

Antihistamines for Myeloid Growth Factor Induced Bone Pain

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Disclosure Statement



- Julia Mwangi, PharmD
- No conflict of interest
- Did not receive funding for this program
- Presentation is educational in nature and abides by non-commercial guidelines

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Learning Objectives



1. Recognize the likely causes for bone pain due to myeloid growth factor (MGF) administration.
2. Describe the probable mechanism by which antihistamines can relieve Myeloid Growth Factor induced bone pain.
3. Discuss available treatments for MGF induced bone pain.

• **Target Audience: Pharmacists**

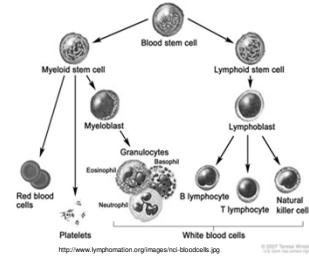
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Hematopoiesis



- Bone marrow stem cells develop into all cell types present in the blood

Cell Type	Life span
Neutrophils	1-5 days
Platelets	5-10 days
Erythrocyte	120 days



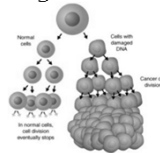
Grazovsky Curt Open Hematol 2010;1:17-565-9
 Pflay Blood 2010;29: 625-7
 Kruza Control Neptrol 2008;181:247-54

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Chemotherapy and Myelosuppression



- Chemotherapy- death of rapidly dividing cells
- Myelosuppression: neutropenia, anemia, thrombocytopenia, pancytopenia
 - Major dose-limiting toxicity of chemotherapy
- Some studies have shown that 25% to 40% of treatment-naïve patients develop febrile neutropenia



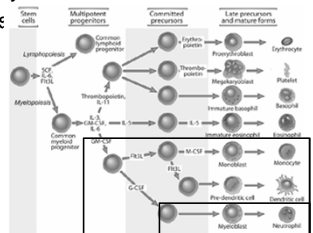
<https://sites.duke.edu/seeklabacco2/the-role-of-tobacco-in-the-development-of-cancer/the-content/>

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Myeloid Growth Factors



- MGF's – stimulate hematopoietic progenitors to form mature cells
 - Two types currently available: G-CSF and G-MCSF
- Decrease incidence of neutropenia



<http://histocout.jp.co.uk/Haematology/Bone-Marrow.aspx>

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MGF Induced Bone Pain



- One of the most common adverse reactions to MGF's is mild to moderate pain.
 - Occurs in ~ 10% - 30% of patients (higher incidence in clinical practice)
 - No known risk factors that would predict occurrence of pain
- Pain primarily located in back and legs.

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Pharmacologic Treatments



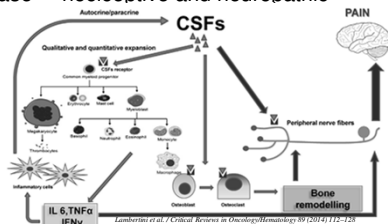
- Acetaminophen
- Opioids
- Corticosteroids
- NSAIDs
 - Only agent studied in a randomized controlled trial (Kirshner et al. 2012)
 - Found that there was a reduction in % of patients who experienced any pain from 71.3% to 61.1% (P=0.02)
 - >60% of patients still experienced pain even after NSAID administration

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Proposed Mechanisms of MGF Induce Bone Pain



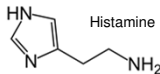
- Bone marrow expansion
- Stimulation of cytokines which can result in inflammation
- Histamine release → nociceptive and neuropathic pain



Antihistamine Use



- Retrospective cohort study by Gavioli et al. 2016.
 - **Purpose:** Determine the analgesic effects of double histamine blockade for G-CSF induced bone pain
 - Retrospective cohort from January to November 2015 of patients who had received G-CSF for primary or secondary prophylaxis and had received at least 4 cycles of myelosuppressive chemotherapy
 - Patients that developed bone pain received prophylaxis at next G-CSF dose with combination of famotidine 20mg and loratadine 10mg 30 min prior to G-CSF administration
 - Bone pain scores were lower by a mean of 1.21 (P=0.019) in patients that received prophylaxis with antihistamines



