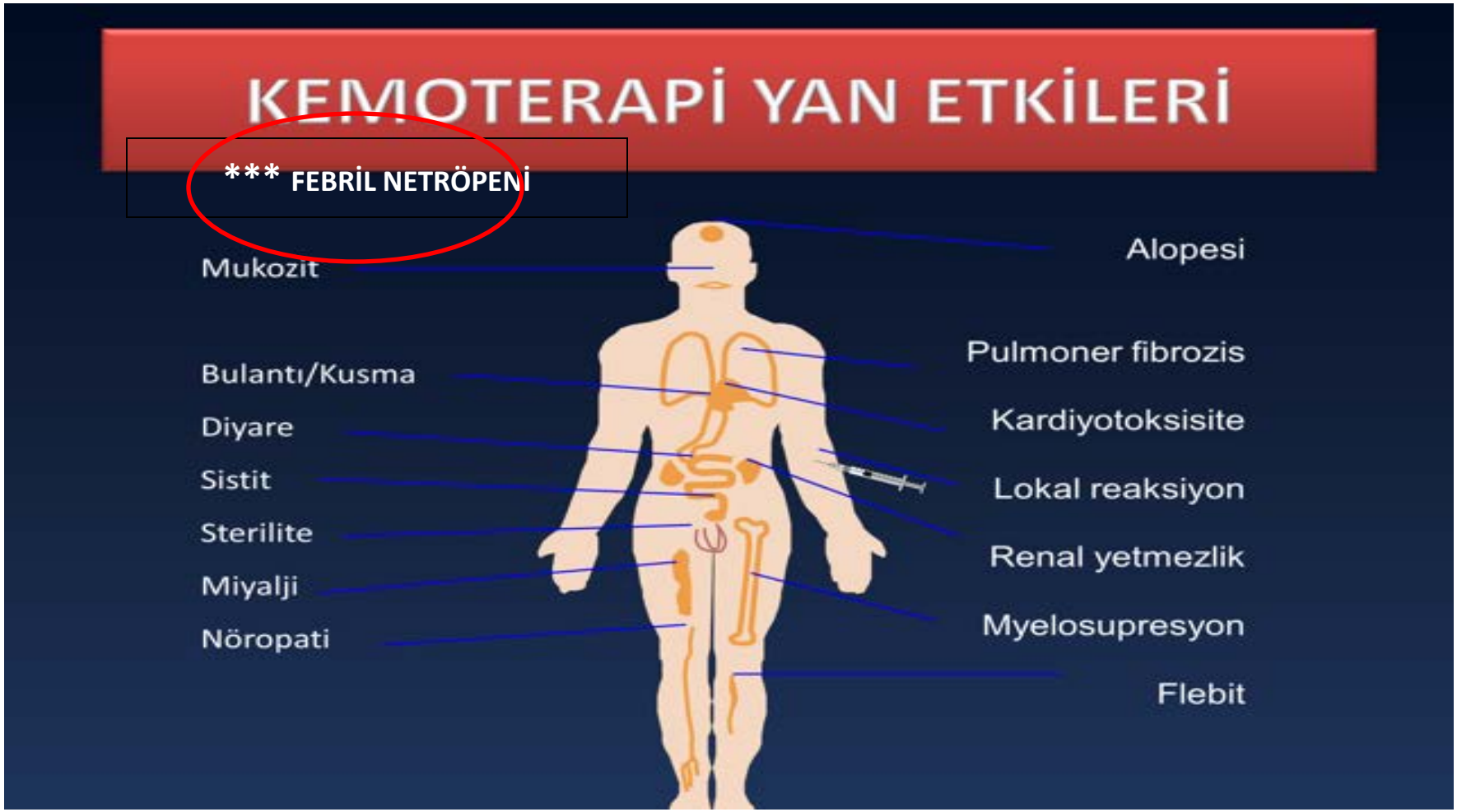
ONKOLOJİK ACİLLER

Dr. Deniz Tural
Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

Ders Planı

- *Febril Nötropeni*
- *Hiperkalsemi*
- *Vena-kava süperiyor sendromu*
- *Santral ve periferik sinir sistemi metastazı*
- *Uygunsuz ADH sendromu*

Yüksek Doz Kemoterapi



Primer G-CSF proflaksisi için hangisi doğrudur?

A- ≥%20 febril nötropeni riski yapacağı varsayılan kemoterapi rejimlerinden sonra

B-Adjuvan doz yoğun kemoterapi sonrası

C- Febril nötropeniye bağlı ciddi komplikasyon riski olacağı varsayılan hastalarda

D-Hepsi

40 yaşında kadın hasta, meme kanseri nedeniyle adjuvan doz yoğun antrasiklin, siklofosfamid kemoterapisi alıyor, kemoterapi sonrası primer proflaksi amaçlı filgrastim veriliyor. 3. kür sonrası, şiddetli sol üst kadran ağrısı ile acile geliyor. Hasta hipotansif, anemik(hgb: 9 g/dl) olarak acilden danışılıyor. Ön tanı?

A-Kemoterapiye bağlı

B- Hastalık ilerlemesi

C-Demir eksikliği

D-Splenik rüptür

Kemoterapi ve Febril Nötropeni

Febril nötropenik (FEN'k) hasta: Tanımı

- Nötrofil: <500/mm³ veya 48 saat içinde <500 düşmesi beklenen

- Oral ateş (timpanik; İnfared): Tek kez ≥ 38.3˚C veya
  Bir saat süreyle > 38˚C

Clin Infect Dis 2011; 52: 56-93

Yüksek Doz Kemoterapi

Kanser KT'si sonucu FEN atak gelişme sıklığı

- Solid Tm'lü hastaların; <%50 (%10-50)
- Hematolojik kanserlilerin; ~ %100 (>%80)
- Miyeloablasyon başta nekadar fazla ise hematolog için iyi, enfeksiyoncu için kötü

Clin Infect Dis 2004; 39: S32-7
Ann Oncol 2010; 21: 252-56

Nötropeni Süresi Ciddi Enfeksiyon Gelişmesini Etkiler

Ciddi nötropeni süresiyle enfeksiyon ilişkisi

- **<1 hafta → İnvaziv Fungal İnfeksiyon gelişmez (düşük riskli grup)**
- **≥1 haftayı → İnvaziv kandidiyaz**
- **≥2 haftayı → İnvaziv aspergiloz gelişebilir**
- **Nötropeni ≥ 3 hafta → Tümünde enfeksiyon gelişir**

Annu Rev Med 2004; 55: 519-26
Clin Infect Dis 2011; 52: 56-93

FEN Risk Gurubuna Göre Mortalite Değişir

FEN ataklarında mortalite oranı

- Düşük riskli grupta (solid tümörlülerde) → < %5 (~%1)
- Yüksek riskli grupta (hematolojik kanserlilerde) → < %10

- MASCC skoruna görede mortalite değişir
  - Skor >21 ise → <%5 (düşük riskli grup)
  - Skor <15 ise → > %20

FEN'de Risk Gurubuna Göre Mortalite Oranı Değişir

MASC prognoz skoru (bir klinik skorlamadır; lab yok)
(Multinational Association for Supportive Care)

Parametre	Puan
Hafif semptom	5
Orta semptom	3
Ciddi semptom	0
Hipotansiyon yokluğu	5
Dehidratasyon yokluğu	3
KOAH yokluğu	4
Solit TM / Lenfoma	4
Ateşi toplumda başlamış	3
Yaş <60	2

- Skor ≥ 21 ise düşük riskli hasta (Toplam puan 29)

FEN'de Ayakta Oral Tedavi Kimlere Verilebilir?

