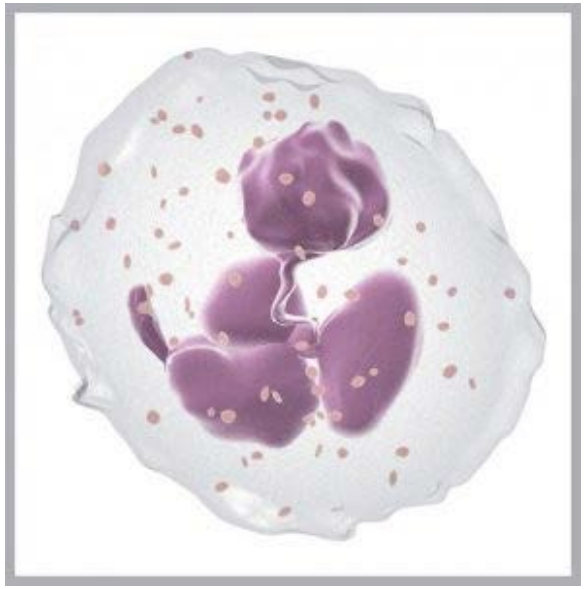
Neutropenia febrila preventie vs monitorizare – punctul de vedere al medicului oncolog



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Conferinta de Antibioterapie si Imunodepresie, online
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Introducere

- Tratamentul cancerului cu CHT mielosupresoare se asociaza cu riscul de neutropenie indusa de chimioterapie (CIN)
- Neutropenia creste riscul de complicatii amenintatoare de viata, inclusiv neutropenie febrila (FN), se asociaza cu utilizarea de antibiotice, spitalizare si cresterea mortalitatii
- In plus, oncologii pot fi nevoiti sa reduca D de CHT, ceea ce duce la o intensitate relativa scazuta a dozei (RDI), cu impact negativ asupra rezultatelor tratamentului/OS

1. Lyman GH. J Oncol Pract 2019;15(1):27-9. 2. Lalami Y. Crit Rev Oncol Hematol 2017;120:163-79.

Introducere

- Factorii de stimulare ai coloniilor de granulocite (G-CSF), introdusi pentru prima data in clinica in anii 1990, au redus incidenta acestor complicatii si au imbunatatit prognosticul pacientilor
- Nevoia de injectii zilnice a fost inlaturata de dezvoltarea pegfilgrastimului
- Costul a fost partial atenuat prin introducerea biosimilarelor
- Cu toate acestea, durerea osoasa indusa de G-CSF si vulnerabilitatea la infectii in prima saptamana dupa CHT raman nevoi medicale neacoperite
- Mai multe terapii emergente cu mecanisme de actiune diferite de cele ale agentilor G-CSF standard sunt fie recent aprobate, fie in stadiu avansat de dezvoltare si au potentialul de a imbunatati managementul CIN si FN

1. Crawford J. N Engl J Med 1991;325(3):164-70. 2. Holmes FA. Ann Oncol 2002;13(6):903-9. 3. Dinan MA. J Natl Compr Canc Netw 2015;13(1):e1-7. 4. Schwartzberg LS. Clinicoecon Outcomes Res 2018;10:493-500. 5. Crawford J. J Natl Compr Canc Netw 2008;6(2):109-18. 6. D'Souza A. Transfus Med Rev 2008;22(4):280-90. 7. Kubista E. Clin Breast Cancer 2003;3(6):391-8. 8. Moore DC. Ann Pharmacother 2017;51(9):797-803.

Consecintele clinice ale CIN

- Durata si severitatea neutropeniei – factori majori de risc pentru dezvoltarea FN si infectii amenintatoare de viata
- Neutropenia este clasificata conform CTCAE v.5.0.

AE	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia, (ANC)	ANC <LLN–1500 cells/mm^3	ANC 1000–1500 cells/mm^3	ANC 500–1000 cells/mm^3	ANC <500 cells/mm^3
FN	–	–	ANC <1000 cells/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for >1 hour	Life-threatening consequences; urgent intervention indicated

Abbreviations: ANC, absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events; FN, febrile neutropenia; LLN, lower limit of normal; mm^3, cubic millimeter.

1. Wood AJJ. N Engl J Med 1993;328(18):1323-32. 2. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE)_Version 5.0. Updated November 27, 2017.

Consecintele clinice ale CIN

- Febra (T > 38ºC) in asociere cu neutropenia severa (nr. absolut de neutrofile [ANC] < 500 celule/mm^3) definesc FN, in timp ce neutropenia profunda este considerata cea mai severa forma de neutropenie si este definita ca ANC < 100 celule/mm^3
- Consecintele clinice ale CIN includ – FN, utilizarea orala/iv a antibioticelor, prezentarea in UPU, spitalizari si risc de deces
- In plus, reducerea D si intarzierea ciclurilor ulterioare de CHT pot avea un impact negativ asupra prognosticului pacientilor

1. Lalami Y. Crit Rev Oncol Hematol 2017;120:163-79. 2. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE)_Version 5.0. Updated November 27, 2017. 3. Punnapuzha S. In: StatPearls.Treasure Island (FL): StatPearls Publishing. Copyright © 2021, StatPearls Publishing LLC.; 2021.

