Febrile Neutropenia – Guidelines Update and Approach to Management of Both High- and Intermediate-Risk Patients

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SOUTH AFRICA

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Tesaro	x	x	x	x					Speakers' bureau
Teva	x	x							Speakers' bureau
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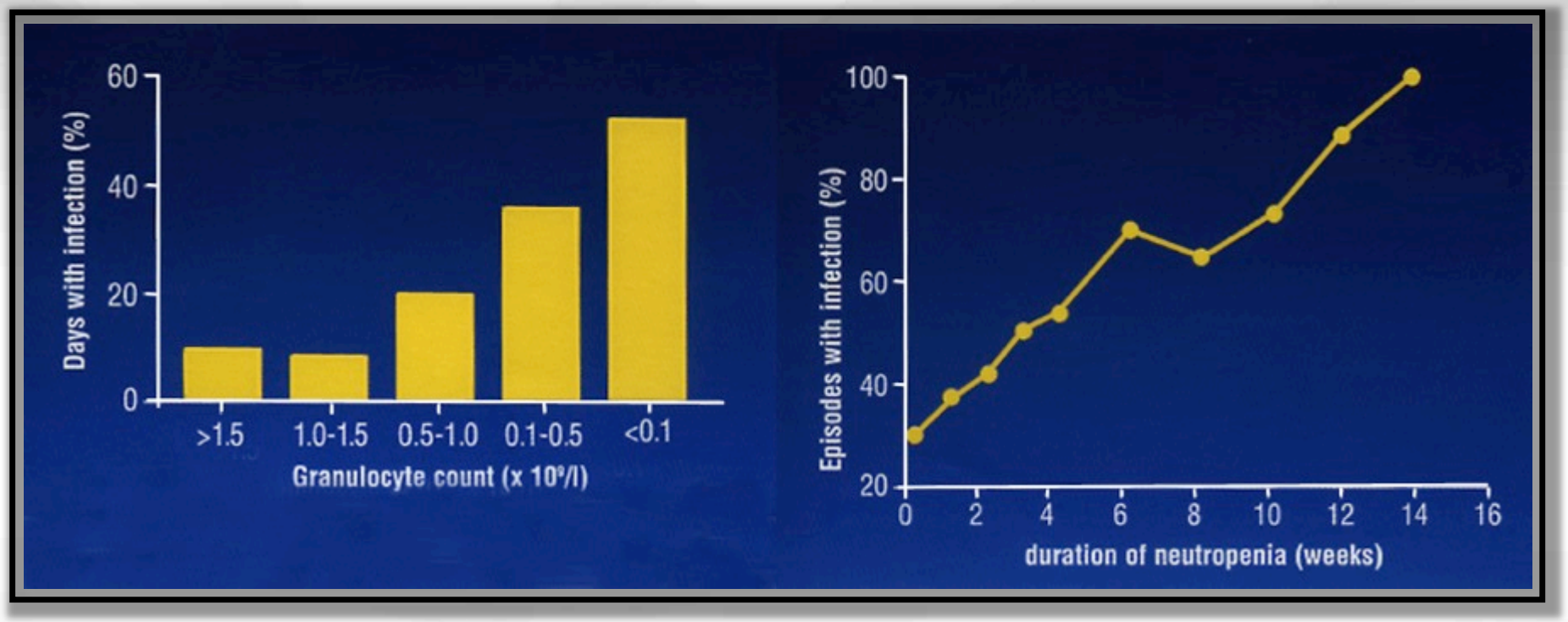
Introduction

- Despite major advances in prevention and treatment, FN remains one of the most frequent and serious complications of cancer chemotherapy
- Major cause of morbidity, healthcare resource use
- Compromised treatment efficacy resulting from delays and dose reductions of cancer chemotherapy
- Mortality from FN has diminished steadily, but remains significant

The risk of infection increases with the severity and duration of neutropenia



G.P. Bodey, Ann Int Med, 1966

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Complications of Myelosuppressive Cancer Chemotherapy

Myelosuppressive chemotherapy

Short-term effects

Long-term effects

Neutropenia

Febrile neutropenia (FN)

Chemotherapy dose delays and dose reductions

Complicated life-threatening infection and prolonged hospitalization

Decreased relative dose intensity (RDI)

Reduced survival

Kuderer NM et al. *Cancer* 2006;106:2258–2266
Chirivella I et al. *J Clin Oncol* 2006;24;abstract 668
Bosly A et al. *Ann Hematol* 2007