Düşük riskli FEN'ik hasta⟶ Kimlere oral ayaktan AB verebiliriz

- GD iyi olacak
- Bulantı-kusma olmayacak
- Hipotansiyon olmayacak
- Enfeksiyon odağı olmayacak (pnömoni, PN, SVK)
- Organ yetmezliği olmayacak (Kc ve böbrek)
- PNL <100 olmayacak

FEN’de Ayakta Oral Tedavi Kimlere Verilebilir

Düşük riskli FEN’ik hasta⟶ Kimlere oral ayaktan AB verebiliriz

- Bu grup hastalara ayaktan oral veya yatırılarak parenteral AB verme mortalite yönünden farksız (Onkologların %80’i bunu tercih ediyor)
- Siprofloksasin (2x750) + AM/KL (3x625) veya moksifloksasin monoterapisi
- Oral verdikten sonra 6 saat veya 24 saat gözlemek daha uygun gibi
- Ateş düşene kadar günlük haberleşmek lazım
- Durumu ağırlaşırsa 1 saat içinde acile gelmesi tembihlenmelidir
- Bu faktörlerden birkaçını içerenler yatırılıp standart tedavi (PİP/TZ) verilir
- Parenteral başlanıp oral tedaviye geçilip taburcu edilebilir

FEN Riskinde Primer Proflaktik G-CSF

- Solid TM ve lenfoma hastalarında KT ile ≥ %20 ciddi nötropeni oluşacaksa önerilmektedir

ASCO: American Society of Clinical Oncology
NCCN: National Comprehensive Cancer Network
EORTC: European Organisation for Research and Treatment of Cancer
ESMO: European Society for Medical Oncology

G-CSF Primer Proflaksisi

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Myeloid Growth Factors

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Discussion

EVALUATION PRIOR TO FIRST CHEMOTHERAPY CYCLE[a]

Evaluation of risk for febrile neutropenia following chemotherapy in adult patients with solid tumors and non-myeloid malignancies[b]

RISK ASSESSMENT FOR FEBRILE NEUTROPENIA[c]

- Disease
- Chemotherapy regimen[d]
  - High-dose therapy
  - Dose-dense therapy
  - Standard-dose therapy
- Patient risk factors[d]
- Treatment intent (curative vs. palliative)

PROPHYLACTIC USE OF CSF FOR FEBRILE NEUTROPENIA[c,e]

	CHEMOTHERAPY TREATMENT INTENT		
	CURATIVE/ ADJUVANT[f]	PROLONG SURVIVAL/ QUALITY OF LIFE	SYMPTOM MANAGEMENT/ QUALITY OF LIFE
High (>20%)	CSFs (category 1 for G-CSFs)[g]	CSFs (category 1 for G-CSFs)[g]	CSFs[i]
Intermediate (10%-20%)	Consider CSF	Consider CSF[i]	Consider CSF[i]
Low (<10%)	No CSFs[h]	No CSFs	No CSFs

CSFs= Colony-stimulating factors

See Evaluation Prior to Second and Subsequent Chemotherapy Cycles (MGF-2)

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PATIENT RISK FACTORS FOR DEVELOPING FEBRILE NEUTROPENIA

In addition to the risk of the chemotherapy regimen and the specific malignancy being treated, these factors need to be considered when evaluating a patient's overall risk for febrile neutropenia.

- Older patient, notably patients age 65 and older (See NCCN Guidelines for Senior Adult Oncology)
- Previous chemotherapy or radiation therapy
- Preexisting neutropenia or bone marrow involvement with tumor
- Preexisting conditions
  - Neutropenia
  - Infection/open wounds
  - Recent surgery
- Poor performance status
- Poor renal function
- Liver dysfunction, most notably elevated bilirubin
- HIV-infected patient

FEN Gelişmesi Yönünde Yüksek Risk Kategorisine Olan KT rejimleri Primer G-CSF Proflaksisi Kulanılması

Kanıt düzeyi: Kategori 1

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Examples of Disease Settings and Chemotherapy Regimens with a High Risk for Febrile Neutropenia (>20%)

- The type of chemotherapy regimen is only one component of the Risk Assessment. (See Patient Risk Factors for Developing Febrile Neutropenia, MGF-B)
- *This list is not comprehensive*; there are other agents/regimens that have a high risk for the development of febrile neutropenia.
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive versus heavily pretreated patients). (See MGF-1)

Acute Lymphoblastic Leukemia (ALL)
- ALL induction regimens (See NCCN Guidelines for ALL)

Bladder Cancer
- MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) (neoadjuvant, adjuvant, metastatic)[1]

Breast Cancer
- Docetaxel + trastuzumab (metastatic or relapsed)[2]
- Dose-dense AC followed by T* (doxorubicin, cyclophosphamide, paclitaxel) (adjuvant)[3]
- TAC (docetaxel, doxorubicin, cyclophosphamide) (adjuvant)[4]

Esophageal and Gastric Cancers
- Docetaxel/cisplatin/fluorouracil[5]

Hodgkin Lymphoma
- BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[6]

Kidney Cancer
- Doxorubicin/gemcitabine[7]

Non-Hodgkin's Lymphomas
- CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab) (CLL with del(17p), relapsed/refractory)[8,9]
- ICE (ifosfamide, carboplatin, etoposide) (DLBCL, PTCL, 2nd line, salvage)[10]
- RICE* (rituximab, ifosfamide, carboplatin, etoposide)[11]
- CHOP-14* (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab[12,13]
- MINE (mesna, ifosfamide, novantrone, etoposide) (DLBCL, PTCL, 2nd line, refractory)[14]
- DHAP (dexamethasone, cisplatin, cytarabine) (peripheral T-cell lymphomas, diffuse large B-cell lymphoma, 2nd line)[15]
- ESHAP (etoposide, methylprednisolone, cisplatin, cytarabine) (DLBCL, PTCL, 2nd line, recurrent)[16]
- HyperCVAD + rituximab (cyclophosphamide, vincristine, doxorubicin, dexamethasone + rituximab)[17,18]

Melanoma
- Dacarbazine-based combination (dacarbazine, cisplatin, vinblastine) (advanced, metastatic, or recurrent)[19]
- Dacarbazine-based combination with IL-2, interferon alfa (dacarbazine, cisplatin, vinblastine, IL-2, interferon alfa) (advanced, metastatic, or recurrent)[19]

Myelodysplastic Syndromes
- Antithymocyte globulin, rabbit/cyclosporine[20]

Ovarian Cancer
- Topotecan[21]
- Paclitaxel[22]
- Docetaxel[23]

Soft Tissue Sarcoma
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[24]
- Doxorubicin[25]
- Ifosfamide/doxorubicin[26]

Small Cell Lung Cancer
- Topotecan[27]

Testicular Cancer
- VeIP (vinblastine, ifosfamide, cisplatin)[28]
- VIP (etoposide, ifosfamide, cisplatin)
- BEP (bleomycin, etoposide, cisplatin)[29,30]
- TIP (paclitaxel, ifosfamide, cisplatin)[31]

*In general, dose-dense regimens require growth factor support for chemotherapy administration.

