Granulocyte-Colony Stimulating Agents (G-CSF)

Filgrastim

รูปแบบ sterile sol

บัญชี ง

เงื่อนไขการสั่งใช้

กรณีการรักษา

1. ใช้สำหรับปลูกถ่ายไขกระดูกหรือเซลล์ต้นกำเนิดเม็ดเลือด เพื่อเคลื่อนย้าย progenitor cell จากไขกระดูกออกมาในเลือดของผู้ให้หรือผู้ป่วย เพื่อนำไปใช้ทั้งใน allogeneic และ autologous transplantation

2. ใช้สำหรับรักษา febrile neutropenia ที่เกิดจากยาเคมีบำบัด ให้พิจารณาในผู้ป่วยที่ต้องรับเข้าให้การรักษาในโรงพยาบาลร่วมกับการให้ยาต้านเชื้อจุลชีพในผู้ป่วยความเสี่ยงสูง โดยมีข้อใดข้อหนึ่งดังต่อไปนี้

- Profound neutropenia ซึ่งมี absolute neutrophil count น้อยกว่า 100 /mm^3
- มีปอดอักเสบชนิด bacterial pneumonia หรือ lobar pneumonia หรือ มีภาวะ septicemia

กรณีการป้องกันโรค

3. Primary prophylaxis

3.1 ในผู้ป่วยที่จะได้รับยาเคมีบำบัดด้วยสูตรที่มีความเสี่ยงสูงต่อการเกิด febrile neutropenia มากกว่าร้อยละ 20

3.2 กรณีที่ผู้ป่วยมีความเสี่ยงต่อการเกิด febrile neutropenia 10 - 20% ร่วมกับการประเมินปัจจัยเสี่ยงของผู้ป่วยอย่างน้อยหนึ่งข้อ

- อายุมากกว่า 65 ปี
- มี performance status ที่ไม่ดี (ECOG >= 2)
- มีภาวะ neutropenia (absolute neutrophil count $\leq$ 1,500/mm^3) หรือมีโรคแทรกซ้อนในไขกระดูกที่เกิดจากโรคมะเร็งดังกล่าว

4. Secondary prophylaxis

ใช้ในผู้ป่วยที่เคยเกิด febrile neutropenia จากการรับยาเคมีบำบัดในครั้งก่อน และเป็นผู้ป่วยที่มีเป้าหมายการรักษาเพื่อหายขาด (curative aim)

หมายเหตุ:

1. ไม่แนะนำให้ใช้ยากลุ่ม Granulocyte-Colony Stimulating Factors (G-CSF) ในกรณีที่ผู้ป่วยได้รับเคมีบำบัดโดยไม่ได้หวังผล curative aim (ในกรณีของ palliative chemotherapy แนะนำให้ลดขนาดยาเคมีบำบัดลงตามมาตรฐาน)
2. Febrile neutropenia หมายถึง ภาวะที่ผู้ป่วยมีไข้ร่วมกับนิวโทรฟิลในเลือดต่ำ โดย

   ภาวะไข้ คือ อุณหภูมิกายของผู้ป่วยซึ่งวัดทางปาก ณ เวลาใดๆ *ที่* $\geq$ *38.3°C* หรือ มีอุณหภูมิกายซึ่งวัดทางปาก $\geq$ *38.0°C* นานติดต่อกันเกิน 1 ชั่วโมง

   นิวโทรฟิลในเลือดต่ำ คือ มีจำนวนนิวโทรฟิลในเลือด (absolute neutrophil count) < 0.5 x 10^9/L หรือ มีจำนวนนิวโทรฟิลในเลือด < 1.0 x 10^9/L ซึ่งคาดว่าจะลดลงเหลือ $\leq$ 0.5 x 109/L ภายใน 48 ชั่วโมง

Lenograstim

รูปแบบ sterile powder

บัญชี ง

เงื่อนไขการสั่งใช้ เช่นเดียวกับ filgrastim

Pegfilgrastim

รูปแบบ sterile sol 6 mg/10 mL

ไม่คัดเลือก เนื่องจากประสิทธิภาพและความปลอดภัยของ pegfilgrastim และ filgrastim ไม่แตกต่างกัน การศึกษา cost effectiveness เป็นการศึกษาเปรียบเทียบด้วยราคายาที่เป็น original เหมือนกัน จึงดูเหมือนว่า pegfilgrastim มีความคุ้มค่ามากกว่า อย่างไรก็ตาม หากเปรียบเทียบราคายาที่แตกต่างกันมากขึ้นด้วยยา generic อาจมีผล cost effectiveness ต่ำกว่า และ pegfilgrastim มีความคุ้มค่าน้อยกว่า