ESMO Guidelines
Neutropenia Risk

There is a clear relationship between the severity of neutropenia (which directly influences the incidence of FN) and the intensity of chemotherapy

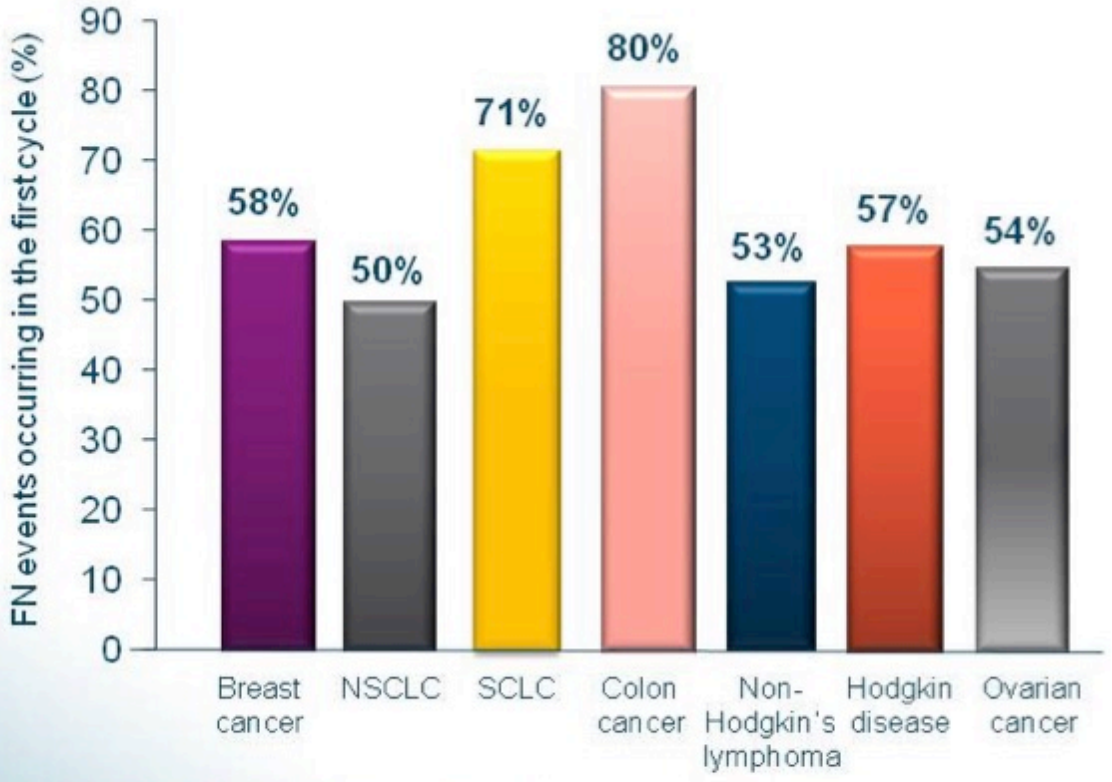
Currently, the different regimens are classified

- High risk (>20%)
- Intermediate risk (10%–20%)
- Low risk (<10%) of FN

FN Risk of > 20%

• Lymphoma	R-ICE
• Adjuvant breast	FEC 100
• Adjuvant breast	FEC 100 T
• Neo-adjuvant or Adjuvant breast	TAC
• Burkitts Lymphoma	R-CODOX-M
• Bladder	MVAC
• Sarcoma	MAID
• Sarcoma	Doxorubicin-ifosfamide
• Small-cell lung cancer	CAE
• Testicular cancer	VIP

More than half of the FN episodes occur in the first cycle of chemotherapy



NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer

Crawford et al. J Natl Compr Canc Netw 2008;6:109–18.

