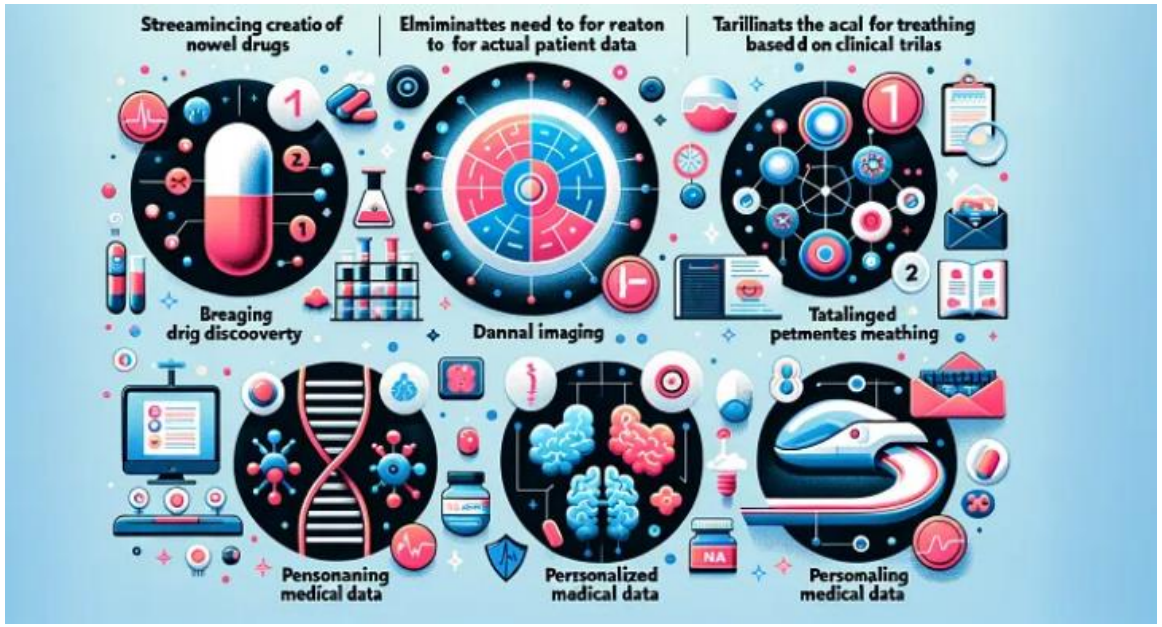
Nötropenik Ateş

25.05.2024

- Dr. Ahmet Gülmez

İç Hastalıkları A.B.D, Tıbbi Onkoloji B.D.

- Adana Başkent Üniversitesi Hastanesi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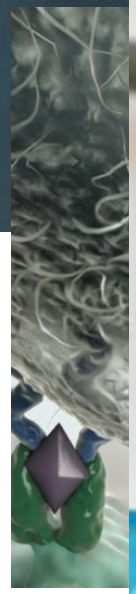

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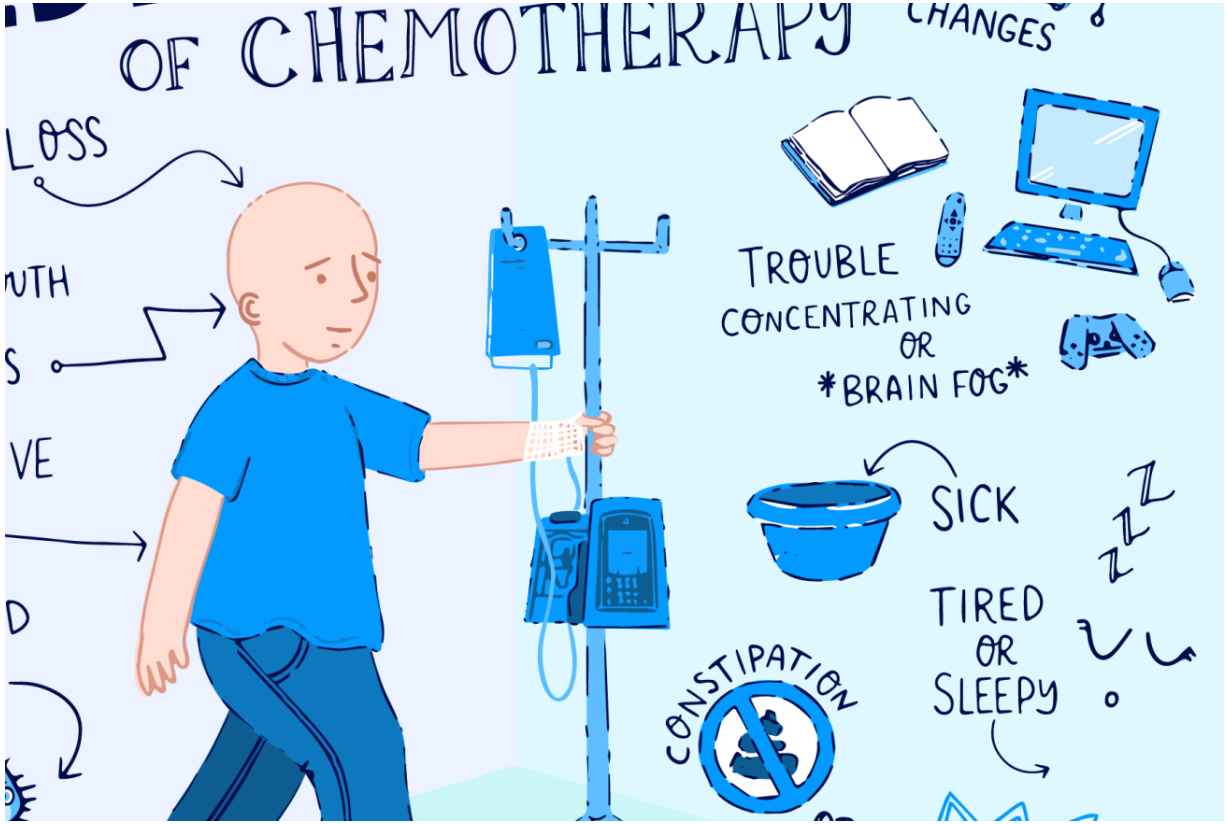
OF CHEMOTHERAPY
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EMERGENCY
HEALTHCARE
PROFESSIONAL
HOSPITAL
SPECIALIST
PRIMARY
TRANSPLANT
HELPING
HEALER
PERSON
CARE
PODIATRY

