Recommendations for the Use of White Blood Cell Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update

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## Clinical Question 1, Primary Prophylaxis

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<tr>
<td>NCCN 2014¹</td>
<td>Guideline</td>
<td>To provide guidelines on the use of myeloid growth factors.</td>
<td>Primarily addresses adult patients with solid tumors and non-myeloid malignancies</td>
<td></td>
<td>Process starts with risk assessment. Consider disease type, chemotherapy regimen, patient risk factors, and treatment intent. Recommends prophylactic CSF if FN risk is ≥20%.</td>
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<td>Vehreschild 2014²</td>
<td>Guideline</td>
<td>To provide evidence-based recommendations for the use of G-CSF, pegylated G-CSF, and biosimilars to prevent infectious complications in cancer patients undergoing chemotherapy, including those with hematological malignancies</td>
<td>Comprehensive literature search and expert panel consensus</td>
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<td>Confirmed many key recommendations given by international guidelines. Evidence for growth factors during acute myeloid leukemia induction chemotherapy and pegfilgrastim use in hematological malignancies was rated lower compared with other guidelines.</td>
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| Lyman 2013^4      | Meta-analysis    | To provide a systematic review and evidence summary of the impact of G-CSF support on chemotherapy dose intensity and overall mortality. | 59 RCTs with 61 separate comparisons. Considered studies of cancer patients receiving conventional dose chemotherapy for solid tumors or malignant lymphoma and randomized to primary G-CSF support in one arm versus a control group without initial G-CSF. | RR for mortality  
Group 1 (same dose and schedule of chemotherapy):  
RR=0.96, 95% CI 0.92 to 1.01  
Group 2 (dose-dense chemotherapy in one arm):  
RR=0.89, 95% CI 0.85 to 0.94  
Group 3 (dose-escalated chemotherapy in one arm):  
RR=0.92, 95% CI 0.85-0.99  
Group 4 (substitution or addition of a drug in one arm):  
RR=0.94, 95% CI 0.89-0.99  
Overall:  
RR=0.93, 95% CI 0.90-0.96 | All-cause mortality is reduced in patients receiving chemotherapy with primary G-CSF support. The greatest impact was observed in RCTs in patients receiving dose-dense schedules |
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| Kirshner 2012⁴ | RCT | To assess an intervention for pegfilgrastim-induced bone pain. | **Study population:** adults with a diagnosis of nonmyeloid cancer, scheduled for their first dose of pegfilgrastim on day 2, 3, or 4 of their chemotherapy cycle  
**Intervention:** Naproxen vs placebo in patients receiving pegfilgrastim. Naproxen (500 mg two times per day) on the day of pegfilgrastim and continuing for 5 to 8 days after pegfilgrastim  
**Sample size:** Arm 1: 257  
Arm 2: 253 | Mean AUC for pain  
Naproxen: 6.04  
Placebo: 7.71  
p=0.037  
Maximum pain  
Naproxen: 2.59  
Placebo: 3.40  
p=0.005  
Overall pain incidence  
Naproxen: 61.1%  
Placebo: 71.3%  
p=0.020  
Pain duration  
Naproxen: 1.92 days  
Placebo: 2.40 days  
p=0.009  
Severe pain incidence  
Naproxen: 19.2%  
Placebo: 27.0%  
p=0.048 | Naproxen at a dose of 500 mg twice per day is effective in reducing the incidence and severity of pegfilgrastim-induced bone pain. |
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| Renner 2012⁵ | Meta-analysis    | To assess the effect of prophylactic colony-stimulating factors (CSFs) in reducing the incidence and duration of FN, and all-cause and infection-related mortality during chemotherapy in patients with breast cancer | Selected RCTs comparing CSFs (any dose) with placebo or no treatment in patients with breast cancer at any stage, at risk of developing FN while undergoing any type of chemotherapy. Included eight RCTs, involving 2156 participants, carried out between 1995 and 2008. | Proportion of patients with FN: RR 0.27; 95% CI 0.11 to 0.70 (with heterogeneity)  
Infection-related mortality:  
RR 0.14; 95% CI 0.02 to 1.29  
Risk for hospitalization:  
RR 0.14; 95% CI 0.06 to 0.30  
IV antibiotics:  
RR 0.35; 95% CI 0.22 to 0.55 | In patients with breast cancer receiving chemotherapy, CSFs have shown evidence of benefit in the prevention of FN. There is evidence, though less reliable, of a decrease of all-cause mortality during chemotherapy and a reduced need for hospital care. No reliable evidence was found for a reduction of infection-related mortality, a higher dose intensity of chemotherapy with CSFs or diminished rates of severe neutropenia and infections. The majority of adverse events reported from CSF use were bone pain and injection-site reactions but no conclusions could be drawn regarding late-term side effects. |
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<td>Aapro 2011°</td>
<td>Guideline</td>
<td>To update EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumors</td>
<td>Systematic literature review up to July 2009. Excluded studies of children, cost analyses, studies of leukemia.</td>
<td>Recommends that patient-related adverse risk factors, such as elderly age (≥65 years) and neutrophil count be evaluated in the overall assessment of FN risk before administering each cycle of chemotherapy. It is important that after a previous episode of FN, patients receive prophylactic administration of G-CSF in subsequent cycles. Prophylactic G-CSF continues to be recommended in patients receiving a chemotherapy regimen with high risk of FN. When using a chemotherapy regimen associated with FN in 10-20% of patients, particular attention should be given to patient-related risk factors that may increase the overall risk of FN. In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF support is recommended. Similarly, if reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis may be used to maintain chemotherapy. Clinical evidence shows that filgrastim, lenograstim and pegfilgrastim have clinical efficacy and we recommend the use of any of these agents to prevent FN and FN-related complications where indicated. Filgrastim biosimilars are also approved for use in Europe.</td>
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<td>Cooper 20117</td>
<td>Meta-analysis</td>
<td>To assessed the effectiveness of G-CSFs pegfilgrastim, filgrastim or lenograstim) in reducing FN incidence in adults undergoing chemotherapy for solid tumors or lymphoma.</td>
<td>Assessed 20 studies of primary G-CSF prophylaxis with no primary G-CSF prophylaxis: five studies of pegfilgrastim; ten of filgrastim; and five of lenograstim. Five studies compared pegfilgrastim with filgrastim</td>
<td>Reduction in FN incidence with primary versus no primary G-CSF Pegfilgrastim: RR 0.30, 95% CI 0.14 to 0.65 Filgrastim: RR 0.57, 95% 0.48 to 0.69 Lenograstim: RR 0.62, 95% CI 0.44 to 0.88 Pegfilgrastim vs filgrastim RR 0.66, 95% CI 0.44 to 0.98</td>
<td>Primary prophylaxis with G-CSFs significantly reduces FN incidence in adults undergoing chemotherapy for solid tumors or lymphoma. Pegfilgrastim reduces FN incidence to a significantly greater extent than filgrastim.</td>
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| Kuderer 2011⁸ | Meta-analysis   | To assess primary prophylaxis with G-CSF in adults with a solid tumor or malignant lymphoma | 17 RCTs | Febrile neutropenia  
G-CSF: 22.4%  
Control: 39.5%  
RR=0.54, 95% CI 0.43 to 0.67  
Infection-related mortality  
G-CSF: 1.5%  
Control: 2.8%  
RR=0.55, 95% CI 0.34-0.90  
Early all-cause mortality  
G-CSF: 3.4%  
Control: 5.7%  
RR=0.60, 95% CI 0.43-0.83  
Relative dose intensity  
G-CSF: median 95.5%  
Control: median 88.5%  
Bone and musculoskeletal pain  
G-CSF: 19.6%  
Control: 10.4%  
RR=4.02, 95% CI 1.56-7.52 | Confirmed that primary prophylaxis with G-CSF significantly reduces the risk of FN in patients undergoing conventional chemotherapy across a broad range of baseline risk.  
There was a reduction in infection-related and all-cause early mortality in patients randomized to receive primary prophylaxis with G-CSF. |
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<td>Wildiers 2011&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Systematic review</td>
<td>To help define the impact of relative dose intensity (RDI) and the role of growth factor support on outcomes in breast cancer and aggressive non-Hodgkin's lymphoma</td>
<td>English-language publications between 1995 and 2008 evaluating standard 3- or 4-weekly chemotherapy regimens. 30 breast cancer studies and 15 lymphoma studies.</td>
<td>Many breast cancer patients do not achieve planned RDI. Older age, obesity and febrile neutropenia are associated with reduced RDI, which leads to worse survival in several studies, particularly those including anthracyclines. G-CSF prophylaxis improved RDI in most, but not all, studies.</td>
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<td>Lyman 2010&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td>To evaluate the risk of acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and overall mortality in patients receiving chemotherapy with or without G-CSF</td>
<td>Searched through October 2008. Eligibility included solid tumor or lymphoma patients randomly assigned to chemotherapy with or without G-CSF support, &gt; or = 2 years of follow-up, and reporting AML/MDS or all second malignancies. In the 25 eligible RCTs, 6,058 and 6,746 patients were randomly assigned to receive chemotherapy with and without initial G-CSF support, respectively.</td>
<td>The RR for all-cause mortality associated with G-CSF was 0.897 (95% CI, 0.857 to 0.938) Greater RR reduction for mortality was seen for both larger studies (P = .05) and greater chemotherapy dose-intensity (P = .012). RR for AML/MDS associated with G-CSF support was 1.92 (95% CI, 1.19 to 3.07) The AR increase of AML/MDS among patients randomly assigned to G-CSF was four per 1,000 patients (AR 0.41%; 95% CI, 0.10% to 0.72%) Delivered chemotherapy dose-intensity and risk of AML/MDS are increased but all-cause mortality is decreased in patients receiving chemotherapy with G-CSF support. Greater reductions in mortality were observed with greater chemotherapy dose-intensity.</td>
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<td>Herbst 2009(^1)</td>
<td>Systematic review</td>
<td>To compare prophylactic antibiotics or G(M)-CSF for the prevention of infections and improvement of survival in cancer patients undergoing chemotherapy</td>
<td>Randomized controlled trials comparing prophylaxis with G-CSF or GM-CSF versus antibiotics in cancer patients of all ages receiving chemotherapy or bone marrow or stem cell transplantation were included for review. Both study arms had to receive identical chemotherapy regimens and other supportive care. Search 1980-2007 Two studies were included (total of 195 patients)</td>
<td>Both trials showed non-significant results favoring antibiotics for the prevention of fever or hospitalization for febrile neutropenia.</td>
<td>There is no evidence for or against antibiotics compared to G(M)-CSFs for the prevention of infections in cancer patients</td>
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<td>Bohlius 2008&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td>To assess whether G-CSF and GM-CSF improve dose intensity, tumor response, and overall survival in patients with malignant lymphoma</td>
<td>Searched January 1980-April 2008 Randomized controlled trials comparing prophylaxis with G-CSF or GM-CSF versus placebo/no prophylaxis in adult patients with malignant lymphoma undergoing chemotherapy were included for review. Both study arms had to receive identical chemotherapy and supportive care Included 13 RCTs with a total of 2607 patients.</td>
<td>G-CSF/GM-CSF versus no prophylaxis&lt;br&gt;Severe neutropenia: RR 0.67; 95% CI 0.60 to 0.73&lt;br&gt;Febrile neutropenia: RR 0.74; 95% CI 0.62 to 0.89&lt;br&gt;Infection: RR 0.74; 95% CI 0.64 to 0.85&lt;br&gt;Intravenous antibiotics: RR 0.82; 95% CI 0.57 to 1.18&lt;br&gt;Infection-related mortality: RR 0.93; 95% CI 0.51 to 1.71&lt;br&gt;OS: HR 0.97; 95% CI 0.87 to 1.09&lt;br&gt;Freedom from treatment failure: HR 1.11; 95% CI 0.91 to 1.35&lt;br&gt;Complete tumor response: RR 1.03; 95% CI 0.95 to 1.10</td>
<td>G-CSF and GM-CSF, when used as a prophylaxis in patients with malignant lymphoma undergoing conventional chemotherapy, reduce the risk of neutropenia, febrile neutropenia and infection. However, based on the randomized trials currently available, there is no evidence that either G-CSF or GM-CSF provide a significant advantage in terms of complete tumor response, FFTF or OS.</td>
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| Balducci 2007 | RCT            | To evaluate the incidence of febrile neutropenia and related events in elderly cancer patients receiving pegfilgrastim beginning with cycle 1 (proactive) in comparison with pegfilgrastim initiated after cycle 1 at the physician’s discretion reactive). | **Study population:** ≥65 years old with lung, breast, or ovarian cancer, or NHL  
**Intervention:** Pegfilgrastim beginning in cycle 1 (arm 1) versus pegfilgrastim administered after cycle 1 at physician’s discretion (arm 2)  
**Sample size:**  
Solid tumors  
Arm 1: 349  
Arm 2: 352  
NHL  
Arm 1: 75  
Arm 2: 76  
**s.c. injection of 6 mg pegfilgrastim once per cycle 24 hours after chemotherapy completion**  
**Sample size:**  
Solid tumors  
Arm 1: 349  
Arm 2: 352  
NHL  
Arm 1: 75  
Arm 2: 76  | Solid tumors, incidence of FN across all cycles  
Arm 1: 4%  
Arm 2: 10%  
p=0.001  
NHL, incidence of FN across all cycles  
Arm 1: 15%  
Arm 2: 37%  
p=0.004  
Solid tumors, grade 3 or 4 neutropenia across all cycles  
Arm 1: 30%  
Arm 2: 80%  
NHL, grade 3 or 4 neutropenia across all cycles  
Arm 1: 82%  
Arm 2: 90%  
Solid tumors, hospitalization across all cycles  
Arm 1: 5%  
Arm 2: 9%  
NHL, hospitalization across all cycles  
Arm 1: 17%  
Arm 2: 37%  
Solid tumors, dose delay across all cycles  
Arm 1: 16%  
Arm 2: 28%  
NHL, dose delay across all cycles  
Arm 1: 29%  
Arm 2: 23%  | Results, con’t  
Solid tumors, dose reduction across all cycles  
Arm 1: 7%  
Arm 2: 14%  
NHL, dose reduction across all cycles  
Arm 1: 16%  
Arm 2: 8%  
Bone pain, solid tumors  
Arm 1: 12%  
Arm 2: 5%  
Bone pain, NHL  
Arm 1: 9%  
Arm 2: 4%  
Proactive pegfilgrastim use effectively produced a lower incidence of febrile neutropenia and related events in elderly patients with either solid tumors or NHL receiving an array of mild to moderately neutropenic chemotherapy regimens. |
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<tr>
<td>Kuderer 2007&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td>To assess the impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy</td>
<td>Adult cancer patients receiving conventional-dose chemotherapy for solid tumors or malignant lymphoma and randomly assigned to primary G-CSF prophylaxis versus a placebo or untreated control group</td>
<td>Infection-related mortality Controls: 2.8% G-CSF: 1.5% RR=0.55, 95% CI, 0.34 to 0.90</td>
<td>Prophylactic G-CSF reduces the risk of FN and early deaths, including infection-related mortality, while increasing RDI and musculoskeletal pain. There are insufficient data to assess the impact of G-CSF on disease-free and overall survival</td>
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<td>FN Controls: 39.5% G-CSF: 22.4% RR=0.54, 95% CI 0.43 to 0.67</td>
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<td>Early mortality Control: 5.7% G-CSF: 3.4% RR=0.60, 95% CI 0.43 to 0.83</td>
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<td>Average RDI Controls: 86.7% G-CSF: 95.1%</td>
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<td>Average difference in RDI between study arms: 8.4% (p=0.001)</td>
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<td>Bone and musculoskeletal pain Controls: 10.4% G-CSF: 19.6% RR=4.02, 95% CI 2.16 to 7.52</td>
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<td>Sung 2007</td>
<td>Meta-analysis</td>
<td>To evaluate the benefits of prophylactic hematopoietic CSFs in adults and children receiving cancer chemotherapy or undergoing stem-cell transplantation (SCT)</td>
<td>Searched through 2006 or 2007 Selected 148 trials that were reported in any language that randomly assigned patients to CSFs or to either placebo or no therapy. Prophylactic CSFs were given concurrently with or after initiation of chemotherapy.</td>
<td>Infection-related mortality CSF: 3.1% Placebo/no treatment: 3.8% RR=0.82, 95% CI 0.66 to 1.02 Documented infections CSF: 38.9% Placebo/no treatment: 43.1% RR=0.85, 95% CI 0.79-0.92 FN CSF: 25.3% Placebo/no treatment: 44.2% RR=0.71, 95% CI 0.63 to 0.80 Short-term all-cause mortality CSF: 7.6% Placebo/no treatment: 8.0% RR=0.95, 95% CI 0.84 to 1.08 No interactions by age or population diagnosis group and CSF effect</td>
<td>Prophylactic CSFs may have little or no effect on mortality but do decrease rates of infection in patients receiving cancer chemotherapy or those undergoing SCT.</td>
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| Papaldo 2006<sup>16</sup> | RCT | To assess the effects of G-CSF on hemoglobin (Hb) value in early breast cancer patients receiving high-dose epirubicin and cyclophosphamide (EC) adjuvant treatment. | **Study population:** stage I or stage II female breast cancer patients  
**Intervention:** EC with G-CSF. EC: high-dose epirubicin and cyclophosphamide (120 mg/m2 and 600 mg/m2, respectively) on day 1 every 21 days.  
G-CSF given in one of five schedules:  
(1) 480 mcg sc days 8 to 14; (2) 480 mcg days 8, 10, 12, 14; (3) 300 mcg days 8 to 14; (4) 300 mcg days 8, 10, 12, and 14; and (5) 300 mcg days 8 and 12 | Grade 2 or worse anemia  
EC with G-CSF: 38.8%  
EC without G-CSF: 26.2%  
p=0.005  
No statistically significant difference in platelet count was observed between G-CSF and control arms. | Suggests that a G-CSF dose-related effect may play a role in worsening anemia in patients receiving adjuvant EC. |
**Clinical Question 2, Secondary Prophylaxis**