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Primary Prophylaxis with a CSF

- Starting with the first cycle and continuing through subsequent cycles of chemotherapy is recommended in patients who have an approximately 20% or higher risk for febrile neutropenia on basis of patient-, disease-, and treatment-related factors

- Primary CSF the prophylaxis should also be given in patients receiving dose-dense chemotherapy when considered appropriate

FN Risk of 10-20%

Occult Primary - Adenocarcinoma
- Gemcitabine/docetaxel[29]

Breast Cancer
- Docetaxel every 21 days[30]
- CMF classic (cyclophosphamide, methotrexate, fluorouracil) (adjuvant)[31]
- AC (doxorubicin, cyclophosphamide) + sequential docetaxel (adjuvant) (taxane portion only)[32]
- AC + sequential docetaxel + trastuzumab (adjuvant)[33]
- FEC (fluorouracil, epirubicin, cyclophosphamide) + sequential docetaxel[34]
- Paclitaxel every 21 days (metastatic or relapsed)[35]
- TC[a] (docetaxel, cyclophosphamide)[36]

Cervical Cancer
- Cisplatin/topotecan (recurrent or metastatic)[37,38,39]
- Paclitaxel/cisplatin[39]
- Topotecan (recurrent or metastatic)[40]
- Irinotecan (recurrent or metastatic)[41]

Colorectal Cancer
- FOLFOX (fluorouracil, leucovorin, oxaliplatin)[42]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[43]
- Epirubicin/cisplatin/5-fluorouracil[44]
- Epirubicin/cisplatin/capecitabine[44]

Multiple Myeloma
- DT-PACE (dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide)[45]
- DT-PACE + bortezomib (VTD-PACE)[46]

Non-Hodgkin's Lymphomas
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (AIDS-related NHL, Burkitt lymphoma, recurrent, other NHL subtypes)[47]
- EPOCH + IT chemotherapy (AIDS-related NHL, DLBCL, recurrent)[47]
- GDP (gemcitabine, dexamethasone, cisplatin) (DLBCL, PTCL, 2nd line)[48]
- GDP (gemcitabine, dexamethasone, cisplatin) + rituximab (DLBCL, 2nd line, Burkitt lymphoma, other NHL subtypes)[48]
- FMR (fludarabine, mitoxantrone, rituximab)[49]
- CHOP + rituximab (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab)[50,51] including regimens with pegylated liposomal doxorubicin[52,53] or mitoxantrone[54] substituted for doxorubicin

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel (advanced/metastatic)[55]
- Cisplatin/vinorelbine (adjuvant, advanced/metastatic)[56]
- Cisplatin/docetaxel (adjuvant, advanced/metastatic)[55,57]
- Cisplatin/etoposide (adjuvant, advanced/metastatic)[58]
- Carboplatin/paclitaxel[b] (adjuvant, advanced/metastatic)[59]
- Docetaxel (advanced/metastatic)[57]

Ovarian Cancer
- Carboplatin/docetaxel[60]

Pancreatic Cancer
- FOLFIRINOX[c]

Prostate Cancer
- Cabazitaxel[d,61]

Small Cell Lung Cancer
- Etoposide/carboplatin[62]

Testicular Cancer
- Etoposide/cisplatin[63]

Uterine Sarcoma
- Docetaxel (advanced or metastatic)[64]

ESMO Guidelines
Age and co-morbidities

- Age plays a major role in the risk of FN and its complications
- Older patients have a higher risk of FN following chemotherapy
- Older patients have the worse morbidity and mortality rates
- Risk of FN and its complications increases when one or several co-morbidities are present in the patient

FN Prophylaxis

- FN can be effectively prevented by the use of G-CSFs
- It is recommended to use G-CSF's in patients receiving chemotherapies with a 10-20% risk of developing FN
- Serious co-morbidities and/or aged >60 years
- Dose reduction deemed detrimental to outcome

ASCO GUIDELINES

CSF for patients with diffuse aggressive lymphoma age 65 years and older

Prophylactic G-CSF for patients with diffuse aggressive lymphoma age 65 years and older treated with curative chemotherapy (CHOP-R) should be considered, particularly in the presence of comorbidities

Multiple Chronic Conditions

- In the case of FN, observational studies have provided important information about the impact of comorbidity

- A 2014 systematic review reported that the presence of comorbid conditions increased the risk of FN among patients with cancer treated with chemotherapy

- Compared with patients with no comorbid conditions, patients with three or more comorbid conditions had an 81% increased risk of FN

- The presence of renal, hepatic, and cardiovascular disease have each been associated with FN or FN–related hospitalization

ESMO Guidelines Neutropenia Risk

Other Risk Factors

- Advanced disease
- History of prior FN
- No antibiotic prophylaxis or G-CSF use
- Mucositis
- Poor PS
- Cardiovascular disease

Secondary Prophylaxis with G-CSFs

- Is recommended for patients who experienced a neutropenic complication from a previous cycle of chemotherapy (for which primary prophylaxis was not received)
- A reduced dose or treatment delay may compromise disease-free or overall survival or treatment outcome
- In many clinical situations, dose reduction or delay may be a reasonable alternative