Febril Nötropeni

TANIM

- Tanı Kriterleri
  - Ateş oral ≥ 38’C(1 saatten fazla)
  - ≥ 38.3’C
- Nötropeni
  - Nötrofil < 500mm3
  - Nötrofil < 1000/mm3, fakat ilk 48 saat içinde 500/mm3’ün altına düşme ihtimali yüksek
- Ağır nötropeni < 100/mm3

Nötropeni Grade

Nötropeni Derecesi	MNS Sayısı / mm^3	Ciddi Enfeksiyon Gelişme Riski %
	>2000	2
1 (Hafif)	1500 - 2000	5
2 (Orta)	1000 - 1500	10
3 (Şiddetli)	500 - 1000	19
4 (yaşamı tehdit eden)	<500	28

MNS= mutlak nötrofil sayısı

1. Annals of Oncology 17 (Supplement 10): x85–x89, 2006 2. National CMNSer Institute Dictionary; 3. CMNSer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, v5.0 4. Annals of Oncology 16 (Supplement 1): i80 –i82, 2005

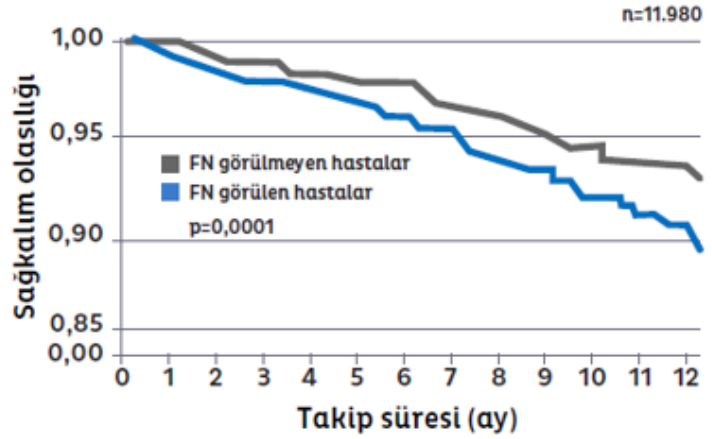
Febril Nötropeni - Mortalite

Febril nötropeni anlamlı derecede yüksek oranda erken* ve genel† mortalite ile ilişkilendirilmiştir.

Febril nötropeni:

- Oral ateş ölçümünün ≥38,3°C veya 1 saat boyunca ≥38,0°C olması
- Nötrofil seviyeleri <500 hücre/mm³ veya <1.000 nötrofil/mm³ ve sonraki 48 saat boyunca ≤500 hücre/mm³'e düşmesinin beklenmesi

Kemoterapi sonrası febril nötropeni görülen ve görülmeyen hastalarda erken mortalite* (ilk 12 ay)



	HR (febril nötropeni görülmeyen hastalara kıyasla)	%95 GA	Anlamlılık
Genel mortalite†	1,15	1,02-1,29	p=0,020
Erken mortalite*	1,35	1,09-1,67	p=0,006

1 yıl içerisinde ölüm riski %35 daha yüksek

Genel ölüm riski %15 daha yüksek

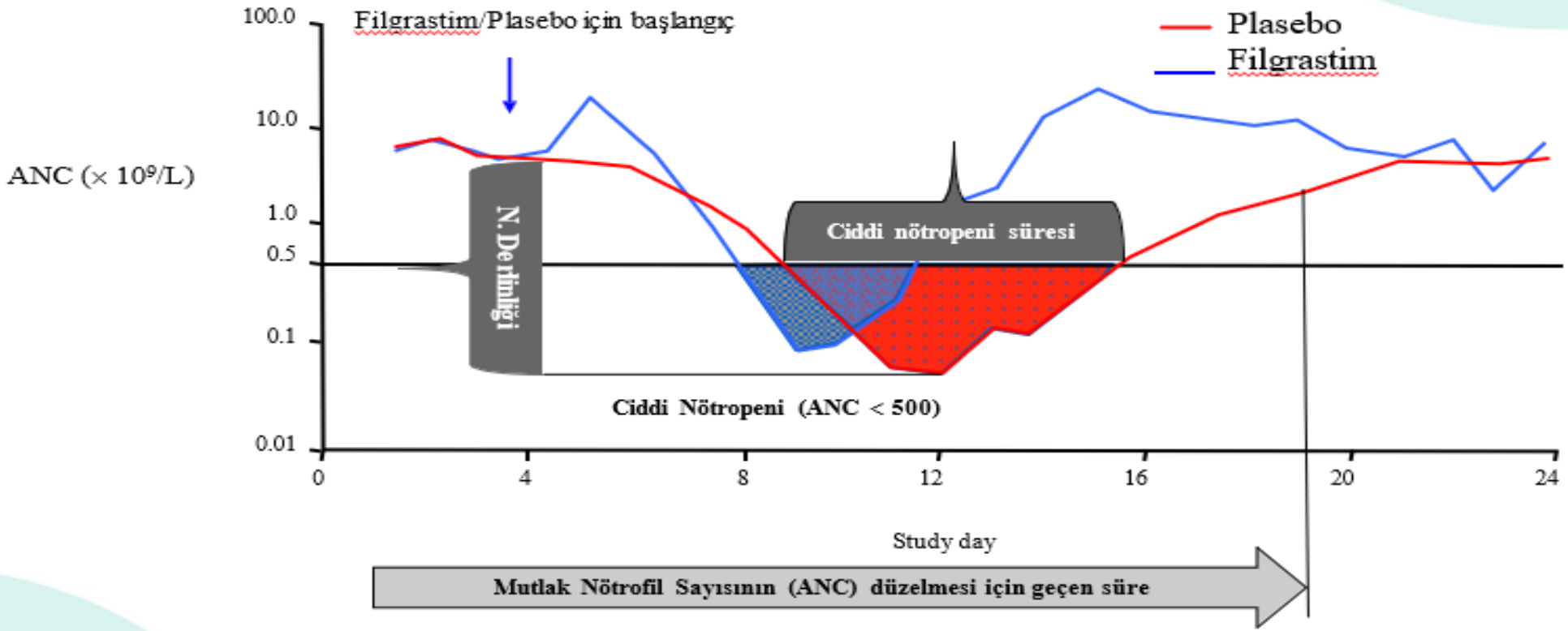
Uyarlandığı kaynak: Lyman GH et al. Cancer. 2010; 116(23): 5555-5563.