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A (2 of 4)

See Chemotherapy Regimen References, MGF-A (3 of 4)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

FEN Gelişmesi Yönünde Orta Risk Kategorisine Olan KT rejimleri Primer G-CSF Proflaksisi Kulanılması Kanıt düzeyi: Kulanılması Düşünülebilinir

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Examples of Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia (10%-20%)

- The type of chemotherapy regimen is only one component of the Risk Assessment. See Patient Risk Factors for Developing Febrile Neutropenia (MGF-B).
- *This list is not comprehensive*; there are other agents/regimens that have an intermediate risk for the development of febrile neutropenia.
- The exact risk includes agent, dose, and the treatment setting (ie, treatment naive versus heavily pretreated patients). (See MGF-1)

Occult Primary - Adenocarcinoma
- Gemcitabine/docetaxel[32]

Breast Cancer
- Docetaxel every 21 days[33]
- CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)[34]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only)[35]
- AC + sequential docetaxel + trastuzumab (adjuvant)[36]
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel[37]
- Paclitaxel every 21 days (metastatic or relapsed)[38]
- TC (docetaxel, cyclophosphamide)[a,39]

Cervical Cancer
- Cisplatin/topotecan (recurrent or metastatic)[40,41,42]
- Paclitaxel/cisplatin[42]
- Topotecan (recurrent or metastatic)[43]
- Irinotecan (recurrent or metastatic)[44]

Colorectal Cancer
- FOLFOX (fluorouracil, leucovorin, oxaliplatin)[45]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[46]
- Epirubicin/cisplatin/5-fluorouracil[47]
- Epirubicin/cisplatin/capecitabine[47]

Hodgkin Lymphoma
- ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)[48]
- Stanford V (mechlorethamine, doxorubicin, vinblastine, bleomycin, etoposide, prednisone)[49]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide[50]
- DT-PACE + bortezomib (VTD-PACE)[51]

Non-Hodgkin's Lymphomas
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt lymphoma, recurrent)[52]
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + IT chemotherapy (AIDS-related NHL, DLBCL, recurrent)[52]
- ACOD (modified CHOP-doxorubicin, cyclophosphamide, vincristine, prednisone)[53]
- GDP (gemcitabine, dexamethasone, cisplatin) (DLBCL, PTCL, 2nd line)[54]
- GDP (gemcitabine, dexamethasone, cisplatin) + rituximab (DLBCL, 2nd line)[54]
- FMR (fludarabine, mitoxantrone, rituximab)[55]
- CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)[56,57] including regimens with pegylated liposomal doxorubicin[58,59] or mitoxantrone[60] substituted for doxorubicin

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel (adjuvant, advanced/metastatic)[61]
- Cisplatin/vinorelbine (adjuvant, advanced/metastatic)[62]
- Cisplatin/docetaxel (adjuvant, advanced/metastatic)[61,63]
- Cisplatin/irinotecan (advanced/metastatic)[64]
- Cisplatin/etoposide (adjuvant, advanced/metastatic)[65]
- Carboplatin/paclitaxel** (adjuvant, advanced/metastatic)[64]
- Docetaxel (advanced/metastatic)[63]

Ovarian Cancer
- Carboplatin/docetaxel[66]

Pancreatic Cancer
- FOLFIRINOX†

Prostate Cancer
- Cabazitaxel‡,[67]

Small Cell Lung Cancer
- Etoposide/carboplatin[68]

Testicular Cancer
- Etoposide/cisplatin[69]

Uterine Sarcoma
- Docetaxel (advanced or metastatic)[70]

**If carboplatin dose is AUC >6 and/or patient is of Japanese ancestry.
†A small retrospective trial had a 17% risk of FN in neoadjuvant setting[72] and a randomized trial had a 5.4% in metastatic setting (G-CSF was administered to 42.5% of patients who received FOLFIRINOX).[73] While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.
‡The published results for cabazitaxel have an 8% rate of febrile neutropenia and neutropenic deaths were reported. Primary prophylaxis with G-CSFs should be considered in patients with high-risk clinical features.
[a]Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.

See Chemotherapy Regimen References, MGF-A (4 of 4)

See Disease Settings and Chemotherapy Regimens with a High Risk for Febrile Neutropenia, MGF-A (1 of 4)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

❑G-CSF Primer Proflaksisi Neden Kullanalım?

- ❑Hastaların Sağkalımı Artıyor mu?
- ❑Maliyet?
- ❑Hastaneye yatış süresi?
- ❑Enfeksiyon riskini ve buna bağlı mortalite azalıyor mu?

Meta-analiz 1:

Primer G-CSF Proflaksisi, FEN, Hastaneye Yatışı azaltıyor, Doz yoğun kemoterapi alma oranı daha fazla, Antibiyotik Kullanımını ve Enfeksiyona Bağlı Mortaliteyi Azalttır. Muskulo-skeletal ağrı daha fazla

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J Clin Oncol. 2007 Jul 20;25(21):3158-67.

Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review.

Kuderer NM[1], Dale DC, Crawford J, Lyman GH.

Author information

Abstract

PURPOSE: Randomized controlled trials (RCTs) of prophylactic granulocyte colony-stimulating factors (G-CSF) have demonstrated a significant reduction in febrile neutropenia (FN) after systemic chemotherapy. Several RCTs have been published recently that investigate the impact of G-CSF on mortality and relative dose-intensity (RDI).

METHODS: A comprehensive systematic review and meta-analysis of all reported RCTs comparing primary prophylactic G-CSF with placebo or untreated controls in adult solid tumor and malignant lymphoma patients was undertaken without language restrictions, using electronic databases, conference proceedings, and hand-searching techniques. Two reviewers extracted data independently. Summary estimates of relative risk (RR) with 95% CIs were estimated based on the method of Mantel-Haenszel and DerSimonian and Laird.

RESULTS: Seventeen RCTs were identified including 3,493 patients. For infection-related mortality, RR reduction with G-CSF compared with controls was 45% (RR = 0.55; 95% CI, 0.33 to 0.90; P = .018); for early mortality (all-cause mortality during chemotherapy period), it was 40% (RR = 0.60; 95% CI, 0.43 to 0.83; P = .002); and for FN, it was 46% (RR = 0.54; 95% CI, 0.43 to 0.67; P < .001). Average RDI was significantly higher in patients who received G-CSF compared with control patients (P < .001). Bone or musculoskeletal pain was reported in 10.4% of controls and 19.6% of G-CSF patients (RR = 4.03; 95% CI, 2.15 to 7.52; P < .001). Significant reductions in FN with G-CSF were observed in studies allowing secondary G-CSF prophylaxis in controls and in the three trials with concurrent prophylactic antibiotics in both treatment arms.

CONCLUSION: Prophylactic G-CSF reduces the risk of FN and early death due to infection-related mortality while increasing RDI and musculoskeletal pain. There is insufficient data to assess the impact of G-CSF on disease-free and overall survival.