1. **ข้อมูลโดยสรุป**

อนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ รอบการพิจารณาปี 2551 - 2552 ไม่เลือก G-CSF ในข้อบ่งใช้ febrile neutropenia เนื่องจาก ยังไม่มีข้อมูลว่าช่วยลดอัตราการตายหรืออัตราการตายที่เกี่ยวข้องกับการติดเชื้อได้ ประกอบกับยามีราคาแพง ผู้ป่วยที่ต้องใช้มีจำนวนมากจึงทำให้มีผลกระทบทางงบประมาณสูง ยังไม่มีเงื่อนไขการสั่งใช้ที่ชัดเจน และมีข้อสงสัยในด้านความคุ้มค่า

เงื่อนไข:

1.เลือกหนึ่งรายการระหว่าง filgrastim และ lenograstim ที่จัดซื้อได้ถูกกว่า

2.ใช้สำหรับปลูกถ่ายไขกระดูกหรือเซลล์ต้นกำเนิดเม็ดเลือด เพื่อเคลื่อนย้าย progenitor cell จากไขกระดูกออกมาในเลือดของผู้ให้หรือผู้ป่วย เพื่อนำไปใช้ทั้งใน allogeneic และ autologous transplantation

3.ไม่แนะนำให้ใช้สำหรับ febrile neutropenia เพราะการใช้ยาไม่เพิ่ม overall survival หรือลด infection related mortality

ในการพิจารณายา G-CSF ในบัญชียาหลักแห่งชาติ ปี 2553 – 2555 ได้มีข้อเสนอเพิ่มเงื่อนไขการสั่งใช้ใน febrile neutropenia อีกครั้ง เนื่องจากเป็นมาตรฐานการรักษาในปัจจุบัน[1, 2] (ดูตารางที่ 2 หน้า 4 เพิ่มเติม) และมีหลักฐานใหม่ที่ชี้ว่าการใช้ G-CSF ในผู้ป่วย febrile neutropenia โดยเฉพาะ prophylaxis ลดอัตราการนอนโรงพยาบาล และอัตราการใช้ยาปฏิชีวนะได้ ประกอบกับราคายา G-CSF ที่ลดลงในปัจจุบัน ส่วนการใช้รักษา febrile neutropenia ก็มีข้อมูลว่าช่วยลดระยะเวลาที่เป็น neutropenia ลดระยะเวลาการใช้ยาปฏิชีวนะ และลดระยะเวลาการนอนโรงพยาบาลลง[2] (รายละเอียดตามข้อความที่คัดลอกมาปรากฏด้านล่าง) คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติได้พิจารณาและมีความเห็นว่า การใช้ยาน่าจะมีความคุ้มค่าโดยอาจประหยัดค่าใช้จ่ายในโรงพยาบาลลงได้ จึงได้เพิ่มเงื่อนไข febrile neutropenia ไว้ในบัญชียาหลักแห่งชาติ[3]

Prophylaxis

"…**Patients at high risk of FN**…

…The guidelines recommended prophylactic CSF if the risk of FN was 20% or greater. The most recent update of the ASCO guidelines and the European Organisation for Research and Treatment of Cancer (EORTC) both adopted the 20% threshold for considering routine prophylactic treatment.[33,34]…

…For example, Vogel and colleagues… The placebo group had an overall incidence of FN of 17%. By contrast, the pegfilgrastim group had a 1% incidence. The incidence of hospitalization was reduced from 14% to 1%, and the use of IV anti-infectives was reduced from 10% to 2%, with all of these differences statistically significant ($p<0.001$). In cycle 1, there

was an 11% rate of FN in the first cycle for the placebo group versus < 1% in the pegfilgrastim group. For cycles 2 through 4, the placebo group had a 6% rate of FN with < 1% in the pegfilgrastim group.

A second trial reported the results of 175 patients with small cell lung cancer who were randomized to receive prophylactic antibiotics with or without prophylactic G-CSF.[6] In cycle 1, 20 patients (24%) in the antibiotics-only group developed FN compared with nine patients (10%) in the antibiotics plus FN group (P = 0.01). In cycles 2 to 5, the incidences of FN were similar in both groups (17% vs. 11%). The authors concluded that primary FN prophylaxis added to primary antibiotic prophylaxis is effective in reducing FN and infections in patients with small cell lung cancer with the first cycle of chemotherapy. Furthermore, this strategy could be considered for other cancer patients with a similar risk of FN…"