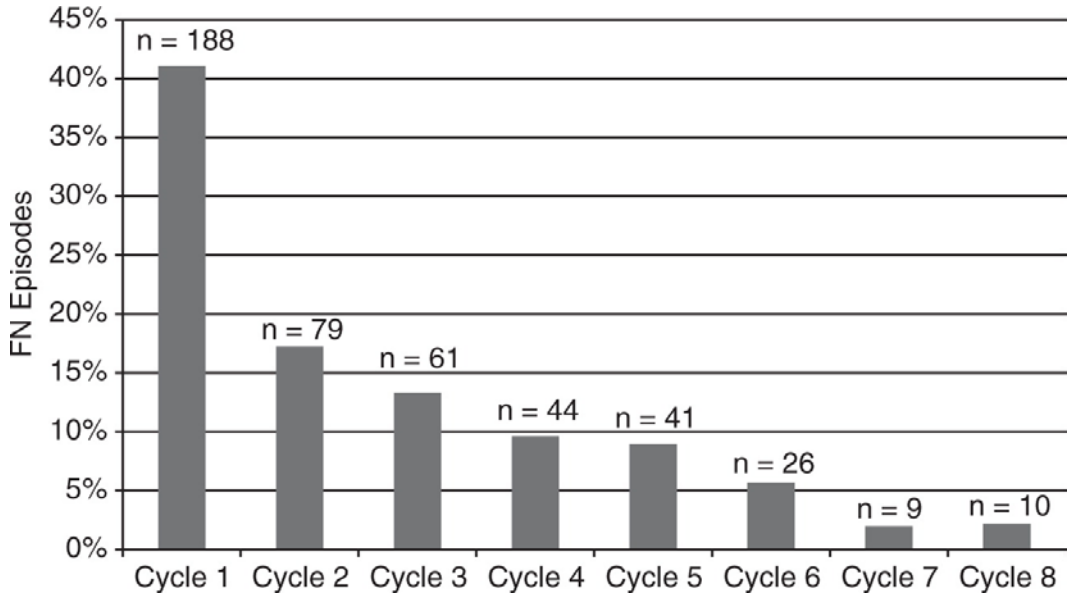
Consecintele clinice ale CIN

- In momentul diagnosticului FN, este indicata initierea antibioterapiei empirice cu spectru larg pana la identificarea agentului patogen etiologic sau pana la refacerea nr. de neutrofile si remisiunea febrei
- In general se utilizeaza antibiotice empirice care acopera tegumentul, intestinul si flora bucala

1. Zimmer AJ. J Oncol Pract 2019;15(1):19-24.

Momentul aparitiei si incidenta FN

- FN apare de obicei dupa C1 de CHT si incidenta scade de la C2, probabil in parte datorita reducerii dozelor de CHT la C2 ca rezultat al FN post C1
- Intr-o analiza retrospectiva care a inclus 2.131 de pacienti cu tumori solide si LMNH tratati cu CHT in intervalul 2007-2010, 401 pacienti au prezentat un total de 458 de episoade FN; 41% din episoadele FN au avut loc in C1, iar incidenta FN a scazut cu fiecare ciclu ulterior: C2=17%, C3=13%, C4=10%)



1. Culakova E. Cancer Med 2014;3(2):434-44. 2. Kawatkar AA. Support Care Cancer 2017;25(9):2787-95. 3. Weycker D. J Oncol Pharm Pract 2014;20(3):190-8.

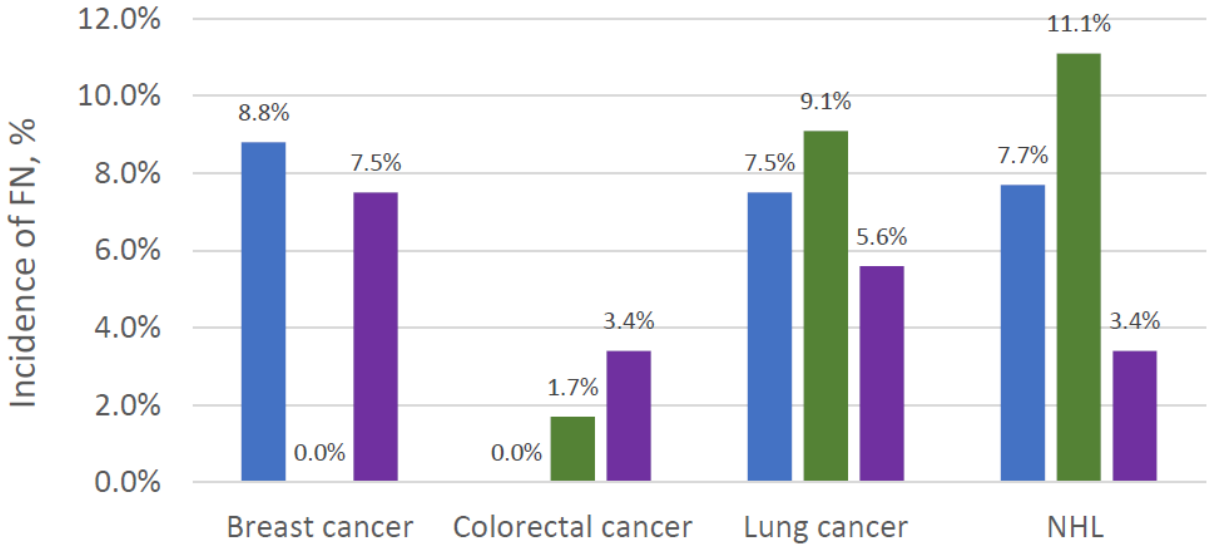
Momentul aparitiei si incidenta FN

- Intr-o analiza din 2003 care a inclus pacienti cu LMNH tratati in SUA, peste jumatate (59%) din spitalizarile prin FN au avut loc in timpul primelor 2 cicluri de CHT
- Incidenta FN variaza in functie de tipul tumoral – o analiza retrospectiva care a inclus 1.457 pacienti cu tumori solide sau LMNH (2009-2017) care au primit regimuri cu risc ridicat de neutropenie, dar fara profilaxie G-CSF, a evidentiat o incidenta similara de FN dupa C1 la pacientii cu CM, CBP si LMNH (7,5-8,8%), in timp ce nu au fost identificate cazuri de FN la pacienti cu CCR