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<td>NCCN 2014†</td>
<td>Guideline</td>
<td>To provide guidelines on the use of myeloid growth factors.</td>
<td>Primarily addresses adult patients with solid tumors and non-myeloid malignancies</td>
<td>If the patient experienced a previous episode of FN or a dose-limiting neutropenic event, and the same chemo dose and schedule is planned for the current cycle, the patient is now in the high-risk group.</td>
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## Clinical Question 3, Therapeutic CSF

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| Mhaskar 2014¹⁷ | Meta-analysis    | To evaluate the safety and efficacy of adding G-CSF or GM-CSF to standard treatment (antibiotics) when treating chemotherapy-induced febrile neutropenia in individuals diagnosed with cancer. | Searched to March 2014 for randomized controlled trials (RCTs) that compared CSF plus antibiotics versus antibiotics alone for the treatment of chemotherapy-induced febrile neutropenia in adults and children. Included 14 RCTs (15 comparisons) including a total of 1553 participants. | Overall mortality: HR=0.74, 95% CI 0.47 to 1.16  
Infection-related mortality: HR 0.75, 95% CI 0.47 to 1.20  
Hospitalized for more than 10 days RR=0.65, 95% CI 0.44 to 0.95  
Duration of neutropenia Standardized mean difference (SMD)=-1.70, 95% CI -2.65 to -0.76 | The use of a CSF plus antibiotics in individuals with chemotherapy-induced febrile neutropenia had no effect on overall mortality, but reduced the amount of time participants spent in hospital and improved their ability to achieve neutrophil recovery. It was not clear whether CSF plus antibiotics had an effect on infection-related mortality. Participants receiving CSFs had shorter duration of neutropenia, faster recovery from fever and shorter duration of antibiotics use. |
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<tr>
<td>NCCN 2014‡</td>
<td>Guideline</td>
<td>To provide guidelines on the use of myeloid growth factors.</td>
<td>Primarily addresses adult patients with solid tumors and non-myeloid malignancies</td>
<td></td>
<td>If previous prophylaxis with filgrastim or sargramostim, continue. If previous prophylaxis with pegfilgrastim, do not treat with additional CSF. Only filgrastim or sargramostim should be administered in the therapeutic setting. If no previous prophylaxis, assess risk of poor outcome. Consider CSF if high risk.</td>
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| Budd 2014¹⁸  | RCT             | To determine the optimal dose and schedule of anthracycline and taxane administration as adjuvant therapy for early-stage breast cancer | **Study population:** male and female patients with high-risk pathologic stage I to III breast cancer | Log-rank test comparing all four arms simultaneously  
DFS: p=0.11  
OS: p=0.04  
DFS hazard ratios (relative to Arm 1)  
Arm 2: 1.32 (95% CI 1.04 to 1.68)  
Arm 3: 1.24 (95% CI 0.98 to 1.59)  
Arm 4: 1.12 (95% CI 0.87 to 1.44)  
OS hazard ratios (Arm 1 is reference group)  
Arm 2: 1.44 (95% CI 1.08 to 1.93)  
Arm 3: 1.46 (95% CI 1.09 to 1.95)  
Arm 4: 1.24 (95% CI 0.91 to 1.68)  
Toxicity was greater for doxorubicin-cyclophosphamide once every 2 weeks with regard to hemoglobin and leukocytes.  
Toxicity was higher for doxorubicin-cyclophosphamide with filgrastim for mucositis and dermatologic toxicity.  
More patients in the arms receiving doxorubicin-cyclophosphamide with filgrastim (11.0%) stopped doxorubicin-cyclophosphamide treatment early because of toxicity compared with those randomly assigned to the arms receiving doxorubicin-cyclophosphamide once every 2 weeks (7.9%; P = 0.006). | Patients achieved a similar DFS with any of these regimens. Subset analysis suggests the hypothesis that once-every-2-weeks dosing may be best for patients with hormone receptor–negative/HER2-negative tumors.  
Additional toxicity results:  
Grade 3 to 4 leukopenia and neutropenia were observed more commonly in patients treated with once-per-week paclitaxel, although the rate of neutropenic fever did not differ between the two schedules. Grade 3 to 4 allergic reactions, musculoskeletal pain, and neurologic toxicity were more commonly observed in patients treated with paclitaxel once every 2 weeks. |