Treatment

"…**Therapeutic use of CSFs (MGF-3)**

Compared to prophylactic use, there is less evidence supporting therapeutic use of CSFs for FN as an adjunctive to antibiotics. In a Cochrane meta-analysis including 1518 patients from 13 trials[46], Clark and colleagues reported a shorter length of hospitalization (HR = 0.63; 95%CI, 0.49 to 0.82; P = 0.0006), shorter time to neutrophil recovery (HR = 0.32; 95%CI, 0.23 to 0.46; P < 0.0001), but no improvement in overall survival associated with therapeutic CSF. An earlier meta-analysis by Berghmans et al[47] again found no difference in mortality, but they were unable to assess other clinical benefits. Of note, Berghmans' analysis did not include a multicenter trial that randomized 210 patients with solid tumors who developed chemotherapy-induced FN and had at least one high-risk factor to therapeutic G-CSF or placebo.[48] The G-CSF arm showed a significantly shorter duration of grade 4 neutropenia (median 2 vs. 3 days, P = 0.0004), antibiotic therapy (median 5 vs. 6 days, P = 0.013) and hospital stay (median 5 vs. 7 days, P = 0.015)…"

Cost analysis

Pharmacoeconomics. 2003;21(18):1295-313.

Economic evaluations of granulocyte colony-stimulating factor: in the prevention and treatment of chemotherapy-induced neutropenia.

Esser M, Brunner H.

Abstract

The prevailing uncertainty about the pharmacoeconomic positioning of granulocyte colony-stimulating factor (G-CSF) in the prevention and treatment of chemotherapy-induced febrile neutropenia has resulted in a number of pharmacoeconomic evaluations published in the past 10 years. These studies vary considerably regarding the approaches used and the results presented. In order to contribute to a clearer pharmacoeconomic positioning of G-CSF, a systematic review of economic evaluations was carried out. The focus of the review was prophylaxis and therapy of chemotherapy-induced neutropenia in patients with cancer. A computerised bibliography search of several databases was conducted yielding 33 studies. The findings demonstrated the cost-saving potential of G-CSF in standard-dose chemotherapy to be limited, with lower costs often seen in the control group. The results of these studies were too heterogeneous to extract a clear recommendation from a cost-saving point of view. The administration of G-CSF after high-dose chemotherapy with stem cell support resulted more often in cost savings in the G-CSF group as compared with standard-dose chemotherapy, illustrating a possible cost-saving potential of G-CSF. In the treatment of established chemotherapy-induced febrile neutropenia, cost savings were found in all studies. This result is surprising but hampered by the small number of studies (n = 5) and remains to be confirmed by more rigourously designed prospective economic analyses. Despite the substantial research on this topic, the economic evaluation of G-CSF is far from being settled and needs further investigation.

2. สรุปข้อแนะนำจากแนวทางการรักษาในต่างประเทศ

ฝ่ายเลขานุการฯ ได้สืบค้นข้อมูลจาก Pubmed, Micromedex®, Uptodate® NICE, NHS, SIGN เมื่อวันที่ 25 มกราคม 2555 คัดเลือกเฉพาะผลลัพธ์ที่มีข้อแนะนำการใช้ G-CSF ใน febrile neutropenia สรุปได้ดังตารางที่ 1

ตารางที่ 1 สรุปการแนะนำ G-CSF ใน febrile neutropenia จากแนวทางการรักษาในต่างประเทศ (รายละเอียดการสืบค้น guidelines ตั้งแต่หน้า 6 เป็นต้นไป)

No.	Guidelines	Year	Recommendations
1	NCCN guidelines[4]	2011	✓
2	EORTC guidelines[1]	2011	✓
3	Australian guidelines[5]	2011	?
4	ESMO guidelines[6, 7]	2005 - 2007	✓
5	Japanese guidelines[8]	2004	✓
6	Micromedex®[9]	2011	✓
7	Uptodate 19.3®[10]	2011	✓
8	BCSH guidelines[11]	2008	✗
9	SIGN 80 (lung cancer)[12]	2005	✗
10	IDSA guidelines[13]	2010	✗