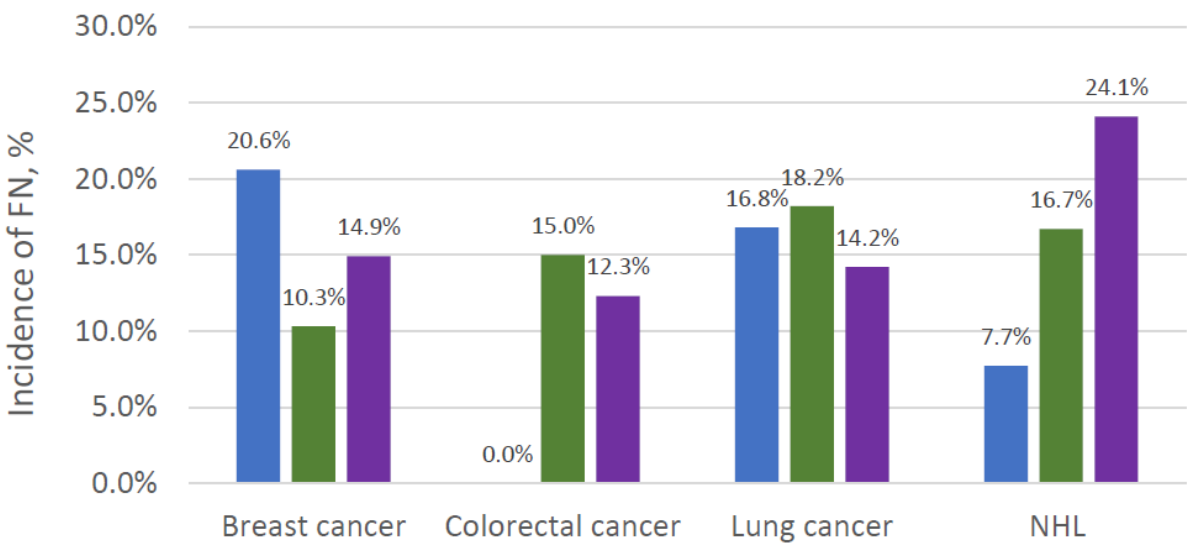
1. Crawford J. J Natl Compr Canc Netw 2008;6(2):109-18. Lyman GH. Cancer 2003;98(11):2402-9. 3. Averin A. Support Care Cancer 2021;29(4):2179-86. 4. Lyman GH. Cancer 2010;116(23):5555-63.

Momentul aparitiei si incidenta FN

Incidenta FN la pacientii care nu au primit profilaxie cu G-CSF in timpul C1



Incidenta FN la pacientii care nu au primit profilaxie cu G-CSF in timpul intregului tratament



High FN-risk chemotherapy
IR chemotherapy + ≥1 risk factor
IR chemotherapy + 0 risk factors or LR/UR chemotherapy

1. Crawford J. J Natl Compr Canc Netw 2008;6(2):109-18. Lyman GH. Cancer 2003;98(11):2402-9. 3. Averin A. Support Care Cancer 2021;29(4):2179-86. 4. Lyman GH. Cancer 2010;116(23):5555-63.

Morbiditatea, mortalitatea, spitalizarile, intarzierile CHT si reducerile de D

- Pacientii care dezvolta FN prezinta un risc crescut de morbiditate si mortalitate
- Dezvoltarea FN predictioneaza mortalitatea precoce (HR=1,15) si mortalitatea globala (HR=1,35) la pacientii cu tumori solide sau LMNH
- Aparitia FN duce la prezentari in UPU si spitalizare – durata medie a spitalizarii la pacientii cu FN variaza de la 4,1-7,9 zile si creste in functie de nr. comorbiditati majore
- Mortalitatea pacienților internati pentru FN este de 10% si este mai mare la pacientii care au comorbiditati multiple sau severe (~20%)

1. Lyman GH. Cancer 2010;116(23):5555-63. 2. Weycker D. Support Care Cancer 2017;25(2):439-47. 3. Fontanella C. Breast Care (Basel) 2014;9(4):239-45. 4. Kuderer NM. Cancer 2006;106(10):2258-66.

Morbiditatea, mortalitatea, spitalizarile, intarzierile CHT si reducerile de D

- Reducerile de D si intarzierile in ciclurile ulterioare de CHT sunt o alta consecinta a FN
- O RDI mai scazuta a CHT influenteaza negativ rezultatele tratamentelor cu viza curativa
- Intarzierea si reducerea D au scazut in timp – prin comparatie, la pacientii cu LMNH agresive, cu celule B, tratati intre 2006-2009, respectiv 1993-2001, reducerea dozelor a scazut (21% fata de 35%), in timp ce procentul de pacienti cu RDI ≥ 85% a crescut (68% vs 52%)
- Acest lucru a fost atribuit cresterii utilizarii G-CSF la pacientii cu LMNH (75% fata de 12%), ceea ce a rezultat in rate mai mici de FN (12% fata de 21%)

1. Nielson CM. Oncologist 2021;26(9): e1609-18. 2. Lyman GH. Leuk Lymphoma 2016;57(2):283-90.

Preventia si tratamentul CIN si FN

- Identificarea pacientilor cu risc crescut de FN este o componenta critica a managementului pacientilor oncologici si are ca scop preventia complicatiile asociate CIN
- Decizia de a utiliza G-CSF ca PP se bazeaza pe riscul specific regimului de CHT de dezvoltare a FN si pe riscul asociat pacientului, bolii si tratamentului

Blayney DW. Cancer Treatment Reviews 2022;109:102427.