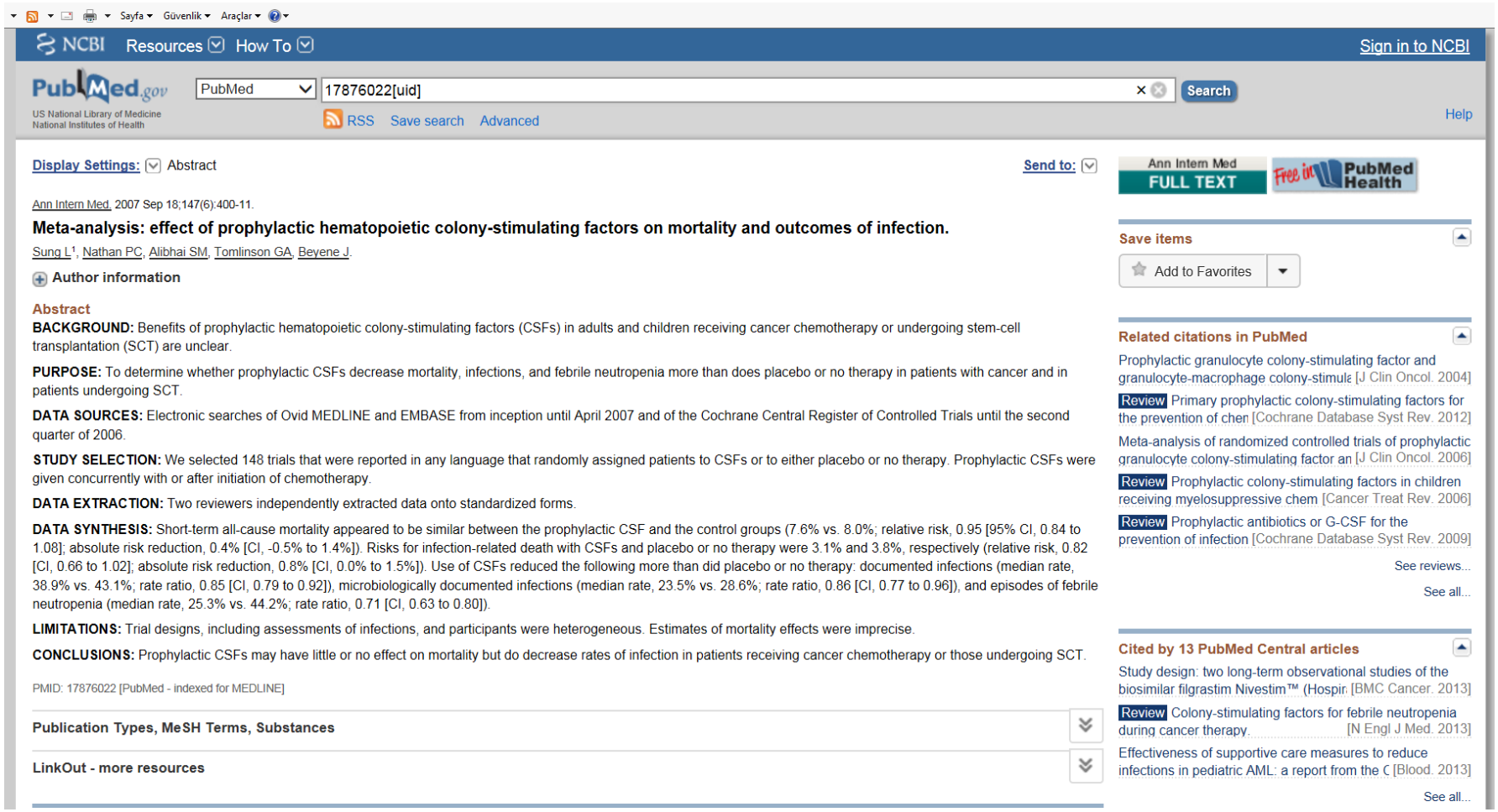
DFS ve Kanser Spesifik Survival Üzerine Etkisi Tartışmalı

Comment in

Study inclusion criteria and presentation of results in a meta-analysis of granulocyte colony-stimulating factor for prevention of febrile neutropenia. [J Clin Oncol. 2010]

Meta-analiz 2:

Primer G-CSF Proflaksisi, FEN, Enfeksiyon Riskini Azaltır, Fakat Total Mortaliteyi Azaltmaz



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Ann Intern Med. 2007 Sep 18;147(6):400-11.

Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection.

Sung L[1], Nathan PC, Alibhai SM, Tomlinson GA, Beyene J.

Author information

Abstract

BACKGROUND: Benefits of prophylactic hematopoietic colony-stimulating factors (CSFs) in adults and children receiving cancer chemotherapy or undergoing stem-cell transplantation (SCT) are unclear.

PURPOSE: To determine whether prophylactic CSFs decrease mortality, infections, and febrile neutropenia more than does placebo or no therapy in patients with cancer and in patients undergoing SCT.

DATA SOURCES: Electronic searches of Ovid MEDLINE and EMBASE from inception until April 2007 and of the Cochrane Central Register of Controlled Trials until the second quarter of 2006.

STUDY SELECTION: We selected 148 trials that were reported in any language that randomly assigned patients to CSFs or to either placebo or no therapy. Prophylactic CSFs were given concurrently with or after initiation of chemotherapy.

DATA EXTRACTION: Two reviewers independently extracted data onto standardized forms.

DATA SYNTHESIS: Short-term all-cause mortality appeared to be similar between the prophylactic CSF and the control groups (7.6% vs. 8.0%; relative risk, 0.95 [95% CI, 0.84 to 1.08]; absolute risk reduction, 0.4% [CI, -0.5% to 1.4%]). Risks for infection-related death with CSFs and placebo or no therapy were 3.1% and 3.8%, respectively (relative risk, 0.82 [CI, 0.66 to 1.02]; absolute risk reduction, 0.8% [CI, 0.0% to 1.5%]). Use of CSFs reduced the following more than did placebo or no therapy: documented infections (median rate, 38.9% vs. 43.1%; rate ratio, 0.85 [CI, 0.79 to 0.92]), microbiologically documented infections (median rate, 23.5% vs. 28.6%; rate ratio, 0.86 [CI, 0.77 to 0.96]), and episodes of febrile neutropenia (median rate, 25.3% vs. 44.2%; rate ratio, 0.71 [CI, 0.63 to 0.80]).

LIMITATIONS: Trial designs, including assessments of infections, and participants were heterogeneous. Estimates of mortality effects were imprecise.

CONCLUSIONS: Prophylactic CSFs may have little or no effect on mortality but do decrease rates of infection in patients receiving cancer chemotherapy or those undergoing SCT.

PMID: 17876022 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

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Prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimul [J Clin Oncol. 2004]

Review Primary prophylactic colony-stimulating factors for the prevention of chen [Cochrane Database Syst Rev. 2012]

Meta-analysis of randomized controlled trials of prophylactic granulocyte colony-stimulating factor an [J Clin Oncol. 2006]

Review Prophylactic colony-stimulating factors in children receiving myelosuppressive chem [Cancer Treat Rev. 2006]

Review Prophylactic antibiotics or G-CSF for the prevention of infection [Cochrane Database Syst Rev. 2009]

See reviews...

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Cited by 13 PubMed Central articles

Study design: two long-term observational studies of the biosimilar filgrastim Nivestim™ (Hospir [BMC Cancer. 2013]

Review Colony-stimulating factors for febrile neutropenia during cancer therapy. [N Engl J Med. 2013]

Effectiveness of supportive care measures to reduce infections in pediatric AML: a report from the C [Blood. 2013]

See all...