**Interventions:**  
Arm 1: AC Q2 week x 6, Paclitaxel Q2 week × 6  
Arm 2: AC weekly x 15, Paclitaxel Q2 week × 6  
Arm 3: AC Q2 week x 6, Paclitaxel weekly × 12  
Arm 4: AC weekly x 15, Paclitaxel weekly × 12  
AC: doxorubicin-cyclophosphamide  
**Sample size:** 2716 randomly assigned in the original design.
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| Choueiri 2014 | Phase II         | To explore the efficacy and safety of neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) with pegfilgrastim support in muscle-invasive urothelial cancer (MIUC). | **Study population:** Muscle-invasive urothelial cancer. Clinical stage T2-T4a and <=N1 disease on imaging.  
**Intervention:** All patients treated with ddMVAC with G-CSF support 2 weeks per cycle with double the dose-intensity of cisplatin and doxorubicin, while reducing the dose of methotrexate and vinblastine by one third  
**Sample size:** 39 patients | No febrile neutropenia or treatment-related deaths  
95% completed all four cycles of chemotherapy.  
Pathologic response (PaR): 49%  
Patients who achieved PaR had a 1-year DFS of 89% compared with 67% for those patients who did not achieve PaR | In patients with MIUC, neoadjuvant ddMVAC was well tolerated and resulted in significant pathologic and radiologic downstaging. |
<p>| NCCN 2014    | Guideline        | To provide guidelines on the use of myeloid growth factors. | Primarily addresses adult patients with solid tumors and non-myeloid malignancies | Pegfilgrastim: there are phase II studies that demonstrate efficacy for chemotherapy regimens given every two weeks. Insufficient data for weekly chemotherapy regimens. |</p>
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| Hertzberg 2014<sup>20</sup> | RCT | To assess the effects of increasing dose intensity of chemotherapy for patients with aggressive NHL | **Study population:** Patients aged at least 16 years with previously untreated histologically confirmed aggressive NHL  
**Intervention:**  
High-dose CEOP (i-CEOP)  
6 cycles, 3-weekly. 
cyclophosphamide 1,500, 
epirubicin 150, vincristine 1.4 mg/m² all on day 1, and prednisolone 100 mg days 1-5. 
Filgrastim 5 mcg/kg/day sc, starting on day 2, until ANC >10 X 10⁹/L to a maximum of 14 days.  
Vs  
Standard-dose CEOP (s-CEOP)  
6 cycles, 3-weekly. 
cyclophosphamide 750, epirubicin 75, vincristine 1.4 mg/m² all on day 1, And prednisolone 100 mg days 1-5. 
Filgrastim was permitted following an episode of febrile neutropenia or in the event of neutropenia by Day 22.  
**Sample size:** 250 | FN  
i-CEOP: 70%  
s-CEOP: 26%  
CR or unconfirmed CR  
i-CEOP: 53%  
s-CEOP: 59%  
p=0.64  
5-yr OS  
i-CEOP: 56.7%  
s-CEOP: 55.1%  
p=0.80  
5-yr PFS  
i-CEOP: 41%  
s-CEOP: 43%  
p=0.73 | In the treatment of aggressive NHL in the pre-rituximab era, increasing DI did not result in improved outcomes, while at the same time lead to increased toxicity. |
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| Cunningham 2013<sup>21</sup> | RCT | To assess whether a benefit of dose intensification with CHOP every 2 weeks is apparent in the presence of rituximab (R-CHOP) in all age groups | **Study population:** aged 18 years and older with previously untreated, histologically confirmed, diffuse large B-cell lymphoma according to the WHO classification. Patients were required to have Ann Arbor bulky stage IA (tumor mass diameter >10 cm) or stage IB to IV disease.  
**Intervention:**  
R-CHOP-14 (with G-CSF). The recombinant human G-CSF lenograstim was administered on days 4 to 12 of each cycle.  
Vs  
R-CHOP-21 (with G-CSF at discretion of investigator)  
**Sample size:**  
R-CHOP-14 : 540  
R-CHOP-21 : 540 | Grade 3 or 4 neutropenia  
R-CHOP-14: 31%  
R-CHOP-21: 60%  
p<0.0001  
Grade 3 or 4 FN  
R-CHOP-14: 5%  
R-CHOP-21: 11%  
p=0.0007  
2-yr OS  
R-CHOP-14: 82.7%  
R-CHOP-21: 80.8%  
HR 0.90, 95% CI 0.70-1.15  
2-yr PFS  
R-CHOP-14: 75.4%  
R-CHOP-21: 74.8%  
HR 0.94, 95% CI 0.76-1.17 | R-CHOP-14 is not superior to R-CHOP-21 chemotherapy for previously untreated diffuse large B-cell lymphoma; therefore, R-CHOP-21 remains the standard first-line treatment in patients with this hematological malignancy. No molecular or clinical subgroup benefited from dose intensification in this study.  
Frequencies of non-hematological AEs were similar in the two groups. |
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| Delarue 2013 | RCT              | To ascertain if a dose-dense R-CHOP regimen administered every 2 weeks (R-CHOP14) was superior to the standard 3-week schedule (R-CHOP21). | **Study population:** Aged 60-80 years with untreated diffuse large B-cell lymphoma and at least one adverse prognostic factor  
**Intervention:**  
R-CHOP-14 (G-CSF decision made by treating doctor)  
R-CHOP-21 (G-CSF decision made by treating doctor)  
**Sample size:**  
R-CHOP-14 : 304  
R-CHOP-21 : 298 | Grade 3-4 neutropenia  
R-CHOP-14: 74%  
R-CHOP-21: 64%  
3-yr EFS  
R-CHOP-14: 56%  
R-CHOP-21: 60%  
HR 1.04, 95% CI 0.82-1.31  
3-yr OS  
R-CHOP-14: 69%  
R-CHOP-21: 72%  
HR 0.96, 95% CI 0.73-1.26  
In individuals who received eight planned treatment cycles: the median relative dose intensity for cyclophosphamide was 88% (IQR 79 to 93) in the R-CHOP14 group and 97% (93 to 99) in the R-CHOP21 group (p<0.0001); for doxorubicin, median relative dose intensity was 88% (78 to 94) and 96% (92 to 99), respectively (p<0.0001).  
RBC transfusion  
R-CHOP-14: 47%  
R-CHOP-21: 31%  
p=0.0001  
Platelet transfusion  
R-CHOP-14: 12%  
R-CHOP-21: 8%  
p=0.2156  
At least one serious adverse event  
R-CHOP-14: 51%  
R-CHOP-21: 47% | In elderly patients with untreated diffuse large B-cell lymphoma and at least one adverse prognostic factor, a 2-week dose-dense R-CHOP regimen did not improve efficacy compared with the 3-week standard schedule. The frequency of toxic side-effects was similar between regimens, but R-CHOP14 was associated with increased need for red-blood-cell transfusion |
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<td>Lyman 2013&lt;sup&gt;1&lt;/sup&gt; Meta-analysis</td>
<td>To provide a systematic review and evidence summary of the impact of G-CSF support on chemotherapy dose intensity and overall mortality.</td>
<td>RR for mortality Group 1 (same dose and schedule of chemotherapy): RR=0.96, 95% CI 0.92 to 1.01 Group 2 (dose-dense chemotherapy in one arm): RR=0.89, 95% CI 0.85 to 0.94 Group 3 (dose-escalated chemotherapy in one arm): RR=0.92, 95% CI 0.85-0.99 Group 4 (substitution or addition of a drug in one arm): RR=0.94, 95% CI 0.89-0.99 Overall: RR=0.93, 95% CI 0.90-0.96</td>
<td>All-cause mortality is reduced in patients receiving chemotherapy with primary G-CSF support. The greatest impact was observed in RCTs in patients receiving dose-dense schedules.</td>
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| Vriens 2013 | RCT             | To determine whether delivering neo-adjuvant chemotherapy at a higher dose in a shorter period of time improves outcome of breast cancer patients. | **Study population:** Women between the ages of 18 and 70, adequate performance status, primary tumor size of 3 cm or more and/or positive regional lymph nodes.  
**Intervention:** Neoadjuvant TAC with G-CSF.  
Six cycles of doxorubicin, cyclophosphamide, and docetaxel at doses of 75, 500, and 50 mg/m², respectively, every 3 weeks.  
Pegfilgrastim 6 mg was recommended as primary prophylaxis.  
Vs  
Neoadjuvant AC-T.  
Four 3-weekly cycles of doxorubicin and cyclophosphamide at a dose of 60 and 600 mg/m², respectively, followed by four 3-weekly cycles of docetaxel (100 mg/m²) | FN  
AC-T: 23%  
TAC: 9%  
pCR of the breast tumor  
AC-T: 21%  
TAC: 16%  
OR=1.44, 95% CI 0.67-3.10  
pCR in axillary nodes  
(along those with positive node(s) at start)  
AC-T: 32%  
TAC: 21%  
OR=1.77, 95% CI 0.74-4.25  
3-yr DFS  
AC-T: 88%  
TAC: 75%  
p=0.21  
3-yr OS  
AC-T: 94%  
TAC: 78%  
p=0.11 | With a higher cumulative dose for the concurrent arm, no differences were observed between the two treatment arms with respect to pCR rate. The differential toxicity profile could partly be explained by different use of primary G-CSF prophylaxis. |
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<td>Gogas 2012</td>
<td>RCT</td>
<td>To explore the impact of dose intensity (DI) in the adjuvant setting of breast cancer.</td>
<td>Study population: Breast cancer, pathological stage T(1-4)N(1-2)M0</td>
<td>5-year DFS: 74% in both study groups (p=0.78) 5-year OS: 86% with E-T-CMF, and 85% with ET-CMF (p=0.45)</td>
<td>No DFS or OS benefit from the dose-dense sequential epirubicin and paclitaxel was detected when compared to the concurrent administration of the same drugs. No additional safety issues were raised with long-term follow-up.</td>
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**Intervention:**
Dose-dense sequential epirubicin and paclitaxel (E-T-CMF). Three 14-day cycles of epirubicin 110 mg/m², followed by three 14-day cycles of paclitaxel 250 mg/m², and three 14-day cycles of intensified CMF. Each cycle supported by G-CSF days 2-10. Vs.
Concomitant epirubicin and paclitaxel (ET-CMF). Four 21-day cycles of combination of epirubicin at 83 mg/m² and paclitaxel at 187 mg/m² followed by three 14-day cycles of intensified CMF. G-CSF given during CMF.

**Sample size:** 1,121
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| Arun 2011   | RCT             | To compare the pathologic complete response (pCR) rate of patients treated FAC versus dose-intense FAC plus G-CSF in the neoadjuvant setting and to compare the delivered dose intensity, disease-free survival and overall survival times, and toxicity between treatment arms in patients with breast cancer. | **Study population:** Histologic diagnosis of breast cancer, stage IIA to IV (ipsilateral supraclavicular disease as the sole evidence of metastatic disease), aged 16 to 75 years, with no prior chemotherapy, radiation therapy, or definitive surgical therapy for breast cancer.  
**Intervention:**  
Neoadjuvant FAC. 5-FU, 500 mg/m²; doxorubicin, 50 mg/m²; cyclophosphamide, 500 mg/m²) every 21 days for four cycles  
Vs  
Neoadjuvant, dose-intense FAC plus G-CSF. 5-FU, 600 mg/m²; doxorubicin, 60 mg/m²; cyclophosphamide, 1,000 mg/m²) plus G-CSF every 18 days for four cycles.  
**Sample size:**  
FAC: 102  
FAC+G-CSF: 100. | pCR  
Arm 1 (FAC): 9.0%  
Arm 2 (FAC+G-CSF): 13.1%  
p=0.35  
Median neoadjuvant dose intensity (mg/m² per week) of doxorubicin  
Arm 1: 15.56  
Arm 2: 20.39  
p<0.0001  
5-yr OS  
Arm 1: 66.3%  
Arm 2: 66.6%  
p=0.61 | A higher delivered dose intensity of doxorubicin with the FAC + G-CSF regimen did not result in a statistically significant higher pCR rate. However, patients who achieved a pCR experienced longer DFS and OS times.  
There were statistically significantly higher rates of grade 3 and 4 neutropenia in the FAC arm. However, the rates of thrombocytopenia, febrile neutropenia, and infection were higher in the FAC plus G-CSF arm. More than half of the patients in the FAC plus G-CSF arm required packed RBC transfusions, compared with 5% of patients in the FAC arm. |
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<td>Ellis 2011**</td>
<td>RCT</td>
<td>To compare standard doxorubicin and cyclophosphamide versus weekly doxorubicin and daily oral cyclophosphamide plus granulocyte colony-stimulating factor as neoadjuvant therapy for inflammatory and locally advanced breast cancer</td>
<td><strong>Study population:</strong> Stage IIB, IIIA, or IIIB disease and candidates for neoadjuvant chemotherapy. <strong>Intervention:</strong> Standard neoadjuvant doxorubicin and cyclophosphamide Vs Continuous neoadjuvant doxorubicin and cyclophosphamide (with G-CSF) <strong>Sample size:</strong> Arm 1 (standard): 186 (179 analyzed) Arm 2 (continuous): 186 (177 analyzed)</td>
<td>pCR Arm 1: 20.7% Arm 2: 24.3% p=0.45 OS hazard ratio for continuous arm versus standard arm: 1.19, 95% CI 0.81-1.74 The standard arm had greater toxicity from neutropenia and febrile neutropenia. The continuous arm had more stomatitis/pharyngitis and hand-foot syndrome.</td>
<td>No significant clinical benefit was seen for the investigational arm in this trial overall.</td>
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<td>Watanabe 2011&lt;sup&gt;27&lt;/sup&gt;</td>
<td>RCT</td>
<td>To compare R-CHOP-21 versus R-CHOP-14 for untreated indolent B-cell NHL.</td>
<td><strong>Study population:</strong> age 20 to 69 years; CD20+ histologically confirmed indolent B-cell NHL, including grades 1 to 3 FL; stage III or IV disease; at least one measurable lymphomatous lesion more than 1.5 cm detected by computed tomography (CT).</td>
<td>Grade 4 neutropenia and grade 3 infections were more common with R-CHOP-21. 3-yr PFS R-CHOP-21: 57% R-CHOP-14: 58% 6-yr-PFS R-CHOP-21: 41% R-CHOP-14: 43% HR 0.92, 95% CI 0.68-1.25 3-yr OS R-CHOP-21: 95% R-CHOP-14: 96% 6-yr-OS R-CHOP-21: 87% R-CHOP-14: 88% HR 1.15, 95% CI 0.57-2.30</td>
<td>The R-CHOP dose-dense strategy failed to improve PFS of patients with untreated indolent B-cell lymphoma.</td>
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**Intervention:**
R-CHOP-21
G-CSF used according to ASCO guideline
Vs
R-CHOP-14 (with G-CSF)
G-CSF was administered daily for a period of 6 days, starting on day 8 and ending 2 days before CHOP of the subsequent cycle