Factori de risc pentru CIN si FN

Treatment-related	Patient-related	Disease-related
• Type of chemotherapy • Intensity of chemotherapy • No prior prophylactic antibiotics • No prophylactic G-CSF use • Prior chemotherapy or radiation therapy	• Age > 65 years • Female gender • Poor performance status • ≥1 comorbidity • Nutritional status • History of prior FN • Recent surgery and/or open wounds • Liver dysfunction • Renal dysfunction • Low WBC • Low hemoglobin levels • Cardiovascular disease • HIV infection	• Advanced disease • Type of cancer • Bone marrow involvement • Infection

Abbreviations: CIN, chemotherapy-induced neutropenia; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; HIV, human immunodeficiency virus; WBC, white blood cell count.

Blayney DW. Cancer Treatment Reviews 2022;109:102427.

Preventia si tratamentul CIN si FN

- Factorul principal asociat cu riscul de FN este regimul de CHT
- Regimurile de CHT sunt clasificate ca avand risc scazut, intermediar si risc ridicat
- Ghidurile ASCO, EORTC și NCCN recomanda PP cu un agent G-CSF incepand de la C1 de CHT si continuand cu ciclurile ulterioare pentru regimuri cu risc de FN de ≥ 20%
- Pentru CHT cu risc intermediar (10-20%), se recomanda PP cu G-CSF la pacientii care au 1 sau mai multi factori de risc asociati
- Pentru regimurile cu risc scazut de FN nu trebuie utilizata PP cu G-CSF
- Reevaluarea riscului trebuie facuta la fiecare ciclu de CHT – daca un pacient a experimentat FN sau un eveniment neutropenic limitator de D si nu a avut G-CSF trebuie luata in considerare PS cu G-CSF la ciclurile ulterioare

1. National Comprehensive Cancer Network. Hematopoietic growth factors: Version 1.2022. 2. Aapro MS. Eur J Cancer 2011;47(1):8-32. 3. Smith TJ. J Clin Oncol 2015;33(28):3199-212.

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 of Cancer by Site 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). (See 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 (See NCCN Guidelines for ALL)

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

Bone Cancer
- VAI (vincristine, doxorubicin or dactinomycin, ifosfamide)[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]

Colorectal Cancer
- FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, irinotecan)[11,d]

Head and Neck Squamous Cell Carcinoma
- TPF (docetaxel, cisplatin, 5-fluorouracil)[12-14]

Hodgkin Lymphoma
- Brentuximab vedotin + AVD (doxorubicin, vinblastine, dacarbazine)[15]
- Escalated BEACOPP[e] (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)[16]

Kidney Cancer
- Doxorubicin/gemcitabine[17]

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

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]

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

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

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

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

See Disease Settings and Chemotherapy Regimens with an Intermediate Risk for Febrile Neutropenia, MGF-A (2 of 5)

[a] Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for Treatment of Cancer by Site.

[b] Growth factor support may not be needed during the paclitaxel portion and can be safely avoided in a large percentage of patients.

[c] Risk for febrile neutropenia has been reported variably as intermediate risk or high risk depending on the study.

[d] Rates of febrile neutropenia vary. Clinical judgment should be exercised as to which patient population needs growth factor support. There can be a high risk of febrile neutropenia in selected patients.

[e] Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSFs. See Toxicity Risks with Myeloid Growth Factors (MGF-C).

[f] A small retrospective trial had a 17% risk of febrile neutropenia in the neoadjuvant setting[39] and a randomized trial had a 5.4% risk in the metastatic setting (G-CSFs were administered to 42.5% of patients who received FOLFIRINOX).[40] While G-CSF was not recommended as primary prophylaxis, it may be considered in patients with high-risk clinical features.

[g] Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (prophylactic G-CSF may be administered after cycle 1) platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).

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

References

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 of Cancer by Site 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). (See MGF-1)
- In general, dose-dense regimens require myeloid growth factor 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[46-48]
- Paclitaxel/cisplatin[a,48]
- Topotecan[49]
- Irinotecan[50]

Colorectal Cancer
FOLFOX[a] (fluorouracil, leucovorin, oxaliplatin)[h,51]

Esophageal and Gastric Cancers
- Irinotecan/cisplatin[a,52]

Non-Hodgkin Lymphomas
- GDP (gemcitabine, dexamethasone, cisplatin/carboplatin)[a,53]
- CHOP[a] (cyclophosphamide, doxorubicin, vincristine, prednisone)[54,55] including regimens with pegylated liposomal doxorubicin[56,57]
- Bendamustine[a]

Non-Small Cell Lung Cancer
- Cisplatin/paclitaxel[58]
- Cisplatin/vinorelbine[59]
- Cisplatin/docetaxel[58,60]
- Cisplatin/etoposide[61]
- Carboplatin/paclitaxel[a,i,62]
- Docetaxel[60]

Ovarian Cancer
- Carboplatin/docetaxel[63]

Prostate Cancer
- Cabazitaxel[j,64]

Small Cell Lung Cancer[g]
- Etoposide/carboplatin[65]

Testicular Cancer
- BEP[e] (bleomycin, etoposide, cisplatin)[66-68]
- Etoposide/cisplatin[69]

Uterine Sarcoma
- Docetaxel[70]

[a] Guidelines apply to chemotherapy regimens with or without monoclonal antibodies (eg, trastuzumab, rituximab). There is the potential for increased neutropenia risk with the addition of monoclonal antibodies. Rituximab has been associated with prolonged neutropenia with or without chemotherapy. For details on when monoclonal antibodies are recommended with the regimens listed above in clinical practice, see NCCN Guidelines for Treatment of Cancer by Site.

[e] Risk of bleomycin-induced pulmonary toxicity may be increased in patients treated with G-CSFs. See Toxicity Risks with Myeloid Growth Factors (MGF-C).

[g] Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (prophylactic G-CSF may be administered after cycle 1) platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for ES-SCLC.

