- Öksürük, dispne, hipoksi, akciğer filminde değişiklikler
- Bazı serilerde %5 oranında bildirilmiş.
- Öncesi ve sonrasında O2 satürasyonu ölçülerek yapılan değerlendirmelerde O2 satürasyonu değişmediği bildirilmiş.
- Amfoterisin B ve granülosit transfüzyonunun birlikte uygulanması pulmoner komplikasyonlarla ilişkili bulunmamış.

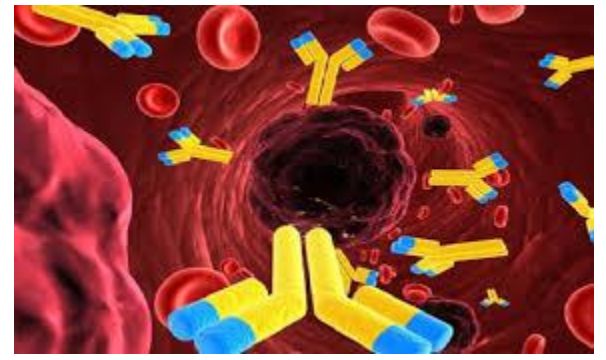
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Granülosit transfüzyonu- Akut Graft Versus Host Hastalığı



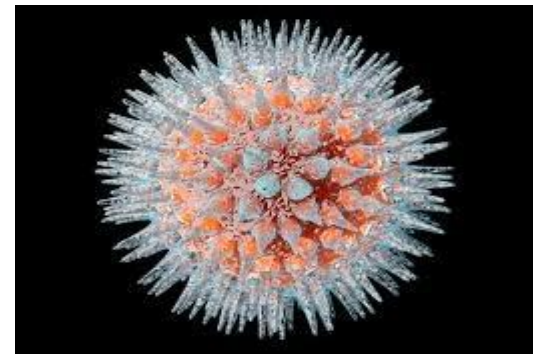
- Nedeni: Granülosit konsantrelerinde canlı fonksiyonel donör lenfositleri bulunması ve bunların alıcıya karşı immunolojik saldırıya geçmesi
- Genellikle immün yetmezlikli hastalarda görülmesine rağmen, immün sistemi normal kişilerde de olabilir.
- Rutin olarak granulosit konsantreleri ışınlanmalı (2500-3000 rad) Bu radyasyon granülosit fonksiyonlarını etkilememekte.

Granülosit transfüzyonu- Alloimmünizasyon



- Aplastik anemili hasta grubunda **%17 oranında**, granülosit transfüzyonu sırasında **HLA antikorları** bildirilmiş, bu hastalarda **daha az lökosit artışları** gözlenmiş.
 - HLA antikorlarının veya granülosit spesifik antijenlerin oluşumu, invivo granülosit yaşam süresini azaltmakta ve granülositlerin anormal migrasyonuna neden olmakta.
 - Bu hastalarda anti-HLA antikorları nedeniyle, trombosit transfüzyonlarına refrakterlik oluşmakta.
-
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Granülosit transfüzyonu- İnfeksiyon



- Diğer kan ürünlerinde olduğu gibi infeksiyon çok önemli
- Toplamadan hemen sonra granülosit süspansiyonu kullanılmalı
- CMV riski yüksek, çünkü CMV periferik kan lökositlerine sığınıyor.
- Seronegatif donör tercih, bunun karıştını savunanlar da var.
- Geçiş olasılığı çok az olduğundan, seronegatif hastaya seropozitif hastadan, yakın CMV viremi monitorizasyonu ve gerekirse erken antiviral tedavi ile transfüzyon yapılabilir.

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Sonuçlar

- Geçmiş çalışmalardaki granülosit transfüzyonu başarısızlığı, transfüzyon için yeterli dozda granülosit toplanmaması ile ilişkili görünmektedir.
- G-CSF bulunması, Granülosit transfüzyonu için yeni bir dönem açmıştır.
- Sağlıklı donörler için G-CSF kullanımı masum olmamakla birlikte, günümüzde uygulamaya engel olacak kadar veri bulunmamaktadır.
- Ancak G-CSF uygulanan donörlerin uzun süreli izlemleri ve saptanan problemlerin geri bildiriminin yapılması gereklidir.
- Yine G-CSF için yürütülmekte olan çalışmaların (NCT00785525, NCT01362179, NCT00115128) sonuçları takip edilmeli ve Türkiye donörlerinin verileri çıkarılmalıdır.

- Premedikasyon olarak **asetaminofen ve difenhidramin**
- Transfüzyon reaksiyonlarını minimuma indirmek için **rutin olarak ışınlanmalı**
- Transfüzyon sırasında por büyüklüğü 170 mikron olan filtreleri içeren standart kan setleri kullanılmalı, **yatak başı lökosit filtreleri asla kullanılmamalı**
- **Uygulama süresi**, hastanın klinik durumu, tedavi planı, tedaviye yanıtı ve donör bulunabilme durumuna göre **3 gün-aylar** arasında değişebilir.

- Erişkinlerde yapılan randomize çalışmada (RING), granülosit transfüzyonunun sonuçları geliştirdiği gösterilememiştir.
- Ancak bu çalışmada etkinliği yeterince değerlendirmek için yeterli sayıda hastaya ulaşamadığı ve uygulanan granülosit miktarının survide farklılıklara yol açtığı bildirilmiştir.

- Çalışma gruplarının heterojenitesi,
- Enfeksiyonların tipi, kullanılan antibiyotik tedavilerinin ve transfüze edilen granülosit süspansiyonlarının doz farklılığı
- Randomizasyon yokluğu

Doğru önerilerde bulunmayı zorlaştırmakla birlikte,

- Granülosit transfüzyonları,tedavisi zor fırsatçı enfeksiyonu olan hastalarda,
- Özellikle primer hastalığı remisyonunda olup,
- Nötrofillerin yükselmesine kadar geçen süre için zamana ihtiyacı olan hastalarda
- Bu süre için köprü görevi görmektedir.

- Kemoterapi ve hematopoetik hücre nakli sonrası oluşan nötropeni, halen bu grupta kullanımı nadir kalsa da, granülosit süspansiyonunun en yaygın kullanım alanıdır.
- Septik, nötropenik yüksek riskli hastaların tedavisinde
- Profilaktik granülosit kullanımının olası rolü????

- **Seçilmiş klinik indikasyonlarda**

MNS <500 hücre/microL;

Bakteriyel veya fungal infeksiyon delili olan;

En az 48 saatlik antibiyotik tedavisine yanıt vermeyen hastalarda

- **Granülosit transfüzyonlarının yeri olduğuna inanmaya devam edilmeli**

- Çocukluk çağında granülosit kullanımı konusunda **randomize kontrollü çalışmalara olan ihtiyaç devam etmektedir.**