*Erken mortalite, ilk kemoterapi döngüsü sırasında meydana gelen tüm nedenlere bağlı mortalite olarak tanımlanmıştır (12 ayda kesilmiştir)

† Genel ölüm çalışma takibi sırasında tüm nedenlere bağlı mortalite olarak tanımlanmıştır (her iki grup için ortalama takip süresi 17,6 aydır)

FEN - Komplikasyonları

Kuderer NM, et al. *Cancer* 2006;106:2258-66. Bosly A, et al. *Ann Hematol* 2008;87:277-83. Lyman GH, et al. *J Natl Compr Canc Netw* 2009;7:99-108. Chirivella I, et al. *Breast Cancer Res Treat* 2009;114:479-84.



Crawford J, et al. *N Engl J Med.* 1991;325:164-170.

Febril Nötropeni Klinik Önemi

Kemoterapi alan solit organ tm'de %0.8 FEN.

FEN gelişen hastaların %20-30 hospitalize edilmekte

Hastane içi mortalitenin %10'u FEN kaynaklı

FEN İlişkili Faktörler

- KT rejimi; >%20, %10-20, <%10
- Yaş
- Önceki FEN geçmişi
- Granülosit koloni uyarıcı faktörü (G-CSF) ve Antb kullanmaması
- Mukozit,
- Kötü performans durumu
- Kardiyovasküler hastalık

FEN İlişkili Faktörler- II

Bakteriyemisi olan hastalarda prognoz en kötüdür

Mortalite Gram-negatif bakteriyemide %18

Gram-pozitif bakteriyemide %5'tir

Pnömoni, apse, selülit vb. klinik bulgular sonucu daha kötü hale getirmektedir.

Mortalite, Multinational Association of Supportive Care in Cancer (MASCC) prognostik indeksine göre değişmektedir

Klastersky J, Ameye L, Maertens J et al. Bacteraemia in febrile neutropenic patients. Int J Antimicrob Agents 2007; 30(Suppl. 1): S51–S59.

MASCC SKORU

MASCC skoru ≥21 ise %5'ten düşük

Ancak MASCC skoru <15 ise muhtemelen %40'a kadar yüksektir

Table 1. MASCC febrile neutropaenia risk index

Characteristics	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP > 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	2

Patients with scores ≥21 are at low risk of complications. Points attributed to the variable 'burden of illness' are not cumulative. The maximum theoretical score is therefore 26 [2]. Reprinted with permission.

BP, blood pressure.

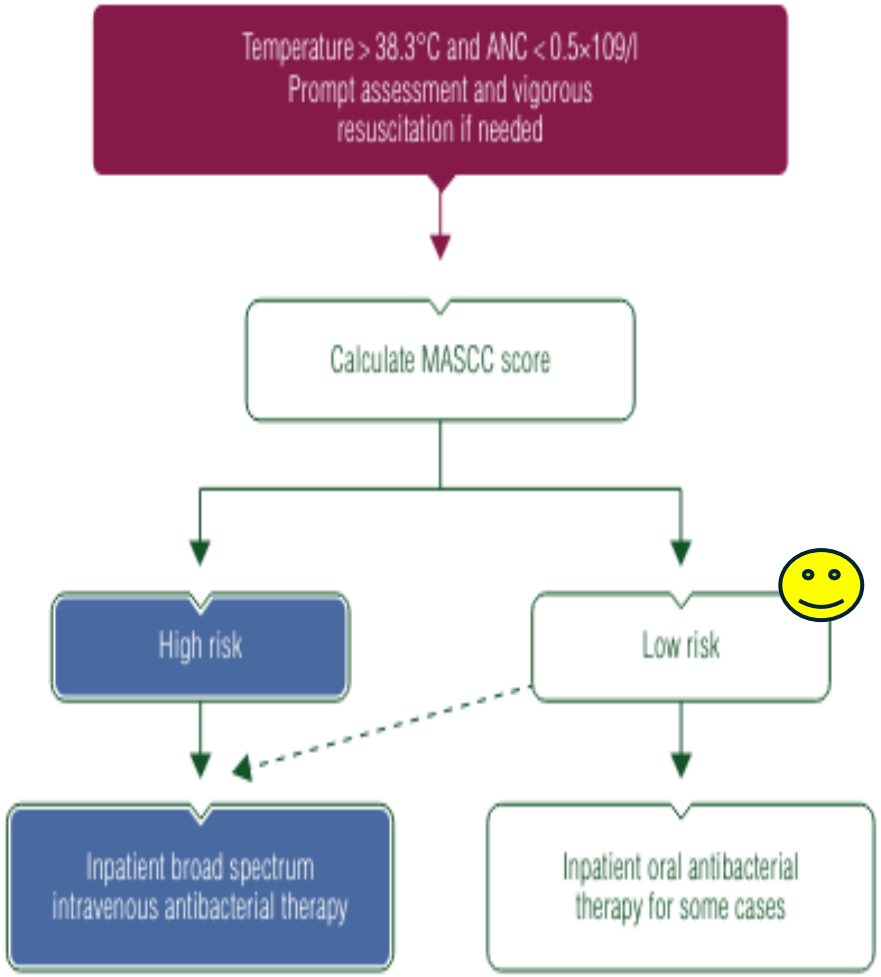


Figure 2. Initial management of febrile neutropaenia. ANC, absolute neutrophil count; MASCC, Multinational Association of Supportive Care in Cancer.