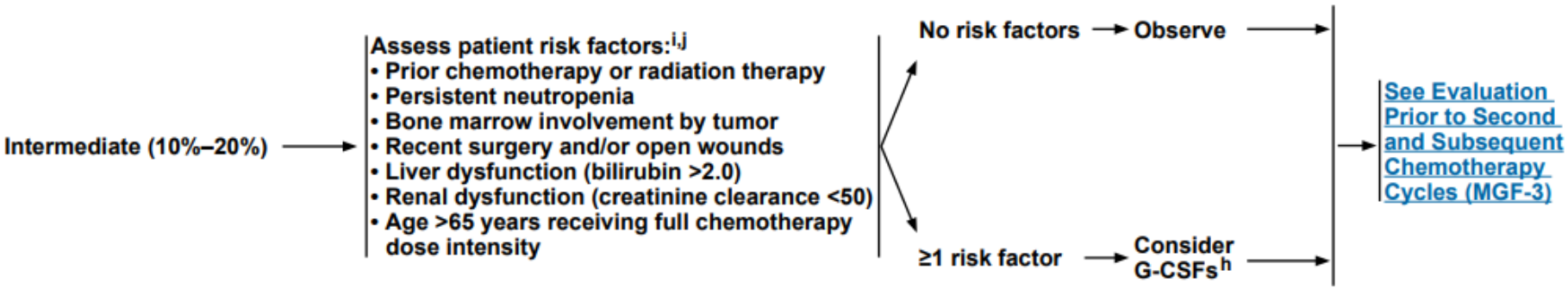
[h] There is variable risk with FOLFOX regimens. Please refer to the risk level of the specified FOLFOX regimen being used for therapy.

[i] If carboplatin dose is AUC ≥6 and/or patient is of Japanese ancestry.

[j] The published results for cabazitaxel have an 8% rate of febrile neutropenia but neutropenic deaths were reported. Primary prophylaxis with G-CSFs is recommended in patients with high-risk clinical features, and should be considered in all patients receiving a dose of 25 mg/m^2.

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

References



[e] Febrile neutropenia is defined as single temperature: ≥38.3 °C orally or ≥38.0 °C over 1 h; and neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[h] See G-CSFs for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

[i] Other possible patient risk factors for febrile neutropenia may include poor performance status or HIV infection (in particular, patients with low CD4 counts). The listed patient risk factors are based on a multivariable risk model using a prospective cohort study of several thousand ambulatory cancer patients receiving chemotherapy. This cohort did not include patients with HIV, acute leukemia, or hematopoietic cell transplant (Lyman GH, et al. Crit Rev Oncol Hematol 2014;90:190-199).

[j] Other factors may warrant the use of G-CSFs (eg, chronic immunosuppression in the post-transplant setting, including organ transplant).

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Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Preventia si tratamentul CIN si FN

- Filgrastim – primul factor de crestere mieloid G-CSF aprobat ca agent profilactic al FN in 1991
- Ulterior, au fost dezvoltate si aprobate pentru uz clinic, biosimilare de filgrastim
- Filgrastim si biosimilarele sale sunt eliminate rapid din organism prin filtrare renala, cu un timp de ½ in circulatie de ~ 4-8h si, prin urmare, necesita administrare zilnica pana la recuperarea neutrofilelor
- Durata de administrare a G-CSF pentru efect optim ar trebui sa fie > 5 zile si pana la 11 zile sau pana la recuperarea post-nadir a neutrofilelor
- Administrarea zilnica este incomoda pentru pacienti – pentru a evita inconvenientele administrarii zilnice, au aparut abordari farmacologice care cresc retentia G-CSF in circulatie → PEGilarea (adaugarea unei cozi inerte de polietilen glicol la G-CSF), care creste dimensiunea moleculei si previne excretia renala a avut cel mai mare succes

1. Crawford J. N Engl J Med 1991;325(3):164-70. 2. Awad M. P T 2017;42(1):19-23. 3. Chen B. Oncologist. 2019;24(4):537-548. 4. Clemons M. Ann Oncol 2020;31(7):951-7. 5. Scott SD. J Manag Care Pharm 2003;9(2Suppl):15-21. 6. Gawade PL. Support Care Cancer 2020;28(9):4413-24. 7. van der Auwera P. Am J Hematol 2001;66(4):245-51. 8. Kumari M. Front Bioeng Biotechnol 2020;8:572077.

Preventia si tratamentul CIN si FN

- PEGilarea creste timpul de ½ plasmatica a G-CSF cu pana la 42h, permitand administrarea unei doze per ciclu
- Pegfilgrastim – primul agent G-CSF PEGilat aprobat pentru utilizare in 2002
- Ulterior, au devenit disponibile mai multe biosimilare cu actiune prelungita
- Momentul administrarii G-CSF este esential pentru beneficiu → conform ghidurilor NCCN agentii G-CSF trebuie administrati intre Z1-Z4 post CHT
- Administrarea in aceeasi zi este suboptimala, iar administrarea in Z8 nu este eficienta

1. Crawford J. Semin Oncol 2003;30(4 Suppl 13):24-30. 2. Drug approval package: Neulasta (pegfilgrastim) injection US Food & Drug Administration. Updated January 2002. 3. Selby C. J Adv Pract Oncol 2021;12(5):541-7. 4. Weycker D. Curr Med Res Opin 2017;33(12):2107-13. 5. Weycker D. Support Care Cancer 2016;24(5):2309-16. 6. Barnes G. Cancer Med 2014;3(6):1477-84. 7. Lyman GH. Support Care Cancer 2017;25(8):2619-29. 8. Schuman SI. J Support Oncol 2009;7(6):225-8. 9. Crawford J. Ann Oncol 1997;8(11):1117-24.