Note: ✓ Recommend to use in selected patients

✗ Recommend not to use routinely

? No comment on therapeutic febrile neutropenia

3. นิยามของคำว่า febrile neutropenia

ตารางที่ 2: นิยามของ febrile neutropenia จากแหล่งข้อมูลต่างๆ

No.	Guidelines	Year	Definition
1	NCCN guidelines[2]	2012	Febrile neutropenia is defined as, single temperature: ≥ **38.3°C orally** or ≥ **38.0°C over 1 h**; neutropenia: < 500 neutrophils/mcL or < 1,000 neutrophils/mcL and a predicted decline to ≤ 500/mcL over the next 48 h.
2	EORTC guidelines[1]	2011	Febrile neutropenia is defined as an absolute neutrophil count (ANC) of <0.5 x 10^9/L, or <1.0 x 10^9/L predicted to fall below 0.5 x 10^9/L within 48 h, with fever or clinical signs of sepsis.[26] Currently, the European Society for Medical Oncology (ESMO) defines fever in this setting as a rise in **axillary temperature to >38.5 °C sustained for at least one hour**.[26] It is suggested that therapy be initiated if a temperature of **>38.0 °C is present for at least 1 hour** or a reading of **>38.5 °C is obtained on a single occasion**.[27]
3	Australian guidelines[5]	2011	For the purposes of these guidelines, neutropenic fever is defined as fever of at least **38.3°C** (or at least 38.0°C on two occasions) in the setting of an absolute neutrophil count less than 0.5 x 10^9 cells/L, or with or less than 1.0 x 10^9 cells/L and predicted fall to lower than 0.5 x 10^9 cells/L.

No.	Guidelines	Year	Definition
4	ESMO guidelines[6, 7]	2005 -2007	Febrile neutropenia is defined as a rise in axillary temperature to above **38.5 °C for more than 1 h** while having an absolute neutrophil count (ANC) <0.5_10^9/l.
5	Japanese guidelines[8]	2004	1. Fever: A single axillary temperature of **≥37.5°C** or a single oral temperature of **≥38.0°C** 2. Neutropenia: A neutrophil count of <1000 cells/μL with a predicted decline to <500/μL
6	Uptodate 19.3®[10]	2011	Neutropenia — Although definitions are variable from institution to institution, neutropenia is defined as an absolute neutrophil count (ANC) of <500 cells/microL, or an ANC that is expected to decrease to <500 cells/microL within the next 48 hours [3]. Profound neutropenia is defined as an ANC <100 cells/microL. Fever — Fever in a neutropenic patient is usually defined as a single temperature **>38.3ºC (101.3ºF)** or a temperature **>38ºC (100.4ºF) sustained for more than one hour** [3]. However, infection can occur in neutropenic patients and other immunocompromised patients in the absence of fever. This occurs more often in elderly patients and those receiving corticosteroids. Presenting signs of infection in such patients may include hypothermia, hypotension, confusion, or clinical deterioration.
7	IDSA guidelines[13]	2010	¤ *Fever* Fever is defined as a single oral temperature measurement of **≥38.3°C (101°F)** or a temperature of **≥38.0°C (100.4°F) sustained over a 1-h period**. Use of axillary temperatures is discouraged, because they may not accurately reflect core body temperature. Rectal temperature measurements (and rectal examinations) are avoided during neutropenia to prevent colonizing gut organisms from entering the surrounding mucosa and soft tissues. ¤ *Neutropenia* Neutropenia is defined as an ANC of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 h. The term ‘‘profound’’ is sometimes used to describe neutropenia in which the ANC is <100 cells/mm^3; a manual reading of the blood smear is required to confirm this degree of neutropenia.

4. การระบุสูตรยาเคมีบำบัดที่มีความเสี่ยงต่อการเกิด febrile neutropenia

คณะอนุกรรมการฯ ได้พิจารณาแนวทางจาก 2 แหล่ง ได้แก่ NCCN® guidelines 2012 และ EORTC guidelines 2011 และมีความเห็นว่า การระบุสูตรยาเคมีบำบัดที่เสี่ยงต่อการเกิด febrile neutropenia นั้นไม่จำเป็นต้องมี เนื่องจากสูตรยามีความหลากหลาย บางสูตรเกี่ยวข้องกับยานอกบัญชี ส่วนใหญ่แพทย์ผู้ทำการรักษาจะทราบอยู่แล้ว อีกทั้งการระบุสูตรยาอาจกลายเป็นข้อจำกัดอีกด้วย