ASCO GUIDELINES

G-CSFs in Afebrile Patients
Guideline Recommendations

G-CSFs should not be routinely used for patients with neutropenia who are afebrile

G-CSFs should not be routinely used as adjunctive treatment with antibiotic therapy for patients with uncomplicated fever and neutropenia

ASCO GUIDELINES

High Risk for Infection-Associated Complications

G-CSFs should be considered in patients with FN

- Prognostic factors that are predictive of poor clinical outcomes
- High-risk features include expected prolonged (> 10 days)
- Profound neutropenia (< 0.1×10^9/L)
- Age older than 65 years
- Uncontrolled primary disease
- Pneumonia
- Hypotension and multiorgan dysfunction (sepsis syndrome)
- Invasive fungal infection
- Being hospitalized at the time of the development of fever

MASCC Index

- Multinational Association for Supportive Care in Cancer
- Prospectively validated tool to rapidly assess risk before access to neutrophil count
- Scores ≥21 are at low risk of complications MASCC scoring index:
  - 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 (not valid in children <18 years) 2

MASCC Score=26

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Klastersky J,J Clin Oncol 2000; 18:3038–51.

Chemoprophylaxis

- Antimicrobials have been used for a long time for the prevention of episodes of FN in chemotherapy treated patients
- This approach has been somewhat successful
- Led to the emergence of resistant strains
- Limiting its efficacy

Chemoprophylaxis

- Guidelines from the EORTC & ASCO recommend that clinicians limit the use of antibacterial prophylaxis to patients at high risk for FN
- Cochrane meta-analysis still recommended the use of ciprofloxacin or levofloxacin in cancer patients undergoing intensive chemotherapy
- Others recommend avoidance
- Fluoroquinolones, should be discouraged

G-CSF prophylaxis

- Several meta-analyses indicate that primary G-CSF prophylaxis (administered after cycle 1) reduces the FN risk by at least 50% in solid tumors patients
- Guidelines recommend G-CSF be administered prophylactically if the risk of FN is >20%
- FN intermediate risk (10%–20%) consider the age, coexisting morbidities, other risk factors

ESMO Guidelines

FN in high-risk situations

• Autologous stem-cell transplant	Common
• Allogeneic stem-cell transplant	Common
• During graft failure	Common
• AML at DX	35%–48%
• ALL during ALL induction	30%

ESMO Guidelines FN-related mortality in high-risk situations

- Autologous transplant 0%–10%
- Allogeneic transplant highly variable
- ALL during induction 2%–10%
- AML during the first 2 months 20%–26%
- Graft failure 80%

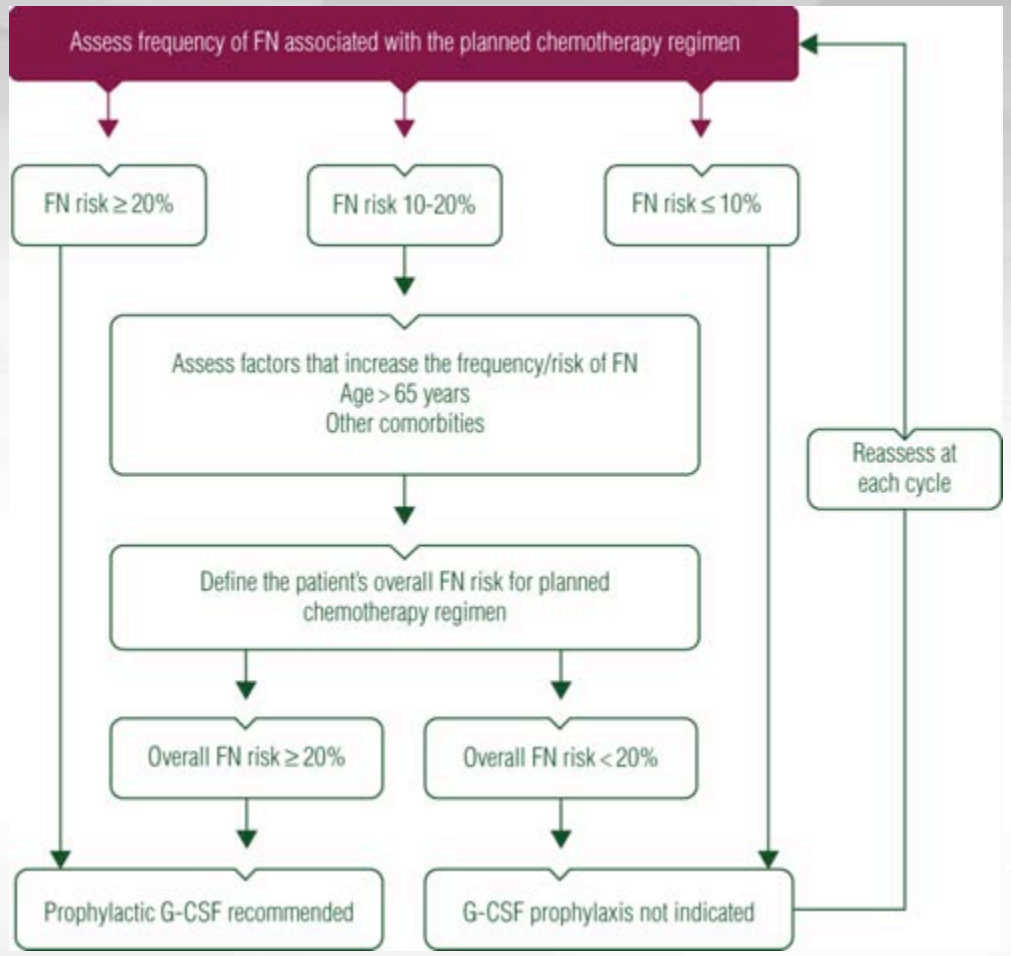
ESMO Guidelines
G-CSF high-risk situations