Probleme clinice asociate cu utilizarea G-CSF

- Principalul AE asociat cu toate G-CSF aprobate este durerea osoasa – apare la 25-83% dintre pacienti
- Durerea osoasa indusa de G-CSF se datoreaza probabil expansiunii MO, activarii circuitelor proinflamatorii si sensibilizarii fibrelor nervoase periferice la stimulii de durere
- Utilizarea profilactica de antihistaminice, NSAI si acetaminophen poate fi utila in tratamentul durerii osoase induse de G-CSF
- Alte AEs raportate includ cefalee (15-70%), greata si/sau varsaturi (3-18%), febra/frisoane/transpiratii (0-27%), oboseala (9-59%), reactii la locul de injectare (1-3%) si mialgii (13-68%)
- Un risc crescut de malignitati secundare, cel mai frecvent LAM si SMD, a fost raportat, de asemenea, dupa administrarea de G-CSF (RR 1,85, $P < 0,01$)

1. Lyman GH. Ann Oncol 2018;29(9):1903-10. 2. Tigue CC. Bone Marrow Transplant 2007;40(3):185-92. 3. Lapidari P. Crit Rev Oncol Hematol 2021;157:103193. 4. Lapidari P. Breast 2021;57:43-8. 5. Lambertini M. Crit Rev Oncol Hematol 2014;89(1):112-28.

Subutilizarea in practica clinica a G-CSF

- Profilaxia FN este adesea subutilizata in practica clinica la pacientii carora li se administreaza regimuri de CHT cu risc ridicat/mediu
- Intr-un studiu retrospectiv care a inclus pacienti cu tumori solide/limfoame tratati in intervalul 2009-2017, G-CSF a fost administrat la 48,5% dintre pacientii cu risc ridicat si la 13,9% din pacientii cu risc intermediar care au avut un factor de risc pentru FN
- Intr-o alta analiza retrospectiva care a inclus pacienti cu tumori solide/limfoame tratati in intervalul 2013-2017, 76% dintre pacientii cu risc crescut au primit G-CSF profilactic, in timp ce doar 28% dintre pacientii cu risc intermediar au primit profilaxie G-CSF
- In plus, 8,5% dintre pacientii cu risc mediu au primit profilaxie G-CSF in aceeasi zi cu CHT, conduita care anuleza beneficiul G-CSF

1. Averin A. Support Care Cancer 2021;29(4):2179-86. 2. Gawade PL. Support Care Cancer 2020;28(9):4413-24. 3. Barnes G. Cancer Med 2014;3(6):1477-84.

Noi agenti pentru preventia si tratamentul CIN si FN

Drug	Study (Name and/or NCT Identifier)	Phase	Population (N)	Treatment	Mean DSN C1[b]	SN[b]	FN	Hospitalization Rate
Trilaciclib	NCT03041311 Daniel et al, 2020 [70]	2	ES-SCLC (N = 107)	Trilaciclib (240 mg/m^2 QD D1–3) **prior to** carboplatin D1 + etoposide D1-3 + atezolizumab D1[c] → atezolizumab maintenance D1 Q21D Placebo (240 mg/m^2 QD D1–3) **prior to** carboplatin D1 + etoposide D1–3 + atezolizumab D1[c] → atezolizumab maintenance D1 Q21D	0 vs 4 days ($P <$ 0.0001)	1.9% vs 49.1% ($P <$ 0.001)	1.9% vs 5.7% ($P =$ 0.3105)	3.8% vs 11.3% ($P = 0.1287$)
	NCT02514447 Hart et al, 2021 [71]	1b/ 2a	ES-SCLC (N = 61)	Trilaciclib (240 mg/m^2 QD D1–3) **prior to (≤4h)** topotecan D1-5[d] Q21D Placebo (240 mg/m^2 QD D1–3) **prior to (≤4h)** topotecan D1–5[d] Q21D	2 vs 7 days ($P <$ 0.0001)	40.6% vs 75.9% ($P = 0.016$)	6.3% vs 17.9%	9.4% vs 21.4% ($P = 0.1879$)
	NCT02499770 Weiss et al, 2019 [72]	1b/2	ES-SCLC (N = 122)	Trilaciclib (200 or 240 mg/m^2 QD D1–3) **prior to** carboplatin D1 + etoposide D1–3[e] Placebo (200 or 240 mg/m^2 QD D1–3) **prior to** carboplatin AUC 5	0 vs 3 days ($P \leq$ 0.001)	5% vs 43% ($P \leq$ 0.0001)	3% vs 8%	Not reported

1. Blayney DW. Cancer Treatment Reviews 2022;109:102427. 2. US FDA. FDA Approves Drug to Reduce Bone Marrow Suppression Caused by Chemotherapy. Updated February 12, 2021. 3. COSELA (trilaciclib) prescribing information [Internet]. G1 Therapeutics. Updated February 2021. 4. Daniel D. Int J Cancer 2020;148(10):2557-70. 5. Hart LL. Adv Ther 2021;38(1):350-65. 6. Weiss JM. Ann Oncol 2019;30(10):1613-21.