Table 2. Initial assessment and investigations

1	Note the presence of indwelling i.v. catheters
2	Symptoms or signs suggesting an infection focus:
	Respiratory system
	Gastrointestinal tract
	Skin
	Perineal region/genitourinary discharges
	Oropharynx
	Central nervous system
3	Knowledge of previous positive microbiology results by checking clinical records
4	Routine investigations:
	Urgent blood testing to assess bone marrow, renal and liver function
	Coagulation screen
	C-reactive protein
	Blood cultures (minimum of two sets) including cultures from indwelling i.v. catheter
	Urinalysis and culture[a]
	Sputum microscopy and culture[a]
	Stool microscopy and culture[a]
	Skin lesion (aspirate/biopsy/swab)
	Chest radiograph
5	Further investigations (profound/prolonger neutropaenia/following allografts)
	High-resolution chest CT (if pyrexial despite 72 h of appropriate antibiotics)
	Bronchoalveolar lavage

FEN Yönetimi - II

İlk Ab dozu 60 dk içinde verilmeli.

Ab için anti-psödomanal kullanılmalı ancak her hastane yerel epidemiyolojisine göre tedavi planı yapmalı. (*seftazidim* veya *sefepim*, *imipenem*, *meropenem* veya *piperasilin-tazobaktam*)

Nötropenik hastalarda enfeksiyon belirti ve semptomları, özellikle kortikosteroid alanlarda veya yaşlı hastalarda minimal olabilir.

Ab öncesi periferik ven ve kalıcı venöz kateterden iki set kan kültürünün

Ab Seçiminde Özel Durumlar

IV kateter: Vankomisin-Teikoplanin

Pnömoni: B- Laktam + Makrolit-Florokinolon. Steroit kullanımı, İS ilaç alımı: TMP- SMX. Derin-uzamış Nötropeni: Antifungal

Veziküler lezyonlar/şüpheli viral enfeksiyon: Asiklovir - Gansiklovir (veya foskarnet)

Selülit: Vankomisin, Linezolid, daptomisin

İshal: Clostridium difficile!! vankomisin veya metronidazol tedavisi uygulanmalıdır.

Kandidiyaz: Yaygın kandidiyazis riski taşıyan hastalar, uzamış nötropenisi olan ve özellikle miyeloablatif tedavi gören hematolojik maligniteleri olan hastalardır. Ateşi geniş spektrumlu antibiyotiklere 3-7 gün düzelme yoksa!!!

Ab Sonrası Takip ve Tedavi Devamlılığı?