FEN'de G-CSF Kulanımı

FEN'ik hastada G-CSF kullanımı⟶ Rutin önerilmez

- Rutin kullanılmamalıdır; meta-analizde mortaliteye katkısı yok
- Lösemiye neden olduğunu söylemek güç
- Düşük riskli FEN'ik hastalarda kullanmıyoruz
- AML / KİT dışı yüksekriskli FEN'ik hastalarda kulanılır
- WBC >3000 olana kadar (< 7 gün)

Ateşsiz Nötropenide, Düşük Riskli FEN'de G-CSF Önerilmez.

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Cancer. 2006 May 15;106(10):2258-66.

Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients.

Kuderer NM[1], Dale DC, Crawford J, Cosler LE, Lyman GH.

Author information

Abstract

BACKGROUND: Hospitalization for febrile neutropenia (FN) in cancer patients is associated with considerable morbidity, mortality, and cost. The study was undertaken to better define mortality, length of stay (LOS), cost, and risk factors associated with mortality and prolonged hospitalization in cancer patients with FN.

METHODS: The longitudinal discharge database derived from 115 US medical centers was used to study all adult cancer patients hospitalized with FN between 1995 and 2000, comprising a total of 41,779 patients. Primary outcomes included mortality, LOS, and cost per episode.

RESULTS: Overall, in-hospital mortality was 9.5%. Patients without any major comorbidities had a 2.6% risk of mortality, whereas 1 major comorbidity was associated with a 10.3% and more than 1 major comorbidity with a > or = 21.4% risk of mortality, respectively. Mean (median) length of stay was 11.5 (6) days, and the mean (median) cost was $19,110 ($8,376) per episode of FN. Patients hospitalized for > or = 10 days (35% of all patients) accounted for 78% of overall cost. Independent major risk factors for inpatient mortality included invasive fungal infections, Gram-negative sepsis, pneumonia and other lung disease, cerebrovascular, renal, and liver disease. Main predictors for LOS > or = 10 days included leukemia, invasive fungal infections, other types of infection, and several comorbid conditions.

CONCLUSION: Factors associated with increased mortality, LOS, and cost in hospitalized adult cancer patients with FN include patient characteristics, type of malignancy, comorbidities, and infectious complications. These factors may be useful in identifying patients at increased risk of serious medical complications and mortality for more aggressive supportive care measures.

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Factors influencing in-hospital length of stay and mortality in cancer patients suffering fr [Asian Pac J Cancer Prev. 2008]

Neutropenia-related costs in patients treated with first-line chemotherapy for advanced n [J Manag Care Pharm. 2009]

Length of stay and mortality associated with febrile neutropenia among children with cance [J Clin Oncol. 2005]

Review Cost effectiveness of myeloid growth factors in cancer chemotherapy. [Curr Hematol Rep. 2003]

Review Is the use of specialized nutritional formulations a cost-effective strategy [JPEN J Parenter Enteral Nutr. 2005]

See reviews...

See all...

Cited by 57 PubMed Central articles

Risk and consequences of chemotherapy-induced neutropenic complications in [BMC Health Serv Res. 2014]

Time to antibiotics and outcomes in cancer patients with febrile neutropenia. [BMC Health Serv Res. 2014]

Patterns of chemotherapy-associated toxicity and supportive care in US oncology practice [Cancer Med. 2014]

See all...

Yüksek Riskli FEN'de G-CSF Kulanılması önerilir

Proflaktik Antibiyotik Terapisi

Ateşsiz nötropenik hastalara profilaktik AB⟶ Rutin önerilmez

- **Düşük riskli ateşsiz nötropenik hastalarda profilaktik AB önerilmez**
- **Yüksek riskli ateşsiz nötropenik hastalarda profilaktik AB kullanımı tartışmalı; bu nedenle rutin kullanılması önerilmiyor**
- **Avrupa FEN rehberi AML / KİT hastalarında FQ profilaksisini öneriyor**

Olgu Sunumu - I

50 yaşında erkek hasta

Şikayeti : Şuur bulanıklığı nedeni ile acile başvuruyor.

Hikayesi: 1 ay önce başlayan öksürük

Sırt bölgesinde ağrı

3 ayda 7 kilo kadar zayıflama

PA Akciğer Grafisi : Sağ akciğer üst lobda opasite

Toraks BT :Sağ akciğer üst lobda 3.5 cm boyutunda kitle ve plevraya uzanan konsolide alan

Olgu Sunumu - I

Üst Batın BT : Karaciğerde metastaz ile uyumlu hipodens alanlar

Bronkoskopik Biopsi ve BAL sitolojisi : Patolojik tanı koydurucu değil

*Hastada gelişen şuur bulanıklığı nedeni ile çekilen **kranial MR** sol inferotemporal bölgede kronik bir infarkt alanı dışında normal

- 4 gün sonra karaciğerdeki lezyondan yapılan biopsi sonucu:

Az diferansiye epidermoid karsinom

Olgu Sunumu - I

- Hasta şikayetlerinin başlamasından 2 ay sonra şuur bulanıklığı nedeni ile yakınları tarafından acil polikliniğimize getiriliyor

ÖZET: 50 yaşında erkek hasta

Evre IV akciğer epidermoid karsinomu

Sebebi açıklanamayan şuur bulanıklığı

Ca^{+} > 14mg /dl

Hiperkalsemi Semptomları

- Yorgunluk, halsizlik
- Kilo kaybı, zayıflama
- Bulantı, kusma
- Konstipasyon
- Poliüri
- Mental konfüzyon, şuur kaybı
- Kardiak aritmi

Hiperkalsemi Nedenleri

- Paratiroid ile ilişkili → % 90
- Maligniteler ile ilişkili
- D vitamini ile ilişkili
- Artmış kemik dönüşümü
- Renal yetersizliğe bağlı

Tümöre Bağlı Bağlı Hiperkalsemi

- Semptomlar daha belirgin
- Akut olarak ortaya çıkabilir
- Acil tedavi gereksinimi fazla
- Kanser tanısından önce ortaya çıkabilir
- Kötü bir prognostik faktördür

Paraneoplastik Hiperkalsemi

- Hiraki and colleagues examined **1149** patients with lung cancer and found 6% to have hypercalcemia
- Among those with hypercalcemia 51% had squamous cell carcinoma, 22% had adenocarcinoma, and 15% had SCLC.
- Most of those patients had advanced disease (stage III or IV).
- **Median survival was only 3.8 months.**

Hiraki A et al, Lung Cancer, 2004

Tümörlere Bağlı Hiperkalsemi

- Akciğer kanseri (%35)
- Meme kanseri (% 25)
- Hematolojik maligniteler (miyelom+lenfoma) (%14)
- Genitouriner tümörler (% 6)
- Diğer (% 20)

Kansere Bağlı Gelişen Hiperkalsemi

- Tümörlerden salınan parathormona benzer peptidlerin (PTHrp) salgılanması (skuamöz hücreli)
- Osteoklastik kemik metastazlarının, sitokinler ve kemokinlerin kemiklerden kalsiyum salınımını arttırması
- Lenfomalarda1.25 dihidroksi vitamin D (Kalsitriol) oluşumu artışı ile
- Ektopik parathormon salınımı ile

Solid Tümörlerde Humoral Hiperkalsemi

- Solid tümörlerde görülen hiperkalseminin % 70’ i humoral
- PTHrP (parathormone related peptide) salınımına bağlı
- PTH ile % 70 benzerlik var