**Sample size:**
Arm 1: 149
Arm 2: 151

Grade 3-4 hemoglobin decrease was more common with R-CHOP-14 (but anemia was also more common at baseline in this group)
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<td>Bonilla 2010&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td>To assess the efficacy and toxicity of the dose-dense chemotherapy approach in nonmetastatic breast cancer</td>
<td>Randomized controlled trials that compared a dose-dense chemotherapy protocol with a standard chemotherapy schedule in the neoadjuvant or adjuvant setting in adult women with breast cancer. Total of 10 studies</td>
<td>In the three trials of &quot;conserved&quot; dose-density chemotherapy OS HR=0.84, 95% CI 0.72 to 0.98 DFS HR=0.83, 95% CI 0.73 to 0.94 In two conserved dose-dense studies, DFS benefit only apparent among women with hormone receptor-negative disease. In six trials of &quot;modified&quot; dose-dense chemotherapy OS HR=0.85, 95% CI 0.75 to 0.96 DFS HR=0.81, 95% CI 0.73 to 0.88 The rate of nonhematological adverse events was higher in the dose-dense chemotherapy arms.</td>
<td>Dose-dense chemotherapy results in better overall and disease-free survival, particularly in women with hormone receptor-negative breast cancer. However, additional data from randomized controlled trials are needed before dose-dense chemotherapy can be considered as the standard of care</td>
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| Moebus 2010\(^{29}\) | RCT | To compare intense dose-dense (IDD) adjuvant chemotherapy with conventionally scheduled adjuvant chemotherapy in patients with high-risk primary breast cancer | **Study population:** Women with histologically confirmed primary breast cancer stages II to IIIA with four or more positive axillary lymph nodes; ages 18-65; M0; R0 resection of primary tumor and axilla with a minimum of 10 axillary nodes removed  
**Intervention:** Intense dose-dense sequential epirubicin, paclitaxel, and cyclophosphamide (IDD-ETC) every two weeks. Epirubicin 150 mg/m\(^2\) q2wX3, Paclitaxel 225 mg/m\(^2\) q2wX3, Cyclophosphamide 2500 mg\(^2\) q2wX3. Filgrastim s.c. 5 mcg/kg/day from days 3 to 10 of each cycle. Vs Conventionally scheduled epirubicin/Cyclophosphamide followed by paclitaxel every three weeks (EC-T). Epirubicin/cyclophosphamide (90/600 mg/m\(^2\) q3wX4) followed by paclitaxel (175 mg/m\(^2\) q3wX4).  
**Sample size:** 1284 (658 to IDD-ETC and 626 to EC-T). Analyzed: 641/611. | 5-year EFS  
IDD-ETC: 70%  
EC-T: 62%  
HR=0.72, 95% CI 0.59 to 0.87  
5-year OS  
idd-ETC: 82%  
EC-T: 77%  
HR=0.76, 95% CI 0.59 to 0.97  |
<p>| IDD-ETC was less well tolerated compared with conventional chemotherapy but significantly improved event-free and overall survivals in patients with high-risk primary breast cancer who had four or more positive axillary lymph nodes. |</p>
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| Fayette 2009 | RCT              | To assess standard versus dose-intensified doxorubicin, ifosfamide and dacarbazine (MAID) in the first-line treatment of metastatic and locally advanced soft tissue sarcoma | **Study population:** 18-70 years of age, inoperable locally advanced or metastatic soft tissue sarcoma, no CNS metastases  
**Intervention:**  
Standard MAID  
Six cycles of doxorubicin 20 mg/m$^2$/day, ifosfamide 2.5 g/ m$^2$/day with mesna 2.5 g/ m$^2$/day, and dacarbazine 300 mg/ m$^2$/day from day 1-3 every 3 weeks.  
Vs  
Dose-intensified MAID with G-CSF support  
Five cycles of doxorubicin 25 mg/m(2)/day, ifosfamide 3 g/ m$^2$/day with mesna 3 g/ m$^2$/day, and dacarbazine 400 mg/ m$^2$/day from day 1-3 every 3 weeks. Also: lenograstim 5 mcg/kg/day s.c. on days 4-14 of each cycle or until neutrophil recovery.  
**Sample size:** 162 (80 in standard arm and 82 in experimental arm) | Objective response rate  
Standard MAID: 35%  
Intensified MAID: 38%  
p=0.72  
Median EFS (weeks)  
Standard MAID: 42  
Intensified MAID: 39  
p=0.79  
Median OS (weeks)  
Standard MAID: 76  
Intensified MAID: 74  
p=0.75  
Grade 3/4 thrombocytopenia and anemia were more common in the intensified group | Treatment with intensified MAID did not improve response rate or survival and cannot be recommended for advanced or metastatic soft tissue sarcoma. |
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| Heigener 2009<sup>31</sup> | RCT | To investigate whether dose-intensified carboplatin and etoposide (CE) with the supplementation of granulocyte-colony-stimulating factor (G-CSF) is more effective than conventional CE in terms of survival with acceptable toxicity. | **Study population:** Age 18-75 with extensive stage small cell lung cancer. No prior chemotherapy or radiotherapy.  
**Intervention:**  
Dose-intensified carboplatin plus etoposide with G-CSF support. Carboplatin AUC 5 on day 1 IV and etoposide 190 mg/m(2) days 1-3 IV with lenograstim 263 mcg s.c. on days 4-13, every 21 days.  
Vs  
Conventional carboplatin plus etoposide. Carboplatin AUC 5 on day 1 IV and etoposide 140 mg/m(2) IV on days 1-3, every 28 days  
**Sample size:** 79 (37 in conventional group and 42 in dose-intensified group) | Median OS (months)  
Conventional: 11.2  
Dose-intensified: 11.9 NS  
Median PFS (months)  
Conventional: 6.7  
Dose-intensified: 7.4 NS  
Complete response  
Conventional: 14%  
Dose-intensified: 22% p=0.60  
Neutropenia was significantly more frequent in the conventional group.  
Thrombocytopenia was significantly more frequent in the dose-intensified group. | Dose-intense CE with GM-CSF support can be administered safely but does not prolong overall or progression-free survival compared with standard therapy |
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| Lewis 2007\(^{32}\) | RCT | To assess intensified chemotherapy for osteosarcoma | **Study population:** Patients aged 40 years or less with a histologically confirmed diagnosis of high-grade osteosarcoma in an extremity long bone.  
**Intervention:**  
Regimen-C (conventional treatment with six 3-week cycles of cisplatin [100 mg/m\(^2\) by 24-hour infusion] and doxorubicin [25 mg/m\(^2\)/day by 4-hour infusion for 3 days]) Vs Regimen-DI (intensified treatment with identical total doses of cisplatin and doxorubicin, planned as six 2-week cycles supported by G-CSF)  
**Sample size:**  
Arm 1: 250 (Regimen C)  
Arm 2: 254 (Regimen-DI) | 5-yr OS  
Regimen-C: 55%  
Regimen-DI: 58%  
HR, 0.94; 95% CI 0.71 to 1.24  
5-yr PFS  
Regimen-C: 39%  
Regimen-DI: 41%  
HR, 0.98; 95% CI 0.77 to 1.24  
The delivered preoperative median dose intensity of cisplatin was 86% in Regimen-C and 111% in Regimen-DI (as the percentage of that planned for the conventional regimen). Postoperative median dose intensity of cisplatin was 82% in Regimen-C and 110% in Regimen-DI (the corresponding figures for doxorubicin dose intensity were similar).  
Grade 3 or 4 toxicity  
White blood cell  
Regimen-C: 81%  
Regimen-DI: 69%  
RR, 0.85; 95% CI 0.77 to 0.95  
Neutrophil  
Regimen-C: 92%  
Regimen-DI: 76%  
RR, 0.83; 95% CI 0.76 to 0.89  
Platelet  
Regimen-C: 58%  
Regimen-DI: 77%  
RR, 1.33; 95% CI 1.17 to 1.52  
Mucositis  
Regimen-C: 27%  
Regimen-DI: 35%  
RR, 1.30; 95% CI 0.99 to 1.70 | Planned intensification of chemotherapy with cisplatin and doxorubicin increased received dose intensity and resulted in a statistically significant increase in favorable histologic response rate, but not in increased progression-free or overall survival. |
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| Ray-Coquard 2007<sup>33</sup> | RCT | To explore the impact of increased dose of cyclophosphamide in a modified CAP regimen on the disease-free survival (DFS) and overall survival (OS) of advanced ovarian cancer patients | **Study population:** histologically documented, chemotherapy-naive ovarian epithelial carcinoma. Age 18 to 70 years, FIGO stage III or IV, initiation of chemotherapy within 4 weeks after initial laparotomy  
**Intervention:**  
Standard CEP  
Six cycles every 3 weeks of cyclophosphamide (C), 500 mg m<sup>-2</sup>, epirubicin (E) 50 mg m<sup>-2</sup>, and cisplatin (P) 75 mg m<sup>-2</sup>  
Vs  
Intensive CEP  
Six cycles every 3 weeks of E and P at the same doses, but with (C) 1800 mg m<sup>-2</sup> and filgrastim 5 mug kg<sup>-1</sup> per day x 10 days  
**Sample size:**  
Arm 1: 85  
Arm 2: 79 | 2-year OS  
Arm 1: 66%  
Arm 2: 64%  
p=0.7  
Median OS  
Arm 1: 32.5 months  
Arm 2: 30 months  
p=0.6  
Median PFS  
Arm 1: 15.9 months  
Arm 2: 14.8 months  
p=0.55 | Increasing cyclophosphamide dose by more than 3 times with filgrastim support in the modified CAP regimen CEP induces more toxicity but not better efficacy in advanced ovarian cancer. |
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<tr>
<td>Verdonck 2007&lt;sup&gt;34&lt;/sup&gt;</td>
<td>RCT</td>
<td>To assess whether dose intensifications with cyclophosphamide and doxorubicin might improve outcome in younger patients with intermediate-risk aggressive NHL.</td>
<td><strong>Study population:</strong> Previously untreated aggressive NHL according to the intermediate-or high-grade Working Formulation (groups D, E, F, G, and H) and an intermediate-risk profile according to the HOVON criteria. <strong>Intervention:</strong> CHOP-21 Cyclophosphamide (750 mg/m² intravenously), doxorubicin (50 mg/m² intravenously), and vincristine (2 mg intravenously) on day 1, and prednisone (100 mg orally) given on days 1 to 5. Patients were treated every 3 weeks for 8 cycles. Vs I-CHOP Cyclophosphamide (1000 mg/m² intravenously), doxorubicin (70 mg/m² intravenously), and vincristine (2 mg intravenously) on day 1, and prednisone (100 mg orally) given on days 1 to 5. Granulocyte colony-stimulating factor was given in the I-CHOP arm only. Patients were treated every 2 weeks for 6 cycles.</td>
<td>Infection grade 3 or 4 CHOP-21: 7% I-CHOP: 26% 6-yr OS CHOP-21: 50% I-CHOP: 61% HR, 0.83; 95% CI 0.62 to 1.11 6-yr DFS CHOP-21: 49% I-CHOP: 55% HR, 0.76; 95% CI 0.51 to 1.15</td>
<td>Although there was a tendency in favor of I-CHOP for overall survival (OS), disease-free survival (DFS), and event-free survival (EFS), the differences were not significant.</td>
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| Sternberg 2006<sup>35</sup> | RCT | To assess high-dose intensity M-VAC and G-CSF versus classic M-VAC in advanced urothelial tract tumors | **Study population:** Distant metastases or unresectable transitional cell carcinoma of the urinary tract with no prior systemic cytotoxic or biologic treatment.  
**Intervention:** High-dose intensity M-VAC with G-CSF  
Methotrexate: 30 mg/m² day 1  
Vinblastine: 3 mg/ m² day 2  
Adriamycin: 30 mg/ m² day 2  
Cisplatin: 70 mg/ m² day 2  
G-CSF: days 3-7 Every 15 days  
Vs  
Classic M-VAC  
Methotrexate: 30 mg/ m² days 1, 15, 22;  
Vinblastine: 3 mg/ m² days 2, 15, 22;  
Adriamycin: 30 mg/m² day 2  
Cisplatin: 70 mg/ m² day 2 Every 28 days | OS  
M-VAC: 14.9 months  
HD-M-VAC: 15.1 months  
HR=0.76, 95% CI 0.58 to 0.99  
**PFS**  
M-VAC: 8.1 months  
HD-M-VAC: 9.5 months  
HR=0.73, 95% CI 0.56 to 0.95  
**CR+PR**  
M-VAC: 58%  
HD-M-VAC: 72%  
p=0.016  
**Grade 4 WBC toxicity**  
M-VAC: 16%  
HD-M-VAC: 8%  
p<0.001  
**Neutropenic fever**  
M-VAC: 26%  
HD-M-VAC: 10%  
p<0.001  
**Grade 4 platelet toxicity**  
M-VAC: 6%  
HD-M-VAC: 11%  
p=0.033 | With longer follow-up initial results have been confirmed, and shows that HD-M-VAC produces a borderline statistically significant relative reduction in the risk of progression and death compared to M-VAC |
# Clinical Question 5, Stem-cell Transplantation