5. ราคายาและค่าใช้จ่ายในการใช้ G-CSF เพื่อป้องกัน febrile neutropenia

ตารางที่ 3 ราคายาและค่าใช้จ่ายในการใช้ G-CSF เพื่อป้องกัน febrile neutropenia

No.	Drugs	Tradename	Preparation	Price list	Propose	%diff price list	%diff DMSIC	Cost
1	filgrastim	Neupogen 30 MU	sterile sol 300 mcg/1 Pre-filled syringe (1 vial)	3,236.75	1,819.00	43.80	-49.75	25,466.00
2	filgrastim	Jilifen	sterile sol 300 mcg/1 ml (5 vials x 1.2 ml)	2,000.00	1,000.00	50.00	n/a	14,000.00
3	filgrastim	Filgen	sterile sol 300 mcg/1 Pre-filled syringe (1 vial)	1,500.00	1,500.00	-	-33.26	21,000.00
4	filgrastim	Filgen	sterile sol 300 mcg/1 vial (1 vial)	1,400.00	1,400.00	-	-62.64	19,600.00
5	filgrastim	Gran	sterile sol 300 mcg/1 Pre-filled syringe (1 vial)	n/a	n/a	n/a	n/a	n/a
6	filgrastim	Filgrastim Injection PFS 300 mcg	sterile sol 300 mcg/1 vial	n/a	n/a	n/a	n/a	n/a
7	filgrastim	Neocyte 300 mcg/mL Injection	sterile sol 300 mcg/1 vial	n/a	n/a	n/a	n/a	n/a
8	filgrastim	Neutromax	sterile sol 300 mcg/1 vial (1 vial)	n/a	n/a	n/a	n/a	n/a
9	filgrastim	Neupogen 48 MU	sterile sol 480 mcg/1 Pre-filled syringe	6,870.47	4,280.00	37.70	n/a	37,450.00
10	filgrastim	Filgen	sterile sol 480 mcg/1 vial (1 vial)	2,000.00	2,000.00	-	n/a	17,500.00
11	filgrastim	Neukine 300 mcg/1.0 mL	sterile sol 300 mcg/1 vial (1 vial)	1,391.00	1,177.00	15.38	n/a	16,478.00
12	filgrastim	Neutromax	sterile sol 480 mcg/1 vial (1 vial)	n/a	n/a	n/a	n/a	n/a
13	lenograstim	Granocyte Injection 100 mcg	injection 100 mcg/1 vial (1 vial)	1,284.00	1,070.00	16.67	8.16	17,976.00
14	lenograstim	Granocyte Injection 250 mcg	injection 250 mcg/1 vial (1 vial)	1,819.00	1,498.00	17.65	19.31	10,066.56
15	pegfilgrastim	Neulastim	6 MG /0.6ML Pre-Filled syringe (1 vial)	25,086.15	13,910.00	44.55	-3.67	13,910.00
16	pegfilgrastim	Peglasta	injection 5 mg/1ml	n/a	n/a	n/a	n/a	n/a

Note:

1) **filgrastim** = 5mcg/kg/day * 14 days (In a randomized, open-label study, a 5 microgram/kilogram (mcg/kg) subcutaneous injection once daily was equivalent in efficacy to a 10 mcg/kg/day continuous subcutaneous infusion, each given for a median of 14 days. The study sample consisted of 86 patients who underwent autologous bone marrow transplantation for Hodgkin's disease or non-Hodgkin's lymphoma. Median time to neutrophil recovery was 11 days in both groups. The incidence of fever and documented infection did not differ between dosages (Stahel et al, 1997).)

2) **lenograstim** = 2mcg/kg/day * 14days (A lenograstim dosage of 2 micrograms/kilogram (mcg/kg)/day subcutaneously or 5 mcg/kg/day were equally efficacious in attenuating neutropenia and reducing the number of days admitted to a hospital for fever in patients receiving chemotherapy. The 2 mcg/kg dose was also more cost effective. In this randomized, crossover trial, lenograstim was started the day after chemotherapy ended and was continued for 14 days or until the post-nadir absolute neutrophil count (ANC) exceeded 10 x 10(9)/liter (L). Bone pain was the most commonly reported adverse event (Toner et al, 1998))

3) **pegfilgrastim** = 1 (For the prevention of febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs, the recommended pegfilgrastim dose is 6 mg subcutaneously once per chemotherapy cycle. The use of pegfilgrastim in the period between 14 days before and 24 hours after chemotherapy is not recommended (Prod Info Neulasta(R) subcutaneous injection, 2010))

6. **รายละเอียดการสืบค้น** guidelines (25/01/2012)

Guidelines searching

6.1 Pubmed

Keywords: (("Neutropenia"[Mesh] AND "Fever"[Mesh]) AND "Granulocyte Colony-Stimulating Factor"[Mesh]) AND "Guideline"[Publication Type])

Results = 7

Related = (NCCN guidelines 2, ESMO guidelines 2)

6.1.1) NCCN guidelines[4]

ในการใช้ G-CSF เพื่อรักษาผู้ป่วยมะเร็งที่มี febrile neutropenia มีแนวทางการใช้ยาดังนี้

Present with febrile neutropenia[1] → Patients who did not receive prophylactic CSF

→ Risk factors not present[2] for an infection-associated complication → No CSF

→ Risk factors present for an infection-associated complication → Consider CSF[3]

Patient risk factors for poor clinical outcomes or for developing infection-associated complications

- Sepsis syndrome
- Age > 65 year
- Severe neutropenia (absolute neutrophil count < 100/mcL)
- Neutropenia expected to be more than 10 days in duration
- Pneumonia
- Invasive fungal infection
- Other clinically documented infections
- Hospitalization at the time of fever
- Prior episode of febrile neutropenia

[1] Febrile neutropenia is defined as, single temperature: ≥ 38°C orally or ≥ 38°C over 1 h; neutropenia: < 500 neutrophils/mcL or < 1,000 neutrophils and a predicted decline to ≤ 500 mcL over the next 48 h.