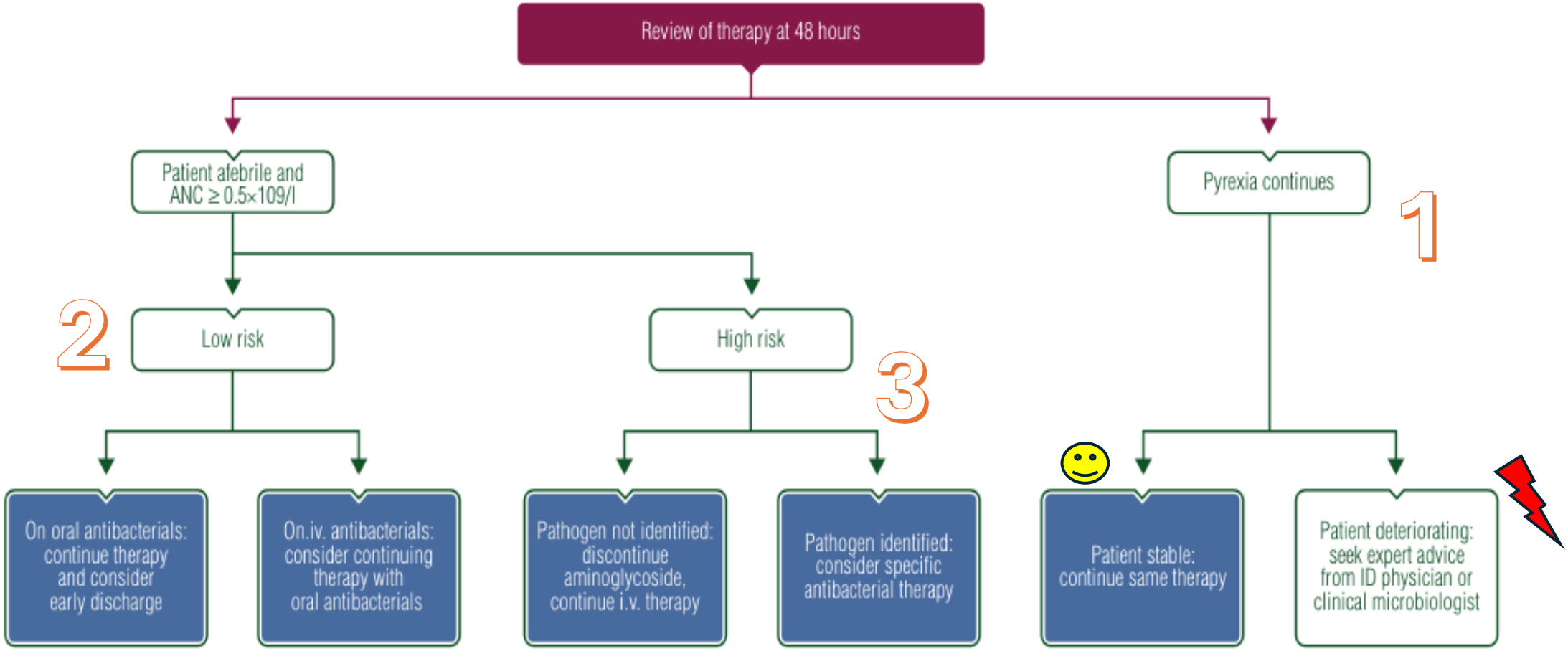
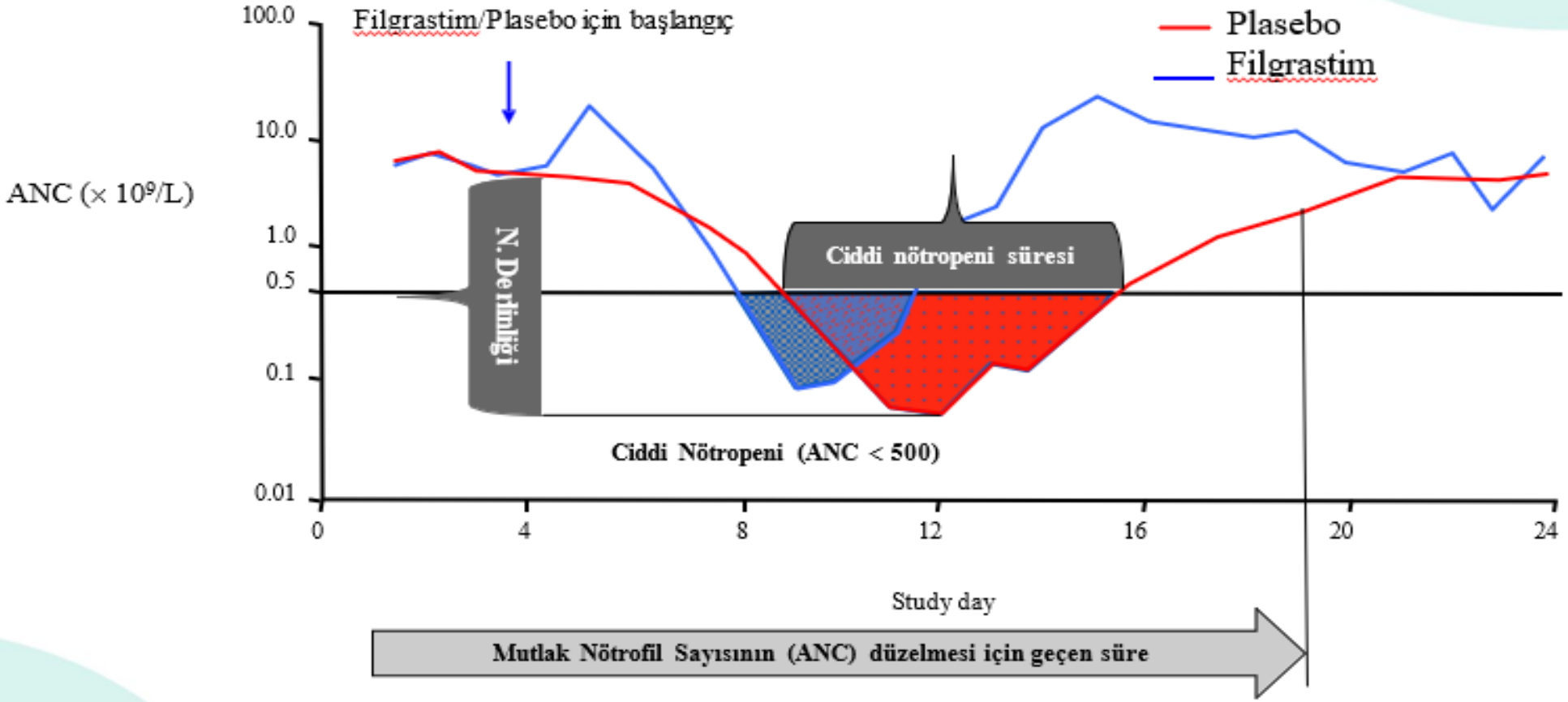
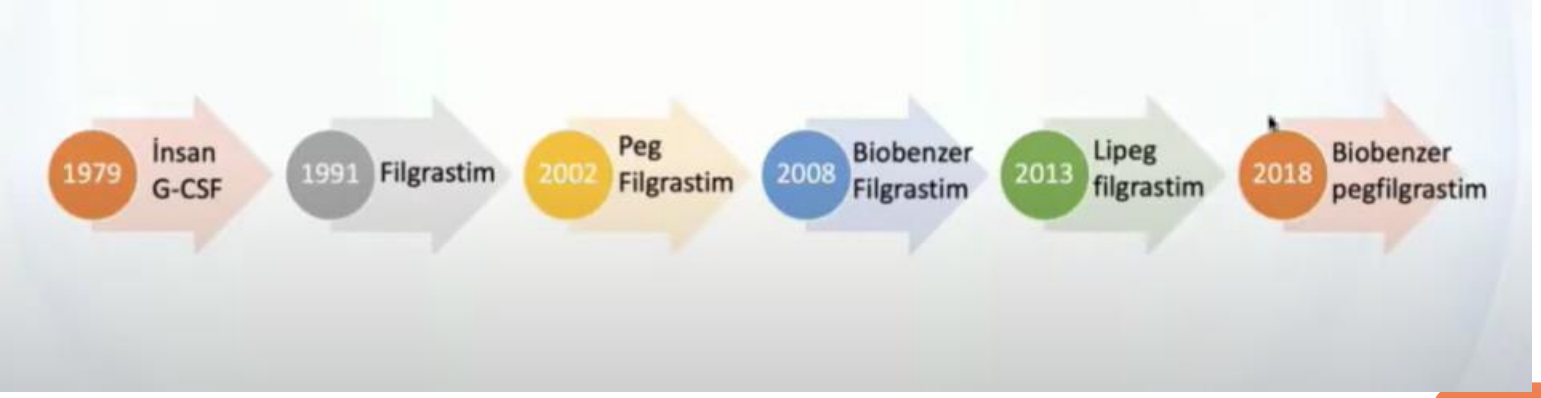
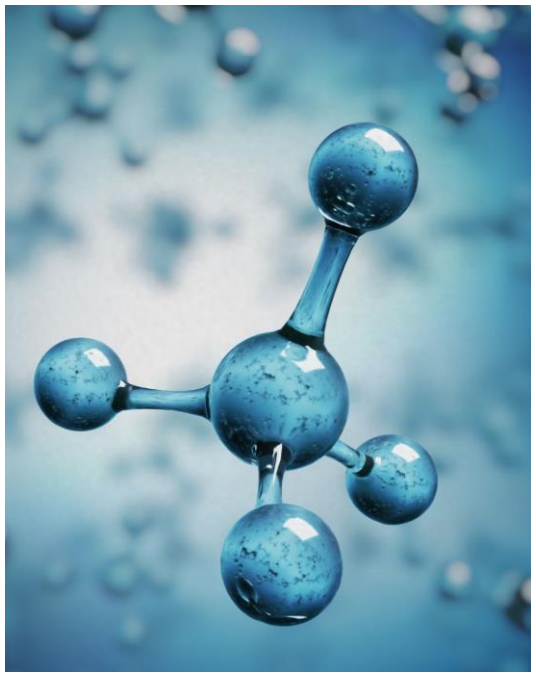


Figure 3. Assessment of response and subsequent management. ANC, absolute neutrophil count; i.v., intravenous; ID, infectious disease.