Solid Tümörlerde Humoral Hiperkalsemi

- PTHrP osteoklast prekürsörleri üstündeki RANK reseptörleri ile etkileşir
- Osteoklast aktivasyonu
- Kemik rezorpsiyonu …… hiperkalsemi
- iPTH düzeyleri düşük , kalsitriol düzeyi normal

Solid Tümörlerde Kemik Metastazları

- Kemikteki metastazlara bağlı osteoklast aktivasyonu kemik rezorbsiyonu
- Meme ve akciğer kanseri
- Her kemik metastazı yapan tümörde görülmez
- Meme Kanseri Kemik metastazı % 85
  Hiperkalsemi % 20

Multiple Miyelom

- Multiple Miyelom da osteoklastları aktive eden sitokinler IL- 1
  TNF- α
  TNF- β
  IL- 6
  RANKL
- Renal yetersizliğe bağlı Ca+ atılımında azalma

Lenfoma

- 1α – hidroksilaz
- 1.25 $(OH)_2D3$ oluşumu
- Gastrointestinal sistemden Ca emilimi

Hiperkalsemi Düzeyi

- Ca + = 11.5 – 12 mg / dl semptomsuz
- Ca + > 12 mg / dl semptomatik
- Ca + > 13 mg / dl acil müdahale
- Ca + > 15 mg / dl koma ve kardiak arest
- **Düzeltilmiş Ca = Ölçülen Ca + 0.8 x (4 – alb)**

TEDAVİ

- Hidrasyon
- Diüretik
- Bisfosfonatlar
- Kalsitonin
- Steroid
- Mithramycin
- Gallium nitrate

TEDAVİ

- **Hidrasyon**
  - İzotonik (100-500ml/saat)
  - Kardiak yetersizliğe dikkat
- **Diüretik**
  - Furosemid (20-40mg /2-4 saatte)
  - Thiazidler kontrendike

BİSFOSFONATLAR

- Sentetik pyrofosfat analogları
- Hidroksiapetit kristallerine afiniteleri var
- Kemik yüzeyine, aktif kemik değişimi olan bölgelere bağlanırlar
- Osteoklastik kemik rezorbsiyonunu önlerler

BİSFOSFONATLAR

- Pamidronat 60-90 mg 2-4 saatte
- Zoledronat 4mg 15-30 dakika
- İbandronat 2-4 mg 2- 4 saat

BİSFOSFONATLAR

- Etkileri 48 saatten sonra başlar
- Uzun dönem kontrol sağlar
- Nefrotoksisiteye dikkat !!!

  Dozu azaltmak

  İnfüzyon süresini uzatmak

Kalsitonin

- Osteoklastik kemik resorbsiyonunu önler
- Böbreklerden Ca+ atılımını arttırır
- Akut etkisi önemli
- Taşiflaksi gelişebilir
- Steroidlerle birlikte kullanımı önerilmekte
- 2-4 saat içinde akut etkili
- 4 – 8 U/kg i.m /s.c 12 saatte bir

Steroid

- 1.25 (OH)$_2$ D3 oluşumunu azaltarak barsaklardan Ca+ emilimini azaltır
- Ca+ atılımını arttırır
- Kalsitonine karşı gelişen taşiflaksiyi azaltır
- Lenfomalarda lenfolitik etkisinden yararlanılır
- Prednisone 40 – 60 mg /gün dozunda kullanılabilir

Mithramycin (Plicamycin)

- Kemik rezorbsiyonunu önler
- 25µg / kg dozunda i.v (3-6 saatte)
- Etkinlik süresi az (3-7 gün arası tekrar)
- Toksisite fazla
- Trombositopeni
- Hepatotoksisite
- Azotemi

Gallium Nitrate

- Kemik resorbsiyonunu önler
- 200mg/m2 / gün
- 5-7 günlük sürekli infüzyonu gerekli
- 24-48 saate etkinliği gözükür
- Bulantı kusma
- Nefrotoksisite

Yeni Tedaviler

- RANKL (receptor activator of nuclear factor κ B ligand) monoklonal antikorlar (AMG 162)
- Osteoprotegrin (OPG)
- PTHrP monoklonal antikorlar

Kansere Bağlı Gelişen Hiperkalsemi

Onkolojik hastalığa yönelik spesifik tedavinin gecikmeden başlatılması

63 yaşında, erkek, yeni tanı konmuş metastatik akciğer skuamöz hc tanısı var. Hasta konfüzyon, konstipasyon ve bulantı ile acile başvuruyor. Wbc: 12.500/mm3, hgb:13.5g/dl, plt: 155.000/mm3, Na: 149 mg/L, BUN:44 mg/dl, kreatinin 1. 8 mg/dl, Albumine 2.8 g/dl ve kalsiyum :13.6 mg/dl.

Uygun tedavi aşağıdakilerden hangisidir?