[2] See Patient Risk Factors for Poor Clinical Outcomes or for Developing Infection-Associated Complications (MGF-E).

[3] See discussion for further detail. There is no data on pegfilgrastim in therapeutic setting. Either filgrastim or sargramostim should be used with initial dosing as outlined on Myeloid Growth Factors for Prophylaxis and Treatment of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-C) and discontinued at time of neutrophil recovery.

(There is category 1 evidence for G-CSF for a reduction of: risk of febrile neutropenia, hospitalization, intravenous antibiotics during the course of therapy. There is category 2A evidence for G-CSF for a reduction in infection related mortality during the course of treatment. [See discussion for further detail])

6.1.2) EORTC 2011[1]

กรณี febrile neutropenia แนะนำให้ใช้ G-CSF รักษาในผู้ป่วยบางราย

In contrast, a recent level I evidence meta-analysis of 12 trials using standard therapy in adult patients with lymphoma and solid tumours showed a significant benefit in adding G-CSF. This study indicated that infection-related mortality was reduced from 2.8% to 1.5% by G-CSF support (RR 0.55; 95% CI 0.34, 0.90; P = 0.018).223 The clinical relevance of the absolute risk reductions seen with G-CSF support in these studies remains to be determined.

Most clinical studies show that infection-related mortality rate in the control groups was low, resulting in a lack of power to detect a treatment effect.

As mortality is generally very low in clinical trials of patients with early disease, more informative data might be obtained if the impact of G-CSF prophylaxis or treatment on infection-related mortality rates were to be examined in a 'real-life' setting. These findings and our recommendations are similar to those of ASCO,74 and we continue to recommend that "G-CSF should not be used routinely as adjunct therapy for the treatment of uncomplicated fever and neutropenia, but may be considered in patients who are at a higher risk of infection-related complications and have prognostic factors that are predictive of poor clinical outcome."

6.1.3) Australian guidelines 2011[5]

ไม่พบข้อมูลที่ระบุชัดเจนว่าแนะนำหรือไม่แนะนำการใช้ G-CSF

Special Issue: Australian consensus guidelines for the management of neutropenic fever in adult cancer patients

Int Med J Volume 41, Issue 1b Pages 75–137

6.1.4) ESMO guidelines 2005 และ 2007[6, 7]

แนะนำให้ใช้ G-CSF เพื่อรักษาผู้ป่วย febrile neutropenia บางราย

- Febrile neutropenia (General) กรณีนี้ไม่แนะนำให้ใช้
- High risk febrile neutropenia (Protracted FNP (>7 days) - Hypotension, sepsis, pneumonia, cellulitis or fungal infection) กรณีนี้แนะนำให้ใช้

ต่อมาได้ออก ESMO guidelines 2007 เนื้อหาคงเดิม แต่ตัด cellulitis ออก

6.1.5) Japanese guidelines 2004[8]

แนะนำให้ใช้ G-CSF เพื่อรักษาผู้ป่วย febrile neutropenia บางราย

G-CSF

1. Use of G-CSFs are considered if the patient remains febrile while taking antibiotics, has a documented infection, or is in a poor condition, or if neutropenia is predicted to persist for >10 days. G-CSF therapy can be withheld for patients who remain in a good, low-risk condition and whose neutrophil count is predicted to recover in 1 week.

2. For patients with acute myelogenous leukemia, control of the disease activity must be achieved with antileukemic agents.

6.2 Micromedex®[9]

แนะนำให้ใช้ G-CSF เพื่อรักษาผู้ป่วย febrile neutropenia บางราย

Keywords: Febrile neutropenia

DISEASEDEX™ Emergency Medicine Clinical Review

Colony Stimulating Factors

Colony-stimulating factors (CSFs) are not routinely recommended as adjunctive therapy to antimicrobials in patients with febrile neutropenia [1]. However, CSFs should be considered under certain conditions, including severe neutropenia (less than 0.1 x 10^9/L) that is expected to last more than 10 days, pneumonia, invasive fungal infections, multiorgan dysfunction due to sepsis, uncontrolled primary disease, hypotension, onset of fever while hospitalized, and in patients over 65 years of age [12].