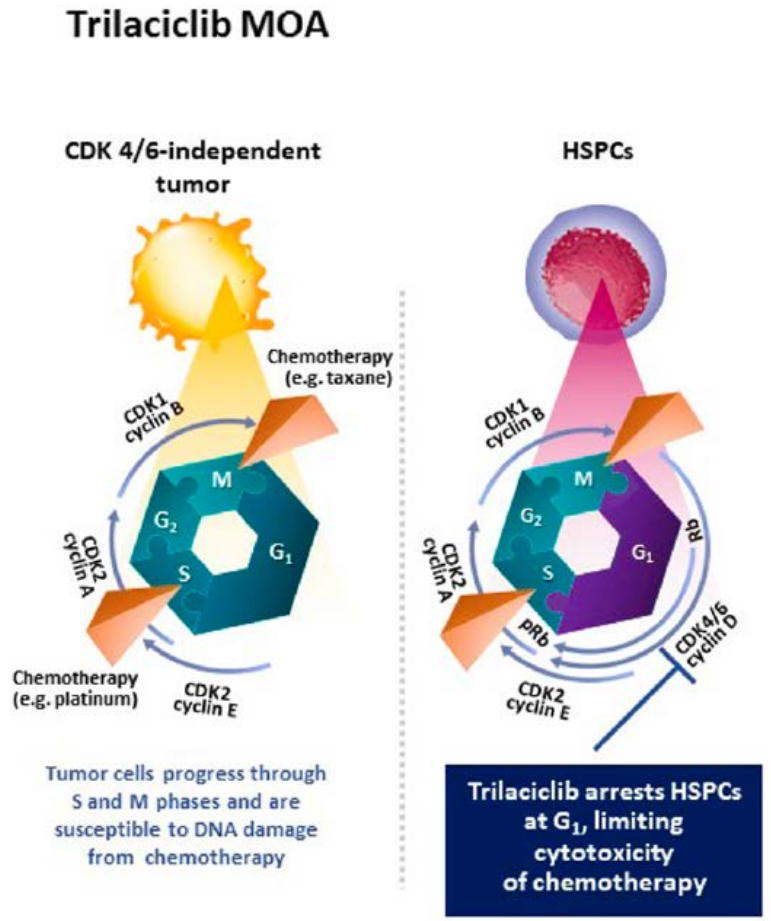
Noi agenti pentru preventia si tratamentul CIN si FN

- Trilaciclib – inhibitor al kinazei ciclin-dependente 4/6 (CDK4/6)
- Trilaciclib – aprobare FDA pentru scaderea riscului de mielosupresie post CHT la pacientii cu ES-SCLC, dupa CHT pe baza de cisplatin/etoposid sau topotecan
- Aprobarea FDA s-a bazat pe datele din 3 RCT de faza 2, controlate placebo, in care trilaciclib a scazut incidenta si durata neutropeniei severe in C1 de CHT
- In studiile preclinice, trilaciclib a indus arestul tranzitoriu si reversibil al celulelor stem hematopoietice murine si umane in ciclul celular in G1 si a protejat progenitorii de epuizarea indusa de chimioterapie
- Deoarece trilaciclib functioneaza ca un protector al progenitorilor medulari, se administreaza cu cateva ore inainte de CHT

1. Blayney DW. Cancer Treatment Reviews 2022;109:102427. 2. US FDA. FDA Approves Drug to Reduce Bone Marrow Suppression Caused by Chemotherapy. Updated February 12, 2021. 3. COSELA (trilaciclib) prescribing information [Internet]. G1 Therapeutics. Updated February 2021. 4. Daniel D. Int J Cancer 2020;148(10):2557-70. 5. Hart LL. Adv Ther 2021;38(1):350-65. 6. Weiss JM. Ann Oncol 2019;30(10):1613-21.

Noi agenti pentru preventia si tratamentul CIN si FN

- Cele mai frecvente AEs atribuite trilaciclibului au fost oboseala (9,6%), greata (7,7%), anemia (5,8%) si reactiile infuzionale (5,8%)
- Pe langa beneficiile observate in populatia de neutrofile (scaderea incidentei neutropeniei grad 4 si a administrarii G-CSF), trilaciclib a demonstrat si un efect de mieloconservare a celorlalte linii hematopoietice – scaderea incidentei anemiei grad 3/4 si a trombocitopeniei, scaderea necesarului transfuzional (MER) in/dupa saptamana 5 si a administrarii de agenti de stimulare ai eritropoiezei, cu imbunatatirea QoL



1. Blayney DW. Cancer Treatment Reviews 2022;109:102427. 2. Daniel D. Int J Cancer 2020;148(10):2557-70. 3. Hart LL. Adv Ther 2021;38(1):350-65. 4. Weiss JM. Ann Oncol 2019;30(10):1613-21.
5. Weiss J. Clin Lung Cancer 2021;22(5):449-60.

Noi agenti pentru preventia si tratamentul CIN si FN

Plinabulin	PROTECTIVE-1/ NCT03102606 Blayney et al, 2021 [74]	3	Breast, lung, and prostate cancer patients (intermediate FN risk) (N = 105)	Docetaxel D1[g] + plinabulin 40 mg D1 + placebo D2	Equal DSN	Not reported	0% vs 1.89%	3.84% vs 1.89%
				Docetaxel D1[g] + placebo D1 + pegfilgrastim 6 mg D2				
	PROTECTIVE-2/ NCT03294577 Blayney et al, 2021; Shi et al, 2021 [75,76]	3	Breast cancer (N = 221)	Docetaxel/doxorubicin/ cyclophosphamide[h] D1 + plinabulin 40 mg D1 + pegfilgrastim 6 mg D2	1.2 vs 1.5 ($P = 0.03$)[i]	21.62% vs 46.36% ($P = 0.0001$) (profound neutropenia C1)	3.6% vs 6.3% ($P = 0.36$)	75% vs 100%
				Docetaxel/doxorubicin/ cyclophosphamide[h] D1 + pegfilgrastim 6 mg D2				
	PROTECTIVE-1/ NCT04345900 Blayney et al, 2020 [77]	2	NSCLC (N = 55)	Docetaxel D1[g] + plinabulin 5, 10, 20 mg/m^2 D1	0.36 vs 0.15 days ($P = 0.76$)[j]	Not reported	n = 1[k]	14% vs 15 %[j]

1. Blayney DW. Cancer Treatment Reviews 2022;109:102427. 2. Blayney DW. J Clin Oncol 2021;39(15_suppl):547. 3. Blayney DW. J Clin Oncol 2021;39(15_suppl):533. 4. Shi Y. J Clin Oncol 2021;39(15_suppl):546. 5. Blayney DW. JAMA Oncol 2020;6(11):e204429.