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| Cesaro 2013[^36] | RCT | To assess the non-inferiority of pegfilgrastim versus filgrastim in speeding the recovery of polymorphonuclear cells (PMN) in pediatric patients who underwent autologous peripheral blood stem cell transplant (PBSCT). | **Study population:** 0 to 17 years of age, affected by leukemia, lymphoma or solid tumor who underwent a first autologous PBSC transplant  
**Intervention:**  
Filgrastim after autologous PBSCT  
9 or more doses of filgrastim 5 mcg/kg/day (maximum 300 mcg/day). Administered beginning from day +3 after PBSC infusion  
Vs  
Pegfilgrastim after autologous PBSCT  
single dose of pegfilgrastim 100 mcg/kg (maximum 6 mg). Administered beginning from day +3 after PBSC infusion  
**Sample size:**  
Filgrastim: 29  
Pegfilgrastim: 32 | Fever of unknown origin  
Filgrastim: 79.3%  
Pegfilgrastim: 78.1%  
p=0.9 | Pegfilgrastim was not inferior to daily filgrastim in pediatric patients who underwent PBSCT |

[^36]: Cesaro (2013)
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<tr>
<td>NCCN 2014</td>
<td>Guideline</td>
<td>To provide guidelines on the use of myeloid growth factors.</td>
<td>Primarily addresses adult patients with solid tumors and non-myeloid malignancies</td>
<td></td>
<td>Stem cell mobilization: G-CSF as single-agent or as part of chemo-mobilization. Combination of plerixafor and G-CSF for selected patients with NHL or multiple myeloma. Filgrastim. Consensus is lacking on the use of growth factors in the post-transplant setting. Limited data suggest pegfilgrastim may be equivalent to filgrastim in these settings. GM-CSF an option for mobilization and post-transplant.</td>
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<td>Bennett 2013</td>
<td>Narrative review</td>
<td>To review the use of CSFs for febrile neutropenia during cancer therapy (filgrastim and pegfilgrastim)</td>
<td></td>
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<td>Notes that “CSFs are not administered after allogeneic stem-cell transplantation because of increased risks of severe graft-versus-host disease, transplantation-related death, and death from other causes.” (page 4)</td>
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| Kim 2012<sup>TM</sup> | Meta-analysis | To assess the effects of G-CSF in cancer patients receiving stem cell transplantation (SCT) after high-dose chemotherapy (HDCT) | Randomized, adults, CSF administered prophylactically 2000-2011 7 studies included | Documented infections RR=0.77, 95% CI 0.68 to 0.87  
G-CSF also reduced time to hematologic recovery  
Infection-related mortality RR=1.44, 95% CI 0.24 to 8.63  
Episodes of fever RR=0.85, 95% CI 0.64 to 1.14  
All-cause mortality RR=0.92, 95% CI 0.70-1.19  
Grade 2-4 GVHD RR=0.82, 95% CI 0.58-1.16 | Prophylactic G-CSF reduced the risk of documented infections and time to hematologic recovery in SCT patients with cancer following HDCT. The G-CSF treated group also showed a decrease in the length of hospital stay. However, there was no difference between G-CSF treatment group and placebo group in regard to all-cause mortality, infection-related mortality, grade 2-4 acute graft-versus-host-disease, and episode of fever. |
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<td>Sheppard 2012</td>
<td>Systematic review</td>
<td>To review RCTs of stem cell mobilization strategies for autologous transplantation for hematologic malignancies</td>
<td>Patients &gt;18 years undergoing peripheral blood HSC collection for autologous transplantation. Study must have compared at least 2 mobilization strategies using a randomized controlled study design. 28 articles reporting on 29 studies.</td>
<td>Growth factor alone after chemotherapy, anestim, or plerixafor provide adequate autologous HSC grafts for the majority of patients. Although some strategies result in higher CD34+ cell yield, this potentially comes at the expense of increased toxicity. As all strategies are reasonable, programmatic, and patient-specific considerations must inform the approach to autologous graft mobilization.</td>
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<td>Orciuolo 2011</td>
<td>RCT</td>
<td>To show a lower incidence of febrile episodes in multiple myeloma patients receiving lenograstim vs. filgrastim after high-dose cyclophosphamide for stem cell mobilization</td>
<td><strong>Study population:</strong> Age 18-70 years; diagnosis of multiple and scheduled to receive high-dose chemotherapy.  <strong>Intervention:</strong> Filgrastim after high-dose cyclophosphamide for stem cell mobilization vs Lenograstim after high-dose cyclophosphamide for stem cell mobilization  Administration of the assigned rHu G-CSF started on day 4 until day 7 at a dosage of 30 MU/day, which was increased to 60 MU/day from day 8 until the end of aphaeresis</td>
<td>Patients with febrile episodes  Filgrastim: 9.1%  Lenograstim: 1.1%  p=0.03  Overall, 10.8% of patients experienced at least one adverse event (any grade). 12.5% (11/88) in the lenograstim and 9.1% (8/88) in the filgrastim group (p = ns).</td>
<td>Lenograstim group presented a significantly higher absolute CD34+ cell number compared with the filgrastim group but no differences were detected for collection efficacy. The study demonstrated a lower incidence of febrile episodes with lenograstim compared to filgrastim.</td>
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| Gerds 2010¹¹ | RCT             | To assess pegfilgrastim versus filgrastim after autologus peripheral blood stem cell transplantation (APBSCT) | **Study population:** Adults undergoing APBSCT for multiple myeloma, lymphoma, testicular cancer, or ovarian cancer. Adequate CD34+ cells collected for transplant.  
**Intervention:**  
Filgrastim after APBSCT  
Filgrastim given daily, s.c., 5 mcg/kg, from day +1 until sustained engraftment or through day +25 posttransplant  
Vs  
Pegfilgrastim after APBSCT  
Pegfilgrastim given as single 6 mg s.c. injection on day +1 posttransplant  
**Sample size:** 78 (39 in each arm) | Median time to neutrophil engraftment: 12 days in both groups  
Reached the cytokine discontinuation engraftment endpoint of ANC $5 \times 10^9$/L X 3 days or $10 \times 10^9$/L X 1 day: Filgrastim: 95%  
Pegfilgrastim: 44%  
Secondary outcomes that were similar in two groups: platelet engraftment, platelet transfusions, positive cultures for bacterial pathogens, days of fever, deaths prior to engraftment, duration of hospital stay | This phase III study failed to demonstrate a difference in time to neutrophil engraftment or any clinical sequelae between pegfilgrastim and filgrastim when given post-APBSCT, with pegfilgrastim achieving a cost savings over filgrastim. |
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| Castagna 2010 | RCT | **To demonstrate the noninferiority of pegfilgrastim compared with filgrastim after high-dose chemotherapy (HDC) and peripheral blood stem cell (PBSC) support** | **Study population:** Age >18; Hematological malignancy or solid tumor; adequate harvest of CD34-positive cells.  
**Intervention:**  
Pegfilgrastim: a single, s.c. fixed dose (6 mg) was administered 24 h after autologous PBSC infusion (day +1).  
Vs Filgrastim: s.c. weight-based daily dose (5 mcg/kg/day) was administered from day +1 until ANC recovery to >0.5 X 10^9/l for two consecutive days.  
**Sample size:** 80 (40 in each group) | Duration of neutropenia  
Filgrastim: 5.97 days  
Pegfilgrastim: 6.20 days  
Mean difference 0.23, 95% CI -0.77 to 1.22  
Mean time to reach an ANC of >0.5 X 10^9/l  
Filgrastim: 11.53 days  
Pegfilgrastim: 10.75 days  
Mean difference -0.78, 95% CI -2.97 to 1.42  
Incidence of fever  
Filgrastim: 62%  
Pegfilgrastim: 56%  
p=0.65 | Pegfilgrastim is not inferior to filgrastim in hematological reconstitution and represents an effective alternative after HDC and PBSC.
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| DiPersio 2009 | RCT             | To evaluate the safety and efficacy of plerixafor in mobilizing hematopoietic stem cells for autologous stem-cell transplantation in non-Hodgkin's lymphoma (NHL) patients | **Study population:** Between 18 and 78 years old with biopsy-confirmed diagnosis of NHL, in first or second complete or partial remission, eligible for autologous HSCT, ≥4 weeks since last cycle of chemotherapy.  
**Intervention:**  
G-CSF plus plerixafor vs G-CSF plus placebo  
Patients received G-CSF (10 mcg/kg) subcutaneously daily for up to 8 days. Beginning on evening of day 4 and continuing daily for up to 4 days, patients received either plerixafor (240 mcg/kg) or placebo subcutaneously. Starting on day 5, patients began daily apheresis for up to 4 days or until ≥5 x 10^6 CD34+ cells/kg were collected  
**Sample size:** 298 total  
G-CSF plus plerixafor: 150  
G-CSF plus placebo: 148 | Collected ≥5 x 10^6 CD34+ cells/kg in ≤4 apheresis days  
G-CSF plus plerixafor: 59.3%  
G-CSF plus placebo: 19.6%  
p<0.001  
Underwent transplantation after initial mobilization  
G-CSF plus plerixafor: 90%  
G-CSF plus placebo: 55.4%  
p<0.001  
Median time to engraftment was similar in both groups.  
The most common plerixafor-associated adverse events were GI disorders and injection site reactions. | Plerixafor and G-CSF were well tolerated and resulted in a significantly higher proportion of patients with non-Hodgkin's lymphoma achieving the optimal CD34+ cell target for transplantation in fewer apheresis days, compared with G-CSF alone |
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| DiPersio 2009⁴⁴ | RCT | To evaluate the safety and efficacy of plerixafor with G-CSF in mobilizing hematopoietic stem cells in patients with multiple myeloma | **Study population:** Between the ages of 18 and 78 years with biopsy-confirmed diagnosis of multiple myeloma before the first mobilization, in first or second complete or partial remission, and eligible for autologous hematopoietic stem cell transplantation  
**Intervention:**  
G-CSF plus plerixafor  
vs  
G-CSF plus placebo  
G-CSF 10 mcg/kg per day s.c. daily for up to 8 days. Beginning on day 4, patients received either plerixafor 0.24 mg/kg or placebo s.c. daily for up to 4 days or until ≥ 6 x 10⁶ CD34+ cells/kg were collected.  
**Sample size:** 302 (148 plerixafor, 154 placebo) | Percentage of patients who collected ≥ 6 x 10⁶ CD34+ cells/kg in ≤2 aphereses  
Plerixafor: 71.6%  
Placebo: 34.4%  
p<0.001 | Plerixafor and G-CSF were well tolerated, and significantly more patients collected the optimal CD34(+) cell/kg target for transplantation earlier compared with G-CSF alone |
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| Jang 2008<sup>15</sup> | RCT | To compare single-versus split-dose lenograstim to enhance engraftment after autologous stem cell transplantation in patients with multiple myeloma or non-Hodgkin's lymphoma | **Study population:** Age 16 to 25 with multiple myeloma or NHL. Scheduled for autologous SCT for symptomatic MM or NHL at chemotherapy-sensitive first relapse or in the first partial response.  
**Intervention:**  
Single-dose lenograstim 5 mcg/kg/day, started one day after peripheral blood progenitor cell infusion and continued until an ANC of at least 1.0 X 10<sup>9</sup>/L  
Vs  
Split-dose lenograstim 2.5 mcg/kg twice a day, started one day after peripheral blood progenitor cell infusion and continued until an ANC of at least 1.0 X 10<sup>9</sup>/L  
 **Sample size:** 40 (21 to single-dose and 19 to split-dose) | Median time to neutrophil engraftment ANC >0.5 X 10<sup>9</sup>/L (days)  
Single dose: 10  
Split dose: 10  
p=0.243  
Median time to platelet engraftment PLT count >20 X 10<sup>9</sup>/L (days)  
Single dose: 11  
Split dose: 14  
p=0.009  
Duration of hospitalization (days)  
Single dose: 18  
Split dose: 22  
p=0.02 | Administration of split doses of lenograstim is not associated with superior clinical efficacy compared with conventional daily single-dose administration for immediate hematopoietic recovery after ASCT |
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<td>Sung 2007</td>
<td>Meta-analysis</td>
<td>To evaluate the benefits of prophylactic hematopoietic CSFs in adults and children receiving cancer chemotherapy or undergoing stem-cell transplantation (SCT)</td>
<td>Searched through 2006 or 2007 Selected 148 trials that were reported in any language that randomly assigned patients to CSFs or to either placebo or no therapy. Prophylactic CSFs were given concurrently with or after initiation of chemotherapy.</td>
<td>Infection-related mortality CSF: 3.1% Placebo/no treatment: 3.8% RR=0.82, 95% CI 0.66 to 1.02 Documented infections CSF: 38.9% Placebo/no treatment: 43.1% RR=0.85, 95% CI 0.79-0.92 FN CSF: 25.3% Placebo/no treatment: 44.2% RR=0.71, 95% CI 0.63 to 0.80 Short-term all-cause mortality CSF: 7.6% Placebo/no treatment: 8.0% RR=0.95, 95% CI 0.84 to 1.08</td>
<td>Prophylactic CSFs may have little or no effect on mortality but do decrease rates of infection in patients receiving cancer chemotherapy or those undergoing SCT. No interactions by age or population diagnosis group and CSF effect</td>
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| Martino 2006⁴⁶ | RCT              | To compare pegfilgrastim vs. filgrastim after high-dose melphalan and autologous peripheral blood stem cell transplantation (APBSCT) in multiple myeloma (MM) patients | **Study population:** de novo diagnosis of multiple myeloma, stages II-III Durie Salmon classification  
**Intervention:** Pegfilgrastim on day +1 after stem cell infusion. Single s.c. injection, 6 mg.  
Vs Filgrastim starting on day +5 after stem cell infusion and continuing until neutrophil engraftment.  
5 mcg/kg/day  
**Sample size:** 37 (18 in pegfilgrastim group and 19 in filgrastim group) | Duration of grade 4 neutropenia (days)  
Pegfilgrastim: 5  
Filgrastim: 6  
p=NS  
Incidence of FN  
Pegfilgrastim: 61.1%  
Filgrastim: 100%  
p=0.003  
Duration of FN (days)  
Pegfilgrastim: 1.5  
Filgrastim: 4  
p=0.005  
Time to platelet engraftment, number of red blood cell or platelet transfusions, and days of hospitalization were similar in the two study groups.  
Incidence of bone pain  
Pegfilgrastim: 10%  
Filgrastim: 12%  
p=NS | Pegfilgrastim can be used with safety and efficacy similar to those provided by daily injections of filgrastim, and is associated with a decreased incidence of infectious events after APBSCT in MM patients |
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| Dekker 2006 | Meta-analysis    | To determine whether prophylactic CSFs after hematopoietic autologous and allogeneic stem-cell transplantation (SCT) reduced documented infections | Randomization between CSFs and placebo/no therapy; CSFs given after SCT and before recovery of neutrophils; SCT conditioning regimen and GVHD prophylaxis were not planned to be different between study arms  
34 studies were included in the meta-analysis. Total of 2,669 participants. | CSF vs placebo/no therapy  
Risk of documented infections  
RR=0.87, 95% CI 0.76-1.00  
Infection-related mortality (autologous SCT)  
RR=1.09, 95% CI 0.44-2.67  
Infection-related mortality (allogeneic SCT)  
RR=0.37, 95% CI 0.13 to 1.05  
Infection-related mortality  
RR=0.76, 95% CI 0.41 to 1.44  
Grade 2 to 4 acute GVHD  
RR=1.03, 95% CI 0.81 to 1.31  
Treatment-related mortality  
RR=1.00, 95% CI 0.78 to 1.29 | CSFs were associated with a small reduction in the risk of documented infections but did not affect infection or treatment-related mortality |
Clinical Question 6, Acute leukemia, MDS