• Autologous transplant	Yes
• Allogeneic transplant	Yes
• Graft failure	Yes
• AML	No
• MDS	No
• ALL	Controversial

AML + MDS

The Update Committee did not provide recommendations regarding the use of G-CSFs in adults with acute myeloid leukemia or myelodysplastic syndromes

FN Management
ESMO Clinical Practice Guidelines



Adapted from European Organisation for Research and Treatment of Cancer guidelines. FN, febrile neutropaenia; G-CSF, granulocyte colony-stimulating factor

Ann Oncol. 2016;27(suppl_5):v111-v118.
doi:10.1093/annonc/mdw325

National Comprehensive Cancer Network®

Evaluation Prior to the First Cycle of Chemotherapy

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;
G-CSFs = Granulocyte colony-stimulating factors

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

G-CSF and pegfilgrastim dose schedule, route of application

- Pegfilgrastim at a total dose of 6 mg
- Equivalent dose of filgrastim is 5 µg/kg/day for ~10 days
- EMA/FDA approved biosimilars can be considered

G-CSF Side Effects

- Bone Pain 25%
- Pain in the extremities 5-10%

G-CSF Side Effects

- Allergic reactions
  - ◊ Skin: rash, urticaria, facial edema
  - ◊ Respiratory: wheezing, dyspnea
  - ◊ Cardiovascular: hypotension, tachycardia, anaphylaxis
- Bleomycin-containing regimens: pulmonary toxicity[4]
- Splenic rupture
- Acute respiratory distress syndrome
- Alveolar hemorrhage and hemoptysis
- Sickle cell crises (only in patients with sickle cell disease)
- MDS and AML[5]

• Precautions

- Cutaneous vasculitis
- Immunogenicity

ESMO
G-CSF Contraindications

- Primary prophylaxis with G-CSF is not indicated during chemoradiotherapy to the chest due to the increased rate of bone marrow suppression associated with an increased risk of complications and death

- There is also a risk of worsening thrombocytopenia when G-CGFs are given immediately before or simultaneously with chemotherapy

Conclusion

FN risk	ESMO	ASCO	NCCN
Moderate to high (> 20 %)	Use G-CSFs	Use G-CSFs	Use G-CSFs
Intermediate (10-20 %)	Consider	Consider	Consider
Consider other risk factors	+++	++	++
Low (< 10 %)	Not specified	Not recommended	Not recommended

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Conclusion
Take home message

1. Myelosuppresive chemotherapy is associated with severe morbidity and mortality

2. ESMO Guidelines (ASCO & NCCN) recommends the usage G-CSF to prevent FN and serious infective complications associated with chemotherapy

3. Clinical evaluation of patients risk factors with every cycle of chemotherapy is imperative

Thank You

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Questions?