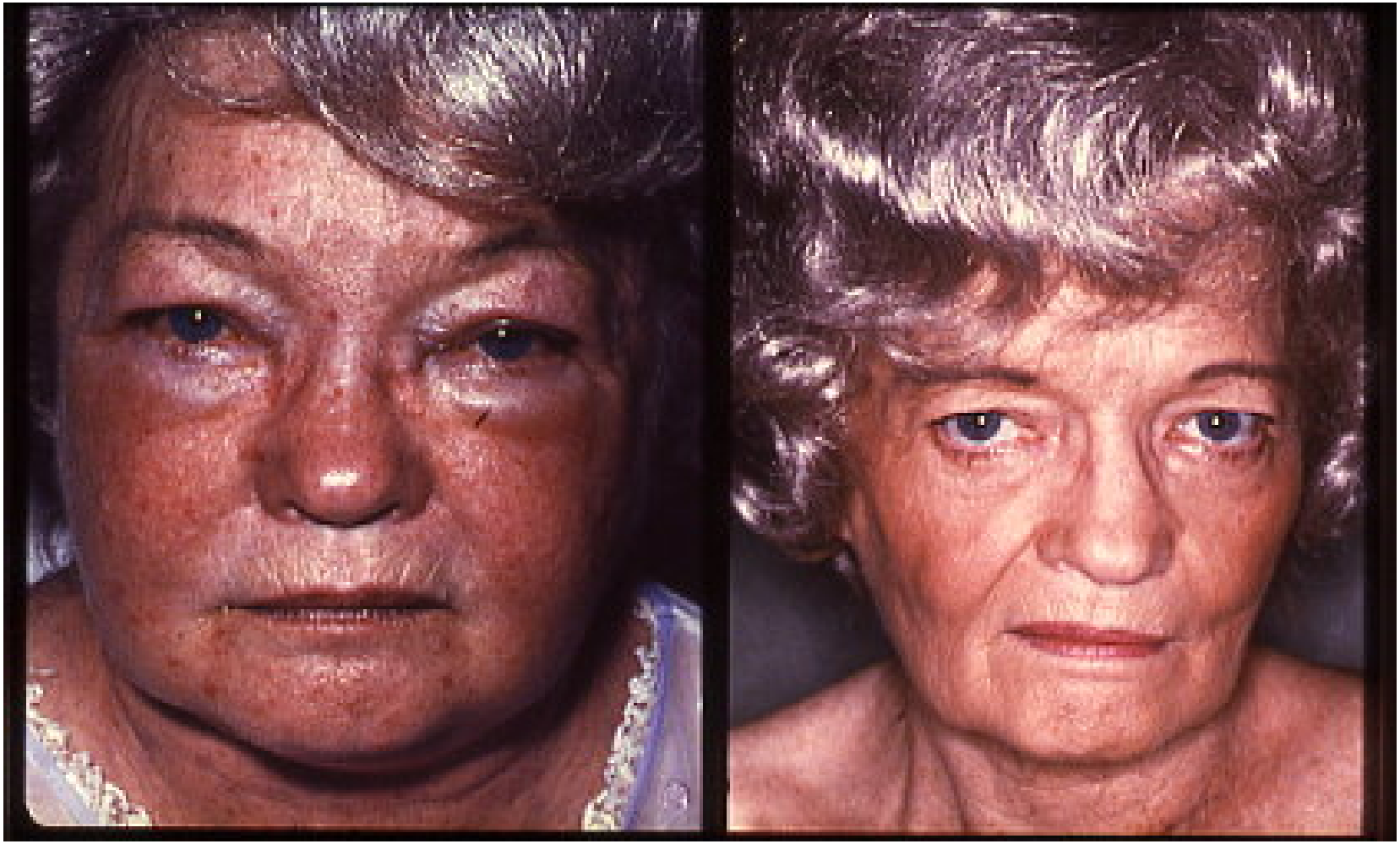
A-İntravenöz sıvı ve bisfosfanat

B-İntravenöz sıvı , bisfosfanat ve kalsitonin

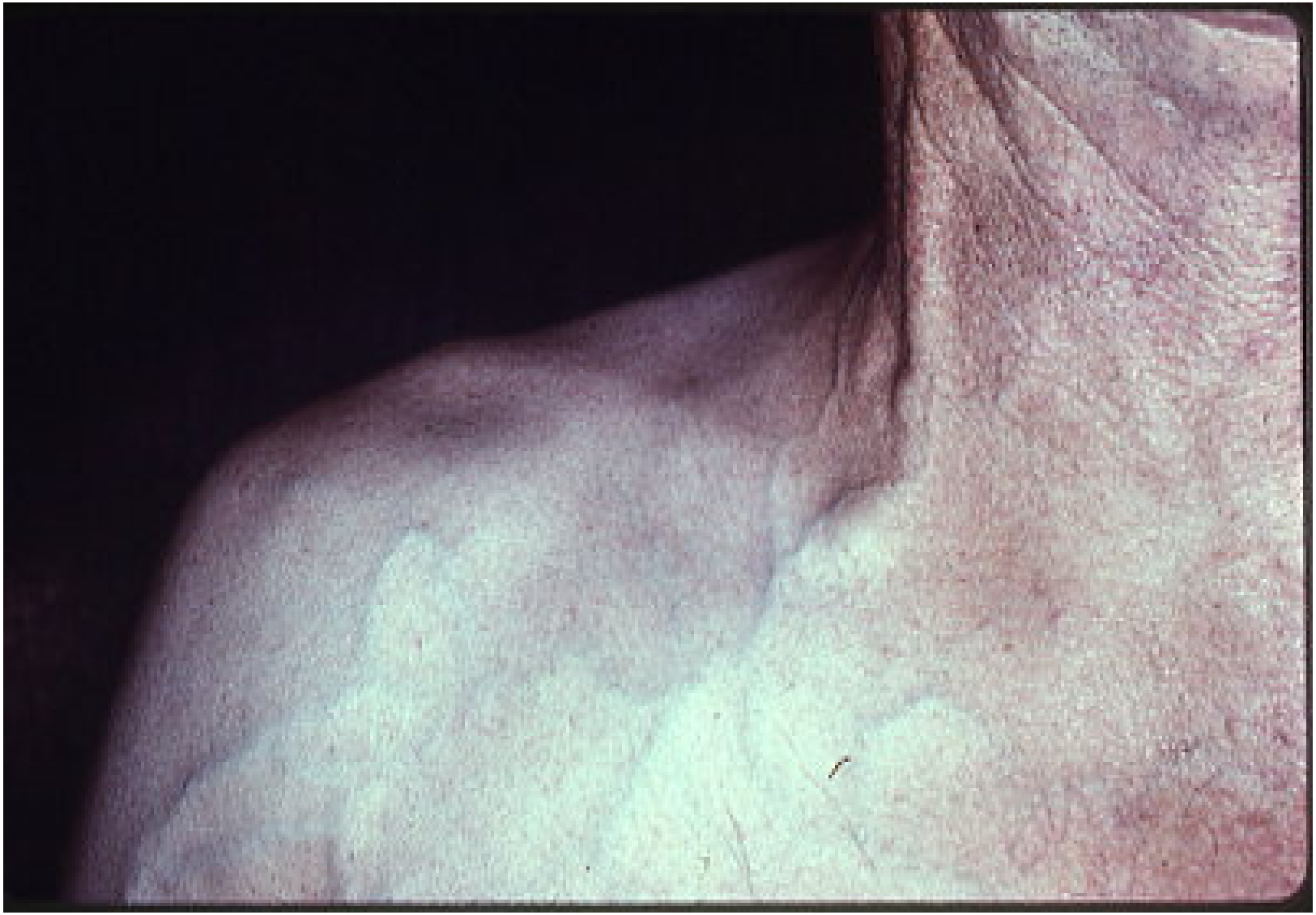
C-İntravenöz sıvı , bisfosfanat ve gallium nitrate

D-İntravenöz sıvı , bisfosfanat ve plicamycin

VENA KAVA SUPERİOR SENDROMU



VENA KAVA SUPERİOR SENDROMU



Vena Kava Superior Sendromu

- Dıştan bası ile kompresyon
- Damarın direk invazyonu
- Tromboz gelişimi

ETYOLOJİ

- % 80 Akciğer kanseri
  - Küçük Hücreli Akciğer Kanseri
  - Epidermoid Akciğer Kanseri
- Lenfoma (NHL)

ETYOLOJİ

- **Metastatik kanserler (% 5-10)**
  - Meme
  - Germ Hücreli Tümörler
  - Gastrointestinal Tümörler
- **Sarkomlar**

ETYOLOJİ

- Timoma
- Kronik infeksiyonlar (Tbc, histoplazmoz..)
- Venöz Kateterler

Semptomlar

- Nefes darlığı
- Öksürük
- Ses kısıklığı
- Baş ağrısı
- Sersemlik hissi
- Görme bozuklukları

Fizik Muayene Bulguları

- Venöz Dolgunluk % 66
- Göğüs duvarında kollateraller % 54
- Yüzde ödem % 46
- Siyanoz % 20
- Pletore % 19
- Kol ödemi % 14

Tedavi

- **Önce histolojik tanı konulmalı**

  (Balgam sitolojisi,torasentez, lenf nodu biopsisi,bronkoskopi, mediastinoskopi, torakostomi, α-FP, ß-HCG)

- **Tedavi acil mi?**

  Ciddi hava yolu obstruksiyonu

  Kardiovaskuler yetersizlik

  KİBAS

Tedavi

- **Semptomatik tedavi**
  - Baş elevasyonu
  - O_2 perfüzyonu
  - Diüretik
  - Kortikosteroid
- **Kemosensitif tümörler; KT +/- RT**
- **Radyoterapi**
- **Antikoagulasyon gerekli mi?**

Tedavi

- **Cerrahi**

  Benign sebepler (granulamatoz hastalık, aort anevrizması, retrosternal guatr…)

  Survi beklentisi 6 aydan fazla, KT ve RT'ye refrakter hasta (leiomiyosarkom…)

- **Perkutan stent**

Spinal Kord Basısı

- Kanserli hastalarda % 1- 5 oranında görülür.
- % 10 olguda ilk başvuru şekli olabilir
- Erken teşhis ile komplikasyonları önleme oranı % 90
- Tedavi öncesi nörolojik disfoksiyon derecesi ve gelişme süresi önemli

Spinal Kord Basısı

- Tedavide gecikme pleji, mesane ve rektumda sfinkter fonksiyon kaybına neden olur

- Etyoloji:
  - % 95 ekstradural metastaz, nadiren epidural
  - En sık primer tm: Akciğer, meme, prostat, lenfoma, myelom ve böbrek tm.