No evidence table; question not addressed by panel.

Clinical Question 7, Concomitant Chemotherapy and Radiation Therapy

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<td>To provide guidelines on the use of myeloid growth factors.</td>
<td>Primarily addresses adult patients with solid tumors and non-myeloid malignancies</td>
<td></td>
<td>Prophylactic CSFs in patients given concurrent chemotherapy and radiation therapy has not been evaluated and is therefore not recommended.</td>
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| Delarue 2013<sup>22</sup> | RCT | To ascertain if a dose-dense R-CHOP regimen administered every 2 weeks (R-CHOP14) was superior to the standard 3-week schedule (R-CHOP21). | **Study population:** Aged 60-80 years with untreated diffuse large B-cell lymphoma and at least one adverse prognostic factor  
**Intervention:**  
R-CHOP-14 (G-CSF decision made by treating doctor)  
R-CHOP-21 (G-CSF decision made by treating doctor)  
**Sample size:**  
R-CHOP-14 : 304  
R-CHOP-21 : 298 | Grade 3-4 neutropenia  
R-CHOP-14: 74%  
R-CHOP-21: 64%  
3-yr EFS  
R-CHOP-14: 56%  
R-CHOP-21: 60%  
HR 1.04, 95% CI 0.82-1.31  
3-yr OS  
R-CHOP-14: 69%  
R-CHOP-21: 72%  
HR 0.96, 95% CI 0.73-1.26 | In elderly patients with untreated diffuse large B-cell lymphoma and at least one adverse prognostic factor, a 2-week dose-dense R-CHOP regimen did not improve efficacy compared with the 3-week standard schedule. The frequency of toxic side-effects was similar between regimens, but R-CHOP14 was associated with increased need for red-blood-cell transfusion |
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| Balducci 2007\textsuperscript{13} | RCT | To evaluate the incidence of febrile neutropenia and related events in elderly cancer patients receiving pegfilgrastim beginning with cycle 1 (proactive) in comparison with pegfilgrastim initiated after cycle 1 at the physician's discretion. | **Study population:** ≥65 years old with lung, breast, or ovarian cancer, or NHL. **Intervention:** Pegfilgrastim beginning in cycle 1 versus pegfilgrastim administered after cycle 1 at physician's discretion. s.c. injection of 6 mg pegfilgrastim once per cycle 24 hours after chemotherapy completion. | Solid tumors, incidence of FN across all cycles:  
Arm 1: 4%  
Arm 2: 10%  
p=0.001  
NHL, incidence of FN across all cycles:  
Arm 1: 15%  
Arm 2: 37%  
p=0.004  
Solid tumors, grade 3 or 4 neutropenia across all cycles:  
Arm 1: 30%  
Arm 2: 80%  
NHL, grade 3 or 4 neutropenia across all cycles:  
Arm 1: 82%  
Arm 2: 90%  
Solid tumors, hospitalization across all cycles:  
Arm 1: 5%  
Arm 2: 9%  
NHL, hospitalization across all cycles:  
Arm 1: 17%  
Arm 2: 37%  
Solid tumors, dose delay across all cycles:  
Arm 1: 16%  
Arm 2: 28%  
NHL, dose delay across all cycles:  
Arm 1: 29%  
Arm 2: 23%  
Solid tumors, dose reduction across all cycles:  
Arm 1: 7%  
Arm 2: 14%  
NHL, dose reduction across all cycles:  
Arm 1: 16%  
Arm 2: 8% | Results, con't  
NHL, dose reduction across all cycles:  
Arm 1: 16%  
Arm 2: 8%  
Bone pain, solid tumors:  
Arm 1: 12%  
Arm 2: 5%  
Bone pain, NHL:  
Arm 1: 9%  
Arm 2: 4%  
Proactive pegfilgrastim use effectively produced a lower incidence of febrile neutropenia and related events in elderly patients with either solid tumors or NHL receiving an array of mild to moderately neutropenic chemotherapy regimens. |
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| Cesaro 2013<sup>36</sup> | RCT | To assess the non-inferiority of pegfilgrastim versus filgrastim in speeding the recovery of polymorphonuclear cells (PMN) in pediatric patients who underwent autologous peripheral blood stem cell transplant (PBSCT). | **Study population:** 0 to 17 years of age, affected by leukemia, lymphoma or solid tumor who underwent a first autologous PBSC transplant  
**Intervention:**  
Filgrastim after autologous PBSCT  
9 or more doses of filgrastim 5 mcg/kg/day (maximum 300 mcg/day). Administered beginning from day +3 after PBSC infusion  
Vs  
Pegfilgrastim after autologous PBSCT  
single dose of pegfilgrastim 100 mcg/kg (maximum 6 mg). Administered beginning from day +3 after PBSC infusion  
**Sample size:**  
Filgrastim: 29  
Pegfilgrastim: 32 | Fever of unknown origin  
Filgrastim: 79.3%  
Pegfilgrastim: 78.1%  
p=0.9  
One-year survival  
Filgrastim: 84%  
Pegfilgrastim: 75%  
p=0.8  
Time to neutrophil engraftment  
Arm 1: 10.48 days (mean)  
Arm 2: 10.44 days (mean)  
p=0.3  
Time to platelet engraftment  
Arm 1: 28.10 days (mean)  
Arm 2: 33.09 days (mean)  
p=0.5  
Grade II-IV mucositis  
Filgrastim: 75.9%  
Pegfilgrastim: 59.4%  
p=0.2 | Pegfilgrastim was not inferior to daily filgrastim in pediatric patients who underwent PBSCT |
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| Sari 2013   | RCT             | To compare the effectiveness, toxicities and the cost of filgrastim and lenograstim in children. | **Study population:** Pediatric patients with solid tumors and a history of FN after first course of chemotherapy  
**Intervention:**  
Filgrastim-lenograstim crossover Vs  
Lenograstim-filgrastim crossover  
Filgrastim 5 mcg/kg  
Lenograstim 150 mcg/m²  
s.c. single dose per day  
G-CSF administered 24 hours after last day of chemotherapy as secondary prophylaxis  
**Sample size:** 29 (15 started with filgrastim and 14 started with lenograstim) | Incidence of FN and infection were similar with filgrastim or lenograstim  
CD34+ levels were higher with lenograstim.  
Lenograstim was more expensive | There is no difference following the administration of either lenograstim or filgrastim for the duration of neutropenia, FEN or hospitalization for pediatric cancer patients. For stem cell mobilization, lenograstim was superior to filgrastim. |
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| Womer 2012⁴⁹ | RCT             | To test the efficacy and safety of chemotherapy intensification through interval compression for Ewing’s sarcoma. | **Study population**: Patients younger than 50 years with newly diagnosed localized extradural Ewing sarcoma. | 5-year EFS  
Arm A: 65%  
Arm B: 73%  
Arm B HR=0.74 (95% CI 0.54 to 0.99)  
5-year OS  
Arm A: 77%  
Arm B: 83%  
Arm B HR=0.69 (95% CI 0.47 to 1.0) | For localized Ewing sarcoma, chemotherapy administered every 2 weeks is more effective than chemotherapy administered every 3 weeks, with no increase in toxicity. |