Noi agenti pentru preventia si tratamentul CIN si FN

BEYONDSPRING PHARMACEUTICALS RECEIVES COMPLETE RESPONSE LETTER FROM THE FDA FOR PLINABULIN NEW DRUG APPLICATION FOR PREVENTION OF CHEMOTHERAPY-INDUCED NEUTROPENIA (CIN)

December 1, 2021

NEW YORK, Dec. 01, 2021 (GLOBE NEWSWIRE) — BeyondSpring Pharmaceuticals (the "Company" or "BeyondSpring") (NASDAQ: BYSI), a global pharmaceutical company focused on the development of cancer therapeutics, today announced it has received a Complete Response Letter (CRL) from the U.S. Food and Drug Administration (FDA) for the New Drug Application (NDA) seeking approval of plinabulin in combination with granulocyte colony-stimulating factor (G-CSF) for the prevention of chemotherapy-induced neutropenia (CIN). The FDA issued the CRL to indicate that they have completed their review of the application and have determined that it cannot be approved in its present form.

The FDA's CRL indicated that the results of the single registrational trial (106 Phase 3) was not sufficiently robust to demonstrate benefit and that a second well controlled trial would be required to satisfy the substantial evidence requirement to support the CIN indication.

1. Blayney DW. Cancer Treatment Reviews 2022;109:102427. 2. Blayney DW. J Clin Oncol 2021;39(15_suppl):547. 3. Blayney DW. J Clin Oncol 2021;39(15_suppl):533. 4. Shi Y. J Clin Oncol 2021;39(15_suppl):546. 5. Blayney DW. JAMA Oncol 2020;6(11):e204429.

Noi agenti pentru preventia si tratamentul CIN si FN

Eflapegrastim	ADVANCE/ NCT02643420 Schwartzberg et al, 2020[80]	3	Breast cancer (N = 406)	Docetaxel + cyclophosphamide D1[m] + eflapegrastim 13.2[o] mg D2 Docetaxel + cyclophosphamide D1[m] + pegfilgrastim 6 mg D2	0.20 vs 0.35 days (P = 0.013)	15.8% vs 24.3% (P = 0.034)	2% vs 1% (P = 0.435)	Not reported
	RECOVER/ NCT02953340 Cobb et al, 2020 [81]	3	Breast cancer (N = 237)	Docetaxel + cyclophosphamide D1[m] + eflapegrastim 13.2[o] mg D2 Docetaxel + cyclophosphamide D1[m] + pegfilgrastim 6 mg D2	0.31 vs 0.39 days (P = 0.0001)	20.3% vs 23.5%	0.8% vs 3.4% (P = 0.370)	Not reported

1. Blayney DW. Cancer Treatment Reviews 2022;109:102427. 2. Schwartzberg LS. Oncologist 2020;25(8):e1233-41. 3. Cobb PW. Cancer Med 2020;9(17):6234-43. 4. Barrett JA. Exp Hematol 2020;92:51-61. 5. Schwartzberg LS. Poster Presented at the Virtual San Antonio Breast Cancer Symposium. 2020;Abstract PS9-59.

Noi agenti pentru preventia si tratamentul CIN si FN

- Eflapegrastim – factor de crestere hematopoietic cu actiune prelungita, constand dintr-un analog rhG-CSF conjugat cu un fragment Fc IgG4 uman aglicozilat, printr-un linker scurt de polietilen glicol
- In studiile preclinice eflapegrastim a demonstrat concentratii serice si la nivelul MO mai mari comparativ cu pegfilgrastim, ceea ce a rezultat intr-o durata mai scurta a neutropeniei atunci cand s-a administrat eflapegrastim la 24h post CHT
- In plus, eflapegrastim a redus semnificativ durata neutropeniei cand s-a administrat concomitent cu CHT sau pana la 5h post CHT, sugerand ca administrarea in aceeasi zi cu CHT este posibila

1. Blayney DW. Cancer Treatment Reviews 2022;109:102427. 2. Schwartzberg LS. Oncologist 2020;25(8):e1233-41. 3. Cobb PW. Cancer Med 2020;9(17):6234-43. 4. Barrett JA. Exp Hematol 2020;92:51-61. 5. Schwartzberg LS. Poster Presented at the Virtual San Antonio Breast Cancer Symposium. 2020;Abstract PS9-59.

Noi agenti pentru preventia si tratamentul CIN si FN

- In 2 RCT de faza 3 la paciente CM in stadii precoce (ADVANCE si RECOVER), eflapegrastim a demonstrat non-inferioritate si siguranta comparabila cu pegfilgrastim
- O analiza combinata datelor din studii a confirmat faptul ca eflapegrastim a redus semnificativ riscul de neutropenie severa comparativ cu pegfilgrastim si a avut un profil de siguranta similar cu pegfilgrastim

1. Blayney DW. Cancer Treatment Reviews 2022;109:102427. 2. Blayney DW. J Clin Oncol 2021;39(15_suppl):547. 3. Blayney DW. J Clin Oncol 2021;39(15_suppl):533. 4. Shi Y. J Clin Oncol 2021;39(15_suppl):546. 5. Blayney DW. JAMA Oncol 2020;6(11):e204429.

Concluzii

- Aparitia CIN are impact negativ asupra prognosticului pacientilor oncologici
- Utilizarea profilactica a G-CSF a redus consecintele clinice ale FN
- Apariția biosimilarelor G-CSF a redus costurile, mentinand eficacitatea si profilul de siguranta al moleculelor originale
- Aprobarea recenta a trilaciclibului ca agent mieloprotector pentru ES-SCLC si noile molecule in dezvoltare au ca scop imbunatatirea strategiilor de preventie a CIN si FN
- Mecanismele alternative de actiune ale trilaciclibului si plinabulin pot oferi mai multe avantaje fata de G-CSF standard, inclusiv administrarea in aceeasi zi cu CHT, absenta durerii osoase si o potentiala activitate antitumorala


Thank you