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Antihistamine Use



- Retrospective chart review by Palowski et al, 2016
 - **Purpose:** To describe the incidence of pegfilgrastim induced bone pain and treatments used for bone pain
 - Chart review conducted from January 2012 to December 2012 of first 100 patients who received pegfilgrastim at any time 6 months prior to study period
 - Mean age of patients was 60 years old. Pegfilgrastim mostly administered for primary prophylaxis
 - Pegfilgrastim associated bone pain documented in 13 (19%) patients
 - Of these patients, 87% used loratadine alone or in combination
 - Limitation: dose and duration of loratadine not captured

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Antihistamine Use



- Randomized phase II trial by J. Moukharskaya et al. 2015
 - **Purpose:** To determine whether loratadine would decrease the incidence of pegfilgrastim induced significant back or leg bone pain in a high risk population
 - Study conducted at seven sites between February of 2011 and December of 2013
 - Patients randomized to either loratadine 10mg once daily (n=22) or placebo daily (n=24) for 7 days
 - 77% of patients that developed bone pain benefited from loratadine, whereas 62.5% developed relief from the placebo
 - Not significant, however, patients were allowed to use other analgesics such as NSAIDs while on this study

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Case Report



- Several case reports of antihistamine used to alleviate MGF induced bone pain.
- 67 year old woman with stage IV ovarian cancer.
 - Treated with paclitaxel/carboplatin. She became neutropenic and received pegfilgrastim
 - Patient failed on naproxen, oxycodone as well as hydromorphone
 - Trial of loratadine 10mg once daily following chemotherapy for pain prevention
 - Patient reported relief of leg pain/myalgias without use of opioids

C. Romeo et al. Severe pegfilgrastim-induced bone pain completely alleviated with loratadine: A case report. J Oncol Pharm Practice 2015, Vol. 21(4) 323-324 13

Case Report



- 49 year old woman with breast cancer
 - 1st chemotherapy cycle of doxorubicin and cyclophosphamide was given 7 days prior to ED arrival and pegfilgrastim was administered 6 days prior to ED visit
 - Patient had received APAP, and IBU 2 hours prior to arrival without relief
 - In the ED, patient received 1mg followed by 2mg of IV dilaudid with minimal relief
 - Patient was then given loratadine 10mg oral
 - On subsequent reassessment, patient reported decrease in bone pain from 10/10 to 5/10

K. Moore et al. When Hydromorphone Is Not Working, Try Loratadine: An Emergency Department Case of Loratadine as Abortive Therapy for Severe Pegfilgrastim-Induced Bone Pain. The Journal of Emergency Medicine, Vol. 52, No. 2, pp. e29-e31, 2017 14

Summary



- MGF induced bone pain is a common side effect and may result in severe bone pain for some patients
- Some proposed mechanisms for MGF induced bone pain include:
 - Bone marrow expansion
 - Inflammatory response
 - Histamine release
- Use of antihistamines can be used to alleviate MGF induced pain in patients that are refractory to other pain treatments
 - Pros: Safe and affordable
 - Cons: Additional studies needed to evaluate efficacy of antihistamines

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Post Test Questions



Which statement is true?

- A. Myeloid growth factors are important at completely preventing bacterial or viral infections
- B. Febrile neutropenia is not a dose-limiting toxicity of chemotherapy
- C. Myeloid growth factors can result in bone pain in <10% of patients.
- D. Loratadine may decrease MGF induced pain through blocking histamine (H1) receptors which may in turn reduce nociceptive pain and neuropathic pain ←

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Post Test Questions



Which of the following class of drugs can be used to treat MGF induced bone-pain?

- A. Corticosteroids and SSRIs
- B. Muscle-relaxers and Acetaminophen
- C. Antihistamines and NSAIDs ←
- D. Antihistamines and SSRIs

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Questions?



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