**Intervention**: All patients received 14 cycles of alternating vincristine-doxorubicin-cyclophosphamide (VDC) and ifosfamide-etoposide (IE) with filgrastim.  
Regimen A (standard): Q3W X 2, then local control, then Q3W X 5  
Regimen B (intensified): Q2W X 3, then local control, then Q2W X 4  
**Sample size**: 568 (284 in each arm)
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| Fox 2009    | RCT             | To compare the effectiveness, tolerance, and pharmacokinetics of a single dose of pegfilgrastim to daily filgrastim in children and young adults with sarcomas treated with dose-intensive combination chemotherapy | **Study population:** Patients ages <26 y with Ewing sarcoma family of tumors, alveolar rhabdomyosarcoma, stage 3 or 4 embryonal rhabdomyosarcoma, and unresectable or metastatic malignant peripheral nerve sheath tumor or synovial sarcoma  
**Intervention:**  
Pegfilgrastim 100 mcg/kg s.c. as a single dose 24 to 36 h after completion of each cycle of chemotherapy  
Vs  
Filgrastim 5 mcg/kg/d s.c., daily starting 24 h and continuing until the postnadir neutrophil count was ≥10,000/mcL after each cycle of chemotherapy  
**Sample size:**  
Arm 1: 17  
Arm 2: 17 | Median duration of severe neutropenia during first two chemotherapy cycles  
Arm 1: 5.5  
Arm 2: 6.0  
p=0.76  
Median duration of severe neutropenia during second two chemotherapy cycles  
Arm 1: 1.5  
Arm 2: 3.75  
p=0.11  
Twelve of 17 patients on the pegfilgrastim arm experienced 18 episodes (29% of cycles) of grade 3 fever and neutropenia requiring hospitalization during the first four cycles of chemotherapy compared with 15 of 17 patients and 32 episodes (47% of cycles) on the filgrastim arm | A single dose per cycle of pegfilgrastim was well tolerated and may be as effective as daily filgrastim based on the duration of severe neutropenia and number of episodes of febrile neutropenia and documented infections after dose-intensive treatment with VDC and IE |
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| Lehrnbecher 2007<sup>51</sup> | RCT | To investigate the impact of G-CSF on hematopoetic recovery and infectious complications and on outcome in children with de novo AML | **Study population:** Children up to the age of 18 with newly diagnosed AML.  
**Intervention:**  
G-CSF vs no G-CSF  
G-CSF started on day 15 after induction therapy. 5 mcg/kg/day either subcutaneously or as an intravenous infusion. Continued until the ANC exceeded 0.5 X 10⁹/L on 3 consecutive days.  
**Sample size:**  
161 to G-CSF  
156 to control group | Neutrophil recovery (days) after first induction  
G-CSF: 18  
No G-CSF: 23  
p=0.01  
Neutrophil recovery (days) after second induction  
G-CSF: 11  
No G-CSF: 16  
p=0.001  
G-CSF did not have a statistically significant effect on platelet recovery or infectious complications  
G-CSF did not have a statistically significant effect on complete remission, relapse, or 5-yr EFS.  
G-CSF had no statistically significant effect on incidence of oral or pharyngeal mucositis grades 3-4. | Since G-CSF does not influence the risk of infectious complications or outcome in children undergoing therapy for AML, one cannot advocate the routine use of G-CSF in this patient group. |
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<td>Wittman 2006&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Meta-analysis</td>
<td>To definitively assess the impact of prophylactic CSFs on the risk of febrile neutropenia in pediatric oncology patients</td>
<td>Included those studies of children ≤ 18 years or those ≤ 25 years of age and being treated on pediatric oncology cooperative group protocols</td>
<td>Incidence of FN with CSF: 59% control group: 68% OR 0.591, 95% CI: 0.431 to 0.810 Incidence of documented infection with CSF: 20% control group: 25% OR 0.747, 95% CI: 0.518 to 1.079 Duration of neutropenia mean decrease of 3.40 days, 95% CI: 1.85 to 4.96 Duration of hospitalization mean decrease of 1.7 days, 95% CI: 0.9 to 2.5</td>
<td>Prophylactic CSFs significantly decrease the incidence of FN and the durations of severe neutropenia, hospitalization, and antibiotic use in pediatric cancer patients, but they do not significantly decrease documented infections</td>
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# Clinical Question 10, Administration and Dosing of CSFs