Crawford J, et al. *N Engl J Med.* 1991;325:164-170.





Filgrastim : Granülosit-koloni stimülan faktör (G-CSF)

Tbo-Filgrastim : Biyobenzer, non-glikolize

Pegfilgrastim

Lipegfilgrastim : G-CSF, uzun etkili

Lenograstim : glikolize, G-CSF

Sargramostim : granülosit-makrofaj-koloni stimülan faktör (GM-CSF)

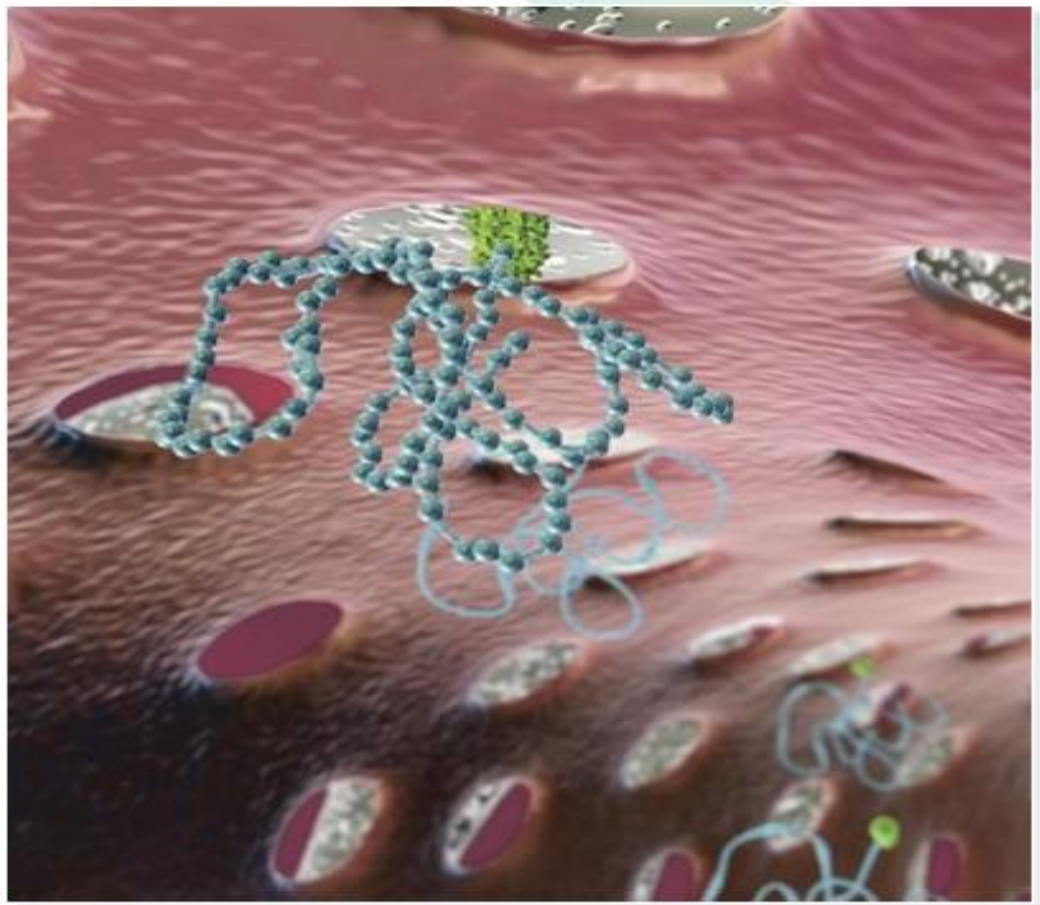
Günlük G-CSF: Filgrastim

Pegfilgrastim

Pegilasyon Düşük Glomerüler Filtrasyona ve Uzamış Etki Süresine Yol Açar.

- Pegilasyonun bir sonucu olarak, uzun etkili G-CSF'ler, glomerüler filtrasyon ve renal atılım gerçekleşmesi için çok büyüktür.

- Azalmış renal klirens uzun etkili G-CSF'lere kemoterapi döngüsü başında tek doz uygulanmasına olanak verir.