Vertebraların Tutulma Oranı

- Torasik % 59 – 78
- Lumber % 16 – 33
- Servikal % 4 - 15

TANI

- Nörolojik anamnez ve nörolojik muayene
- Direk vertebra grafisi
- MRI

PROGNOZ: Tedavi öncesi nörolojik sekele bağlı.

- Mobil hastaların hemen hemen tümü tedavi sonrası hareketleri korunmakta
- Paralizi olanların ancak %10'u tedavi sonrası yürüyebilmektedir

Semptomlar

- Erken bulgular

  Ağrı: %90 olguda lokalize veya radiküler. Nörolojik bulgudan hafta/aylar öncesinde görülür.

- Ara Dönem:Sensöryel kayıp ve kuvvetsizlik

- Geç bulgu: Paralizi, otonom disfonksiyon

  Saatler ve gün içinde irreversibl paralizi gelişir.

Muayene bulguları

- Omurga veya sinir trasesinde ağrı
- Kas zaafiyeti
- Sensöryel his kaybı
- Spastisite
- İnkontinans
- Palpable mesane
- Mesanede postvoiding rezidüel idrar kalması
- Rektal tonusta azalama
- Solunum aresti

TEDAVİ

- **Deksametazon:**
  Nörolojik bulgular başladıktan sonra
  10-100mg yükleme dozu, 6 saatte bir 10 mg ile devam.

- **Cerrahi dekompresyon:**
  Sınırlı bölge
  Ciddi nörolojik fonksiyon bozukluğu veya radyorezistan tümör ise

- **Radyoterapi:**
  Hasarlı vertebranın 2 alt ve üstündeki vertebralar da alan içine alınır.

Uygunsuz ADH sekresyonu sendromu

- Etyoloji
  - SCLC
  - MSS hastalıklar
  - İnfeksiyon: TBC, pnömoni, abse
- İlaç anamnezi varlığı:
  - Hipofizer ADH salınımını arttıran ilaçlar
    - Siklofosfamid,vincristin,cisplatin
    - klorpropamid
    - Amitriptilin

Uygunsuz ADH Sendromu

Check for full text availability | PubMed

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in small-cell lung cancer.

List AF, Hainsworth JD, Davis BW, Hande KR, Greco FA, Johnson DH

J Clin Oncol. 1986;4(8):1191.

Review of clinical data from 350 patients with small-cell lung cancer (SCLC) revealed hyponatremia (sodium less than 130 mEq/L) attributable to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in 40 patients (11%). Although hyponatremia was severe in most instances (median, sodium 117 mEq/L), symptoms attributable to water intoxication were identified in only 27% of hyponatremic episodes. Development of SIADH showed no correlation with clinical stage, distribution of metastatic sites, sex, or histologic subtype of small-cell carcinoma. SIADH occurred most often with initial presentation (33 of 40), and resolved promptly (less than 3 weeks) with initiation of combination chemotherapy in 80% of evaluable patients. The presence of SIADH did not influence response to chemotherapy or overall survival as an independent variable. However, in five patients profound hyponatremia developed immediately following primary cytotoxic therapy (range, one to five days). Despite initial control of SIADH, dilutional hyponatremia recurred in 70% of patients with tumor progression. Our findings suggest that development of clinically demonstrable SIADH in patients with SCLC is dependent on functional properties of the neoplastic cells, rather than tumor burden or metastatic site. The potential for development of clinically significant hyponatremia early in the course of cytotoxic therapy emphasizes the need to closely monitor patients, particularly those receiving chemotherapy regimensrequiring substantial intravenous hydration.

3016206

Check for full text availability | PubMed

The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period.

Hansen O, Sørensen P, Hansen KH

Lung Cancer. 2010;68(1):111.

Hyponatremia is often seen in SCLC, and is thought to be caused by the paraneoplastic syndrome SIADH. Variable results of the prognostic significance of low P-sodium (P-Na) have been reported. This study was performed to investigate the prognostic value of hyponatremia in SCLC. Data was obtained from files from 453 patients diagnosed with SCLC and treated at Odense University Hospital from 1995 to 2005 in which data on P-sodium was available. The standard chemotherapy was six cycles of carboplatin-etoposide. P-Na was<125 mEq/L in 47 patients (11%) and 126-135 mEq/L in 151 (33%), and 255 patients (56%) showed normal values. The median survival was 11.2 months in patients with normal P-Na, and 7.1 months in patients with subnormal values (p=0.0001). In a Cox multivariate analysis of the 402 patients treated with carboplatin-etoposide, hyponatremia was associated with poorer prognosis. Other independent prognostic factors included LDH, gender, age, performance status, stage, and low value of albumin. Treatment prior to year 2000 was of border line significance, while in-significant factors included hemoglobin level, WBC and alkaline phosphatase. In 61 patients with P-Na<130 mEq/L receiving two or more cycles of chemotherapy, only 15 of the 61 patients (25%) normalized the value of P-Na to 136 mEq/L or above at the time of the second cycleof chemotherapy. The patients who did not fully regain normal values of P-Na, had poorer survival compared with the patients who did in a univariate analysis (p=0.027), and in a Cox multivariate analysis. In conclusion, hyponatremia was a significant prognostic factor associated with poor prognosis and so was failure to normalize P-Na within the first two cycles of chemotherapy.

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19535164

Uygunsuz ADH Sendromun %75 SCLC ilişkili, ve SCLC yaklaşık %10 oranında görülür.

Uygunsuz ADH sendromu

- Hastaların çoğu asemptomatiktir.
- Semptomlar hiponatreminin derecesi ve gelişme hızı arttıkça gelişir.

- Erken semptomlar spesifik değil. (İştahsızlık, halsizlik, yorgunluk, bulantı,kusma…)

  Başağrısı,

  Letarji,

  Mental değişiklikler

  Konvülzyon, Koma

TANI

- Na< 135 meq/l
- Plazma ozmolarite <280 mosm/kg
- İdrar Na >20 meq/l

TEDAVİ

- Altta yatan malignite tedavisi
- Akut tedavi(Na <120)

  Hipertonik NaCl
  - IV Furosemid 1mg/kg +elektrolit replasmanı
  - 24 saat Na artışı 10-12mmol /L geçmemeli
  - Aksi takdirde nörolojik hasar: santral pontin myelinoliziz
- Kronik tedavi
  - Su kısıtlaması günde 500-1000ml
  - Demeklosiklin 300-600mg/gün
  - Vasopresin reseptör antagonisti (conivaptan)

Aşağıdakilerden Hangisi Uygunsuz ADH Sendromu İçin Doğru Değildir

A-Normal plazma volümü

B-Plazma ozmolitesi, idrar ozmolitesinden fazla

C-Artmış idrar sodyumu

D-Hiponatremi