Prophylactic use of CSFs during chemotherapy induction is recommended for selected patients considered to be at high risk for febrile neutropenia. Risk factors to consider include the myelotoxicity of the chemotherapeutic regimen, the patient's age and medical history, and the nature of the underlying malignancy[12]. CSFs are recommended when the risk of developing febrile neutropenia is calculated at 20% or higher [1].

6.3 Uptodate 19.3®[10]

แนะนำให้ใช้ G-CSF เพื่อรักษาผู้ป่วย febrile neutropenia บางราย

SUMMARY AND RECOMMENDATIONS — Granulocyte colony stimulating factors (CSFs) have been widely evaluated to minimize the extent and duration of neutropenia associated with intensive cytotoxic chemotherapy or radiation therapy (RT). Despite their effects on neutropenia, prophylactic use of granulocyte CSFs has not been shown to have an impact on survival in most clinical situations.

Patients with neutropenia

- There is no established role for granulocyte CSFs in afebrile patients who have already developed severe neutropenia after chemotherapy, and we recommend against their use in this setting (Grade 1B). (See 'Neutropenia without fever' above.)
- We suggest not using granulocyte CSFs routinely as an adjunct to antibiotics for most patients with established fever and neutropenia (Grade 2B). However, CSF's can be a useful adjunct for patients who remain neutropenic and febrile after the initiation of antibiotics. Consistent with guidelines from the American Society of Clinical Oncology (ASCO), we restrict use of CSFs to patients at high risk for infection-associated complications or who have prognostic factors that are predictive of a poor clinical outcome. High-risk features include expected prolonged (>10 day) or profound (<100 cells/microL) neutropenia, age >65, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever. (See 'Neutropenic fever' above.)

Grade 1B recommendation

A Grade 1B recommendation is a strong recommendation, and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

Explanation:

A Grade 1 recommendation is a strong recommendation. It means that we believe that if you follow the recommendation, you will be doing more good than harm for most, if not all of your patients.

Grade B means that the best estimates of the critical benefits and risks come from randomized, controlled trials with important limitations (eg, inconsistent results, methodologic flaws, imprecise results, extrapolation from a different population or setting) or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimates of benefit and risk, and may change the estimates.

Grade 2B recommendation

A Grade 2B recommendation is a weak recommendation; alternative approaches may be better for some patients under some circumstances.

Explanation:

A Grade 2 recommendation is a weak recommendation. It means "this is our suggestion, but you may want to think about it." It is unlikely that you should follow the suggested approach in all your patients, and you might reasonably choose an alternative approach. For Grade 2 recommendations, benefits and risks may be finely balanced, or the benefits and risks may be uncertain. In deciding whether to follow a Grade

2 recommendation in an individual patient, you may want to think about your patient's values and preferences or about your patient's risk aversion.

Grade B means that the best estimates of the critical benefits and risks come from randomized, controlled trials with important limitations (eg, inconsistent results, methodologic flaws, imprecise results, extrapolation from a different population or setting) or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimates of benefit and risk, and may change the estimates.

6.4 NICE ไม่พบข้อมูล

6.5 NHS (https://www.evidence.nhs.uk/)

Keywords = febrile neutropenia granulocyte colony stimulating factor

Results = 211

HTA = 45

Guidelines = 22 → related 2

6.5.1) Guidelines on the management of invasive fungal infection during therapy for haematological malignancy[11]

British Committee for Standards in Haematology 2008

5 GROWTH FACTORS

A single arm study of recombinant M-CSF in 24 SCT patients with IFI reported a survival of 27% compared to 5% in historical controls (Neumanitis 1991) but this advantage was not confirmed in a subsequent placebo-controlled RCT of prophylactic molgrastim (GM-CSF) in allogeneic SCT patients (Neumanitis 1995). In a prospective RCT of filgrastim (G-CSF) versus no growth factor during intensive consolidation chemotherapy for AML the only benefit for IFI was a significant reduced of the median duration of antifungal therapy but no reduction in documented IFIs (Harousseau et al 2000).

Recommendation

Current evidence does not support use of growth factors as either prophylaxis or supportive therapy of IFI (grade B, level III)

CLASSIFICATION OF EVIDENCE LEVELS (AHCPR)

1. a. Evidence obtained from meta-analysisof randomisedcontrolled trials.
   b. Evidence obtained from at least one randomisedcontrolled trial
2. a. Evidence obtained from at least one well-designed controlled study without randomisation.

b. Evidence obtained from at least one other type of well-designed quasi-experimental study. *

3. Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
4. Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

STRENGTH OF RECOMMENDATION:

A. Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation.
(Evidence levels Ia, Ib).

B. Requires the availability of well conducted clinical studies but no randomisedclinical trials on the topic of recommendation.
(Evidence levels IIa, IIb, III).

C. Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality
(Evidence level IV).

6.5.2) Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients – BCSH and BTS Guidelines[14]

British Journal of Haematology 2010, 149, 693–705

Supportive care

Significant treatment-related morbidity and mortality has been described in patients with PTLD treated with combination chemotherapy, with up to 50% mortality from infection reported. Recent reports incorporating the use of prophylactic granulocyte colony-stimulating factor (G-CSF) and/or prophylactic antibiotics have shown death from infection rates during chemotherapy from 0–30% with chemotherapy. American Society of Clinical Oncology (ASCO) guidance for the use of colony stimulating factors suggests primary prophylaxis in patients with high risk of febrile neutropenia based on coexisting medical problems (Smith et al, 2006). Therefore, it would seem appropriate to use G-SCF as primary prophylaxis in this patient group.

Given the degree of immunosuppression in patients with PTLD, consideration should be given to antibiotic, antifungal and antiviral prophylaxis during therapy, particularly if treatment is associated with neutropenia. Drugs to consider include ciprofloxacin, triazole antifungal drugs and aciclovir.

Some physicians may wish to consider the use of co-trimoxazole prophylaxis in patients with a past history or perceived susceptibility to Pneumocystis jeroveci pneumonia (PCP). Surveillance for cytomegalovirus (CMV) infections should continue to occur in patients with PTLD although initiation of surveillance because the patient has developed PTLD does not seem warranted. Patients with chronic viral infections require special consideration.

Patients with past hepatitis B or C infection should be managed in conjunction with a hepatologist. Those with hepatitis B should receive at least lamivudine prophylaxis starting 1 week before immuno-chemotherapy and for up to a year following completion of chemotherapy to reduce the risk of hepatitis flare. Regular monitoring of liver function is required through treatment, and monitoring of hepatitis Bviral load should be considered.

Patients with HIV infection should be managed under joint care with their HIV physician. The advent of highly active antiretroviral therapy (HAART) has made chemotherapy much more tolerable in the HIV infected non-transplant population with lymphoma.

Recommendation

• Prophylactic GCSF and anti infective agents are recommended for patients receiving chemotherapy (Grade C, level 4).

Table I. Classification of evidence levels.

I.	a. Evidence obtained from meta-analysis of randomized controlled trials
	b. Evidence obtained from at least one randomized controlled trial
II.	a. Evidence obtained from at least one well-designed controlled study without randomization
	b. Evidence obtained from at least one other type of well-designed quasi-experimental study*
III.	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV.	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

*Refers to a situation in which implementation of an intervention is out with the control of the investigators, but an opportunity exists to evaluate its effect.

Table II. Classification of grades of recommendations.

A.	Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation. (Evidence levels Ia, Ib)
B.	Requires the availability of well conducted clinical studies but no randomized clinical trials on the topic of recommendation. (Evidence levels IIa, IIb, III)
C.	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

6.6 SIGN

6.1.1) SIGN 80, Lung Cancer[12]

8.3 REDUCING TOXICITY IN NSCLC AND SCLC

In one systematic review of 65 trials, the use of a haematopoietic growth factor did not improve overall survival, but did increase the rate of recovery from chemotherapy and may have reduced the number of infective episodes.250 A second systematic review of 12 studies with 2,107 patients did not support the use of growth factors to support chemotherapy in SCLC.251 In an RCT with 300 patients, granulocyte-macrophage colony-stimulating factor (GMCSF) had no effect on the ability to deliver higher dose intensities of chemotherapy nor did it reduce the rate of infectious complications.252

A The routine use of growth factors in supporting patients during chemotherapy is not recommended. (1+)

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1++ High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias

1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

1 - Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias2++ High quality systematic reviews of case control or cohort studies

High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2 - Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3 Non-analytic studies, eg case reports, case series

4 Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++

and directly applicable to the target population*; or*

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results*; or*

Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results*; or*

Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4*; or*

Extrapolated evidence from studies rated as 2+

6.7 Others

6.7.1) The Infectious Disease Society of America guidelines 2010 [CID 2011:52][13]

ไม่แนะนำให้ใช้ G-CSF ในผู้ป่วย febrile neutropenia ทั่วไป

X. What Is the Role of Hematopoietic Growth Factors (G-CSF or GM-CSF) in Managing Fever and Neutropenia?

Recommendations

41. Prophylactic use of myeloid colony-stimulating factors (CSFs; also referred to as hematopoietic growth factors) should be considered for patients in whom the anticipated risk of fever and neutropenia is >20% (A-II).

42. CSFs are not generally recommended for treatment of established fever and neutropenia (B-II).

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