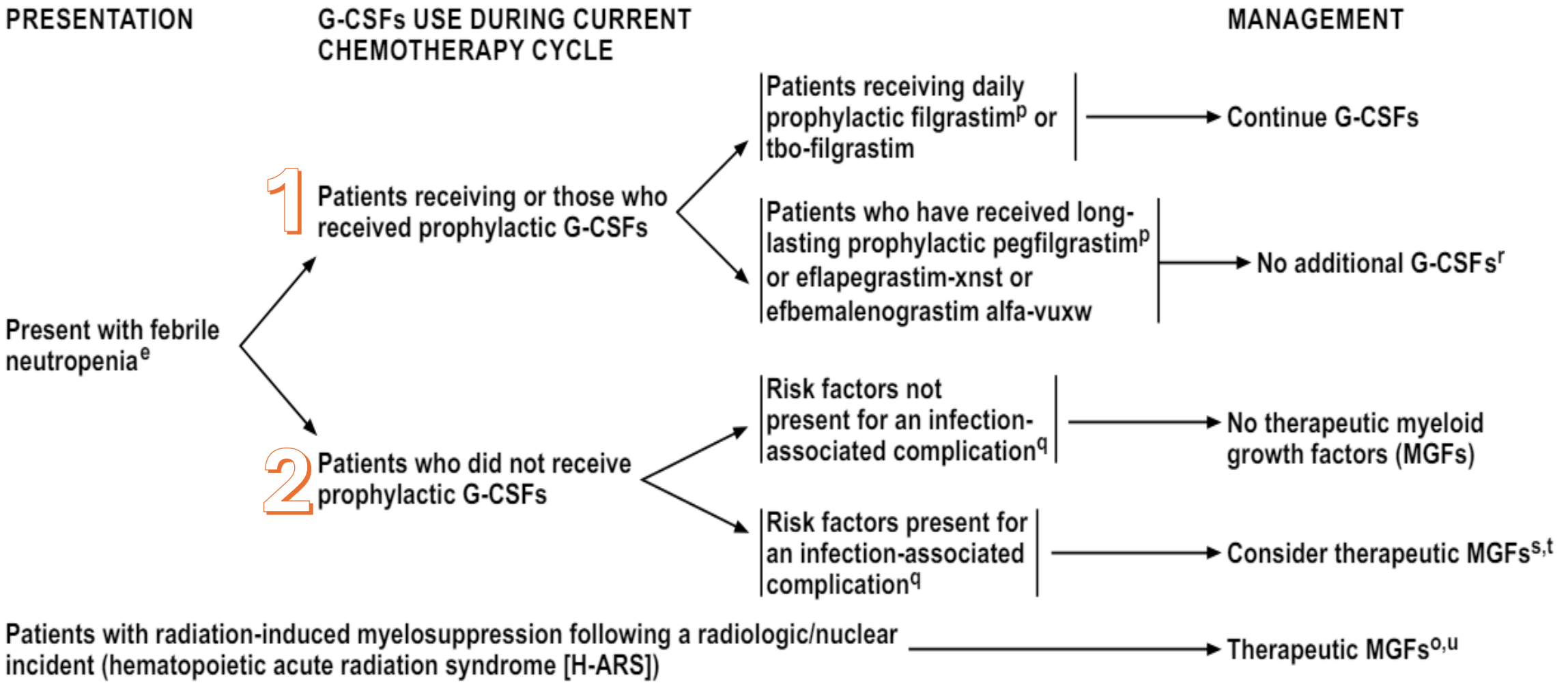


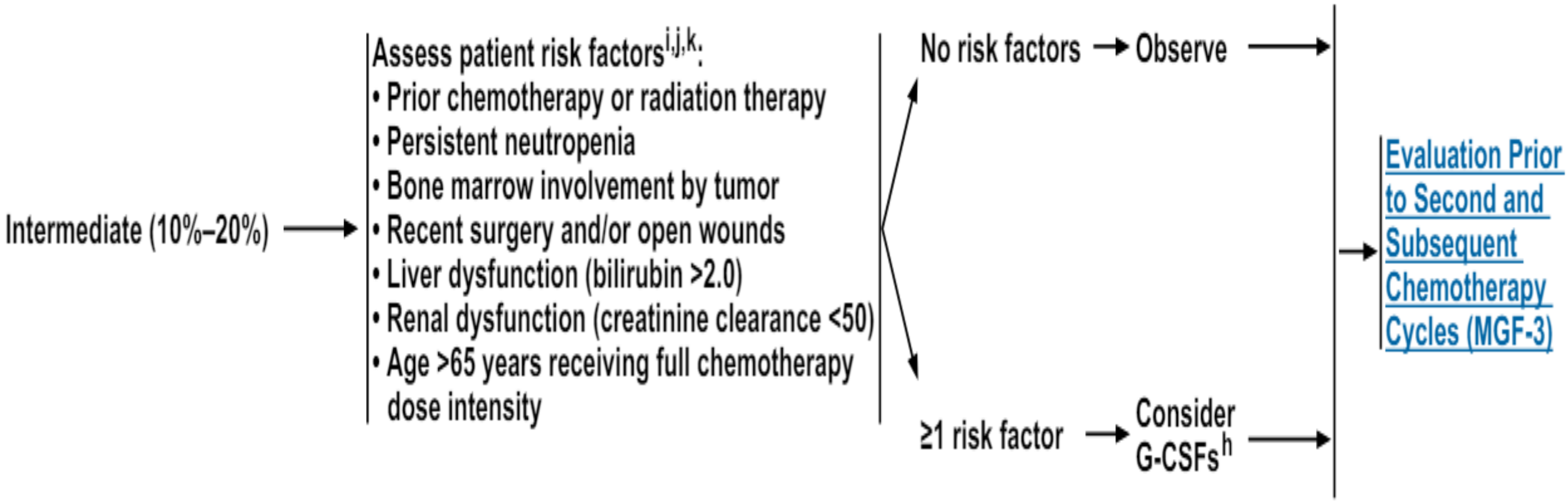
Luftner D, et al. *Onkologie*. 2005;28:595– 602.
Yang BB, et al. *Pharmacotherapy*. 2007;27:1387-1393.

- Activated sugar A1 — S 1
- Activated sugar linked to PEG A2 — S 2 — PEG
- The PEGylation site is threonine 134 (THR^{134})

PEG

THERAPEUTIC USE OF MGFs[e,m,n]




Intermediate (10%–20%)
Assess patient risk factors[i,j,k]:
• Prior chemotherapy or radiation therapy
• Persistent neutropenia
• Bone marrow involvement by tumor
• Recent surgery and/or open wounds
• Liver dysfunction (bilirubin >2.0)
• Renal dysfunction (creatinine clearance <50)
• Age >65 years receiving full chemotherapy dose intensity
No risk factors
Observe
≥1 risk factor
Consider G-CSFs[h]
Evaluation Prior to Second and Subsequent Chemotherapy Cycles (MGF-3)

EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH A HIGH RISK FOR FEBRILE NEUTROPENIA (>20%)[a]

- *This list is not comprehensive*; there are other agents/regimens that have a high risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for Treatment by Cancer Type are considered when updating this list of examples.
- The type of chemotherapy regimen is only one component of the risk assessment (Patient Risk Factors for Developing Febrile Neutropenia, MGF-2).
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients) (MGF-1).
- In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.

Acute Lymphoblastic Leukemia (ALL)
- Select ALL regimens as directed by treatment protocol (NCCN Guidelines for ALL)

Bladder Cancer
- Dose-dense MVAC (methotrexate, vinblastine, doxorubicin, cisplatin)[1]

Bone Cancer
- VAIA (vincristine, doxorubicin, ifosfamide, and dactinomycin)[2]
- VDC-IE (vincristine, doxorubicin or dactinomycin, and cyclophosphamide alternating with ifosfamide and etoposide)[3]
- Cisplatin/doxorubicin[4]
- VDC (cyclophosphamide, vincristine, doxorubicin or dactinomycin)[5]
- VIDE (vincristine, ifosfamide, doxorubicin or dactinomycin, etoposide)[6]

Breast Cancer
- Dose-dense AC followed by dose-dense paclitaxel (doxorubicin, cyclophosphamide, paclitaxel)[7,b]
- TAC (docetaxel, doxorubicin, cyclophosphamide)[8]
- TC[a,c] (docetaxel, cyclophosphamide)[9]
- TCH[a] (docetaxel, carboplatin, trastuzumab)[10]

Head and Neck Squamous Cell Carcinoma
- TPF (docetaxel, cisplatin, 5-fluorouracil)[11-13]

Hodgkin Lymphoma
- Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)[14]
- Escalated BEACOPP[d] (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[15]

Kidney Cancer
- Doxorubicin/gemcitabine[16]

Non-Hodgkin Lymphomas
- CHP (cyclophosphamide, doxorubicin, prednisone) + brentuximab vedotin
- Dose-adjusted EPOCH[a] (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)[17]
- ICE (ifosfamide, carboplatin, etoposide)[a,18,19]
- Dose-dense CHOP-14[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[20,21]
- MINE[a] (mesna, ifosfamide, mitoxantrone, etoposide)[22]
- DHAP[a] (dexamethasone, cisplatin, cytarabine)[23]
- ESHAP[a] (etoposide, methylprednisolone, cisplatin, cytarabine)[24]
- HyperCVAD[a] (cyclophosphamide, vincristine, doxorubicin, dexamethasone)[25,26]
- Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, prednisone)[27]

Melanoma
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa)[28]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[29] ± bortezomib (VTD-PACE)[30]

Ovarian Cancer
- Topotecan[a,31]
- Docetaxel[32]

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[33]
- Doxorubicin[a,34]
- Ifosfamide/doxorubicin[35]

Small Cell Lung Cancer[e]
- Topotecan[36]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[37]
- VIP (etoposide, ifosfamide, cisplatin)
- TIP (paclitaxel, ifosfamide, cisplatin)[38]

EXAMPLES OF DISEASE SETTINGS AND CHEMOTHERAPY REGIMENS WITH AN INTERMEDIATE RISK FOR FEBRILE NEUTROPENIA (10%–20%)[a]

- *This list is not comprehensive*; there are other agents/regimens that have an intermediate risk for the development of febrile neutropenia. Regimens recommended in the NCCN Guidelines for Treatment by Cancer Type are considered when updating this list of examples.
- The type of chemotherapy regimen is only one component of the Risk Assessment. See Patient Risk Factors for Developing Febrile Neutropenia (MGF-2).
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive vs. heavily pretreated patients) (MGF-1).
- In general, dose-dense regimens require MGF support to maintain dose intensity and schedule.

Occult Primary - Adenocarcinoma
- Gemcitabine/docetaxel[41]

Breast Cancer
- Docetaxel[a,42,43]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (taxane portion only)[a,44]
- Paclitaxel every 21 days[a,45]

Cervical Cancer
- Cisplatin/topotecan[46,47]
- Paclitaxel/cisplatin[a,46]
- Topotecan[48]
- Irinotecan[49]

Colorectal Cancer
- FOLFIRINOX (fluorouracil, leucovorin, oxaliplatin, irinotecan)[f,50-52]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[a,53]

Non-Hodgkin Lymphomas
- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)[a,54]
- CHOP[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[55,56] including regimens with pegylated liposomal doxorubicin[57,58]
- Bendamustine[a]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel[59]
- Cisplatin/vinorelbine[60]
- Cisplatin/docetaxel[59,61]
- Cisplatin/etoposide[62]
- Carboplatin/paclitaxel[a,g,63]
- Docetaxel[61]

Ovarian Cancer
- Carboplatin/docetaxel[64]

Pancreatic Cancer
- FOLFIRINOX[h] (fluorouracil, leucovorin, irinotecan, oxaliplatin)

Prostate Cancer
- Cabazitaxel[i,65]

Small Cell Lung Cancer[e]
- Etoposide/carboplatin[66]

Testicular Cancer
- BEP[d] (bleomycin, etoposide, cisplatin)[67-69]
- Etoposide/cisplatin[70]

Uterine Sarcoma
- Docetaxel[71]

[f] There are many factors that need to be evaluated to determine a patient's risk

G – CSF Yan Etki!!!

Kemik Ağrısı

Pulmoner Toksisite

Dalak Rüptürü

Alerjik reaksiyon

Uygulama Yeri Reaksiyonları

Miyalji

Orak Hücre Anemi Krizi

Kutanöz Vaskülit

SONUÇ

- 1- FEN mortal bir klinik tablodur, hızlı bir şekilde tetkik ve tedavi edilmelidir. 60 dk içinde...
- 2- Yaşlı, steroit kullanan yada IS hastalar FEN kriterlerini karşılamayabilir. Hemodinamik tablo önemli...
- 3- Düşük riskli hastada oral ajanlar yeterli olabilir (amoksisilin klavulonat + siprofloksasin yada moksifloksasin)
- 4- Yüksek riskli hastalarda antipsödomanal ajanlarla tedavi edilmelidir.
- 5- Yüksek riskli hastalarda primer proflaksi yapılmalıdır.
- 6- Primer proflakside kısa etkili ajanlar kullanılabilir. Uzun etkililer!!!


BAŞKENT ÜNİVERSİTESİ KIŞLA SAĞLIK YERLEŞKESİ