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<td><strong>NCCN 2014</strong></td>
<td>Guideline</td>
<td>To provide guidelines on the use of myeloid growth factors.</td>
<td>Primarily addresses adult patients with solid tumors and non-myeloid malignancies</td>
<td></td>
<td>Majority of trials administered pegfilgrastim on the day after chemotherapy. Limited data suggest that same-day pegfilgrastim may be considered in certain circumstances.</td>
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| **Aarts 2013** | RCT             | To assess primary granulocyte colony-stimulating factor prophylaxis during the first two cycles only or throughout all chemotherapy cycles in patients with breast cancer at risk for febrile neutropenia | **Study population:** Patients with breast cancer with an indication for every-3-weeks chemotherapy in the adjuvant, neoadjuvant, or advanced setting  
**Intervention:** G-CSF cycles 1-6 Vs G-CSF cycles 1-2  
Pegfilgrastim at a 6-mg fixed dose was administered 24 to 30 hours after chemotherapy administration  
**Sample size:** G-CSF cycles 1-6: 84 G-CSF cycles 1-2: 83 | Percentage of patients who developed FN  
G-CSF cycles 1-6: 10% G-CSF cycles 1-2: 36% | In patients with early breast cancer at high risk for FN, continued use of primary G-CSF prophylaxis during all chemotherapy cycles is of clinical relevance and thus cannot be abandoned. |
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| Inaba 2011* | RCT             | To assess two dosages of prophylactic G-CSF after induction chemotherapy in pediatric acute myeloid leukemia | **Study population:** Children with previously untreated AML or myelodysplastic syndrome  
**Intervention:**  
G-CSF 5 mcg/kg daily with intensive induction therapy for AML. Vs  
G-CSF 10 mcg/kg daily with intensive induction therapy for AML.  
**Sample size:** 46 | No statistically significant differences were observed between the 2 arms in any of the endpoints measured | The higher G-CSF dosage offered no greater benefit than the lower dosage in patients who were receiving intensive chemotherapy for AML |
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<td>Loibl 2011</td>
<td>RCT</td>
<td>To Compare of pegfilgrastim on day 2 vs. day 4 as primary prophylaxis of intense dose-dense chemotherapy in patients with node-positive primary breast cancer.</td>
<td>Study population: Female patients biologically younger than 65 years with histologically confirmed, unilateral or bilateral node-positive primary breast cancer.</td>
<td>Grade 4 leukopenia P2: 47.1% P4: 42% p=0.39 Incidence of infections P2: 29.9% P4: 25.4% p=0.40 Febrile neutropenia P2: 4.7% P4: 8.0% p=0.27 Received all planned cycles of chemotherapy P2: 93.1% P4: 90.2%</td>
<td>This study failed to demonstrate that pegfilgrastim on day 4 was more efficacious than on day 2 with respect to grade 4 leukopenia (the primary endpoint), febrile neutropenia, or infections.</td>
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<td>Intervention: Pegfilgrastim s.c. 6 mg on day 2 (P2) Vs Pegfilgrastim s.c. 6 mg on day 4 (P4) Intense dose-dense ETC (epirubicin, paclitaxel, cyclophosphamide) chemotherapy in both groups</td>
<td>Sample size: 351 (174 to day 2 arm and 177 to day 4 arm)</td>
<td>Mean relative total dose intensity per agent: difference between groups not statistically significant</td>
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| Zwick 2011[^6] | RCT (phase II) | To study the effects of deferring pegfilgrastim until day 4 on the reduction of chemotherapy-induced leukocytopenia. | **Study population:** Age 61-80 with previously untreated biopsy-confirmed aggressive non-Hodgkin’s lymphoma of the B-cell type  
**Intervention:** Pegfilgrastim s.c. 6 mg on day 2 Vs Pegfilgrastim s.c. 6 mg on day 4  
With R-CHOP-14  
**Sample size:** 103 | Percent of chemotherapy cycles with grade 3 or 4 leukocytopenias  
Day 2: 70%  
Day 4: 43.3%  
P < 0.001  
Percent of chemotherapy cycles with grade 4 only leukocytopenias  
Day 2: 47%  
Day 4: 20.5%  
P < 0.001  
Chemotherapy cycles with grade 3 and 4 infections  
Day 2: 9.4%  
Day 4: 6.0%  
P = 0.118  
Chemotherapy cycles with interventional antibiotics  
Day 2: 30.7%  
Day 4: 21.9%  
P = 0.008  
Deaths  
Day 2: 5  
Day 4: 0  
P = 0.027 | Administration of pegfilgrastim on day 4 was more effective in reducing severe leukocytopenias and resulted in fewer deaths during leukocytopenia. |
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| Burris 2010 | Four randomized Phase II trials | To compare data on severe (grade 4) neutropenia duration and febrile neutropenia incidence in patients receiving chemotherapy with pegfilgrastim administered the same day or 24 hours after chemotherapy | **Study population:** Breast cancer, NHL, NSCLC, ovarian cancer. Age ≥18.  
**Intervention:** Pegfilgrastim on same day as chemotherapy  
Vs  
Pegfilgrastim 24 hours after chemotherapy  
**Sample size:** Across the four studies: 279 | Breast cancer: Mean cycle-1 severe neutropenia duration was 1.2 days (95% confidence limit [CL], 0.7 to 1.6) longer in the same-day compared with the next-day group (mean, 2.6 v 1.4 days). Grade 4 neutropenia was reported among 93% of same-day patients and 78% of next-day patients.  
Lymphoma: Mean cycle-1 severe neutropenia duration was 0.9 days (95% CL, 0.3 to 1.4) longer in the same-day compared with the next-day group (mean, 2.1 v 1.2 days). Grade 4 neutropenia was reported among 86% of same-day patients and 64% of next-day patients.  
In both studies, the ANC profile for patients receiving same-day administration was earlier, deeper, and longer than that for patients receiving next-day administration. | For patients receiving pegfilgrastim with chemotherapy, pegfilgrastim administered 24 hours after chemotherapy completion is recommended. |
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<td>Skarlos 2009&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Observational</td>
<td>To evaluate the rate of febrile neutropenia in patients with high-risk early breast cancer receiving dose-dense chemotherapy and, as primary prophylaxis, either pegfilgrastim on the same day as chemotherapy or filgrastim on days 2-10 of each cycle.</td>
<td><strong>Study population:</strong> Breast cancer, pathological stage T1-4, N1-2, M0. All were participants in two randomized trials (HE10/00 and HE10/05), treated with dose-dense sequential chemotherapy and G-CSF support. Pegfilgrastim-treated patients were matched with filgrastim-treated patients. <strong>Exposures of interest:</strong> Pegfilgrastim same-day vs Filgrastim days 2-10. <strong>Sample size:</strong> Total of 214 patients (107 in each group).</td>
<td>Febrile neutropenia Pegfilgrastim: 13% Filgrastim: 1% p=0.001 Severe neutropenia Pegfilgrastim: 38% Filgrastim: 32% p=0.36 Treatment delays (&gt;2 days) Pegfilgrastim: 57% Filgrastim: 61% p=0.65 Dose reductions Pegfilgrastim: 23% Filgrastim: 23% p=1.0</td>
<td>Pegfilgrastim administered as primary prophylaxis on the same day as dose-dense chemotherapy is less efficacious than filgrastim administered on days 2-10 of each chemotherapy cycle.</td>
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| Hashino 2008<sup>59</sup> | RCT | To assess the cost benefit and clinical efficacy of low-dose granulocyte colony-stimulating factor after standard chemotherapy in patients with non-Hodgkin’s lymphoma | **Study population**: >18 years of age with NHL treated with standard combination chemotherapy. Either de novo or relapsed.  
**Exposures of interest**:  
75 mcg filgrastim in first course and 50 mcg (low dose) lenograstim in second course  
Vs  
50 mcg lenograstim in first course and 75 mcg filgrastim in second course  
**Sample size**: 47 | Grade 4 leukocytopenia (N)  
Filgrastim: 2  
Lenograstim: 3  
p=0.6366  
Grade 4 neutropenia (N)  
Filgrastim: 6  
Lenograstim: 10  
p=0.2207  
Infection (N)  
Filgrastim: 2  
Lenograstim: 6  
p=0.1213 | A low dose of lenograstim might be safe, effective and pharmaco-economically beneficial in patients with advanced-stage NHL. |
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<td>Jang 2008*</td>
<td>RCT</td>
<td>To compare single- versus split-dose lenograstim to enhance engraftment after autologous stem cell transplantation in patients with multiple myeloma or non-Hodgkin’s lymphoma</td>
<td><strong>Study population:</strong> Age 16 to 25 with multiple myeloma or NHL. Scheduled for autologous SCT for symptomatic MM or NHL at chemotherapy-sensitive first relapse or in the first partial response. <strong>Intervention:</strong> Single-dose lenograstim 5 mcg/kg/day, started one day after peripheral blood progenitor cell infusion and continued until an ANC of at least 1.0 X 10^9/L Vs Split-dose lenograstim 2.5 mcg/kg twice a day, started one day after peripheral blood progenitor cell infusion and continued until an ANC of at least 1.0 X 10^9/L</td>
<td><strong>Sample size:</strong> 40 (21 to single-dose and 19 to split-dose)</td>
<td>Median time to neutrophil engraftment ANC &gt;0.5 X 10(9)/L (days) Single dose: 10 Split dose: 10 p=0.243 Median time to platelet engraftment PLT count &gt;20 X 10(9)/L (days) Single dose: 10 Split dose: 14 p=0.009 Duration of hospitalization (days) Single dose: 18 Split dose: 22 p=0.02</td>
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| Cesaro 2013³⁶ | RCT             | To assess the non-inferiority of pegfilgrastim versus filgrastim in speeding the recovery of polymorphonuclear cells (PMN) in pediatric patients who underwent autologous peripheral blood stem cell transplant (PBSCT). | **Study population:** 0 to 17 years of age, affected by leukemia, lymphoma or solid tumor who underwent a first autologous PBSC transplant  
**Intervention:**  
Filgrastim after autologous PBSCT  
9 or more doses of filgrastim 5 mcg/kg/day (maximum 300 mcg/day). Administered beginning from day +3 after PBSC infusion  
Vs  
Pegfilgrastim after autologous PBSC  
single dose of pegfilgrastim 100 mcg/kg (maximum 6 mg). Administered beginning from day +3 after PBSC infusion  
**Sample size:**  
Filgrastim: 29  
Pegfilgrastim: 32 | **Fever of unknown origin**  
Filgrastim: 79.3%  
Pegfilgrastim: 78.1%  
*p=0.9*  
**One-year survival**  
Filgrastim: 84%  
Pegfilgrastim: 75%  
*p=0.8*  
**Time to neutrophil engraftment**  
Arm 1: 10.48 days (mean)  
Arm 2: 10.44 days (mean)  
*p=0.3*  
**Time to platelet engraftment**  
Arm 1: 28.10 days (mean)  
Arm 2: 33.09 days (mean)  
*p=0.5*  
**Grade II-IV mucositis**  
Filgrastim: 75.9%  
Pegfilgrastim: 59.4%  
*p=0.2* | Pegfilgrastim was not inferior to daily filgrastim in pediatric patients who underwent PBSCT |
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| Sari 2013** | RCT              | To compare the effectiveness, toxicities and the cost of filgrastim and lenograstim in children. | **Study population:** Pediatric patients with solid tumors and a history of FN after first course of chemotherapy  
**Intervention:** Filgrastim-lengrastim crossover  
Vs  
Lenograstim-filgrastim crossover  
Filgrastim 5 mcg/kg  
Lenograstim 150 mcg/m²  
s.c. single dose per day  
G-CSF administered 24 hours after last day of chemotherapy as secondary prophylaxis  
**Sample size:** 29 (15 started with filgrastim and 14 started with lenograstim) | Incidence of FN and infection were similar with filgrastim or lenograstim  
CD34+ levels were higher with lenograstim.  
Lenograstim was more expensive | There is no difference following the administration of either lenograstim or filgrastim for the duration of neutropenia, FEN or hospitalization for pediatric cancer patients. For stem cell mobilization, lenograstim was superior to filgrastim. |
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| Shi 2013    | RCT             | To compare the efficacy and safety of a single subcutaneous injection of pegylated filgrastim with daily filgrastim as prophylaxis for neutropenia induced by commonly used chemotherapy regimens | **Study population:** Diagnosis of malignant solid tumor, chemotherapy-naïve.  
**Intervention:** Pegfilgrastim cycle 1 and filgrastim cycle 2 or the reverse.  
Pegfilgrastim: single dose of 100 mcg/kg single s.c. injection on day 3 (pegfilgrastim developed by CSPC Baike Biopharmaceutical)  
Filgrastim: daily s.c. injections of filgrastim 5 mcg/kg/day, beginning on day 3 and continuing until ANC at least 10.0 X 10⁹/l after expected nadir, or for a maximum of 14 days  
**Sample size:**  
Arm 1: 173  
Arm 2: 164 | No grade 4 neutropenia, cycle 1  
Peg-filgrastim: 89.7%  
Filgrastim: 89.5%  
Incidence of grade 3/4 neutropenia, FN, and antibiotic administration were similar in the two groups.  
Mean time to ANC recovery  
Pegfilgrastim: 8.99 days  
Filgrastim: 9.64 days  
\(p=0.001\)  
ANC <1.0 X 10⁹/l  
Arm 1: 16%  
Arm 2: 16% | A single subcutaneous injection of pegylated filgrastim 100 mcg/kg provided adequate and safe neutrophil support comparable with daily subcutaneous injections of unmodified filgrastim 5 mcg/kg/day in patients receiving commonly used standard-dose mild-to-moderate myelosuppressive chemotherapy regimens. |
<table>
<thead>
<tr>
<th>Author, year publication type</th>
<th>Objectives</th>
<th>Methods</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper 2011^7</td>
<td>Meta-analysis</td>
<td>To assessed the effectiveness of G-CSFs pegfilgrastim, filgrastim or lenograstim) in reducing FN incidence in adults undergoing chemotherapy for solid tumors or lymphoma.</td>
<td>Assessed 20 studies of primary G-CSF prophylaxis with no primary G-CSF prophylaxis: five studies of pegfilgrastim; ten of filgrastim; and five of lenograstim. Five studies compared pegfilgrastim with filgrastim</td>
<td>Reduction in FN incidence with primary versus no primary G-CSF</td>
</tr>
</tbody>
</table>

Pegfilgrastim: RR 0.30, 95% CI 0.14 to 0.65
Filgrastim: RR 0.57, 95% CI 0.48 to 0.69
Lenograstim: RR 0.62, 95% CI 0.44 to 0.88
Pegfilgrastim vs filgrastim RR 0.66, 95% CI 0.44 to 0.98
<table>
<thead>
<tr>
<th>Author, year</th>
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<th>Results</th>
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</tr>
</thead>
</table>
| Orciuolo 2011<sup>40</sup> | RCT | To show a lower incidence of febrile episodes in multiple myeloma patients receiving lenograstim vs. filgrastim after high-dose cyclophosphamide for stem cell mobilization | **Study population:** Age 18-70 years; diagnosis of multiple and scheduled to receive high-dose chemotherapy.  
**Intervention:** Filgrastim after high-dose cyclophosphamide for stem cell mobilization vs Lenograstim after high-dose cyclophosphamide for stem cell mobilization  
Administration of the assigned rHuG-CSF started on day 4 until day 7 at a dosage of 30 MU/day, which was increased to 60 MU/day from day 8 until the end of aphaeresis | Patients with febrile episodes  
Filtrastim: 9.1%  
Lenograstim: 1.1%  
p=0.03  
Overall, 10.8% of patients experienced at least one adverse event (any grade), 12.5% (11/88) in the lenograstim and 9.1% (8/88) in the filgrastim group (p = ns) | Lenograstim group presented a significantly higher absolute CD34+ cell number compared with the filgrastim group but no differences were detected for collection efficacy. The study demonstrated a lower incidence of febrile episodes with lenograstim compared to filgrastim |
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</thead>
</table>
| Castagna 2010<sup>42</sup> | RCT | To demonstrate the noninferiority of pegfilgrastim compared with filgrastim after high-dose chemotherapy (HDC) and peripheral blood stem cell (PBSC) support | **Study population:** Age > 18; Hematological malignancy or solid tumor; adequate harvest of CD34-positive cells.  
**Intervention:**  
Pegfilgrastim: a single, s.c. fixed dose (6 mg) was administered 24 h after autologous PBSC infusion (day +1).  
Vs Filgrastim: s.c. weight-based daily dose (5 mcg/kg/day) was administered from day +1 until ANC recovery to >0.5 X 10<sup>9</sup>/l for two consecutive days.  
**Sample size:** 80 (40 in each group) | Duration of neutropenia  
Filgrastim: 5.97 days  
Pegfilgrastim: 6.20 days  
Mean difference 0.23, 95% CI -0.77 to 1.22  
Mean time to reach an ANC of >0.5 X 10<sup>9</sup>/l  
Filgrastim: 11.53  
Pegfilgrastim: 10.75  
Mean difference -0.78, 95% CI -2.97 to 1.42  
Incidence of fever  
Filgrastim: 62%  
Pegfilgrastim: 56%  
p=0.65  
Differences between groups in hematological and nonhematological toxicity were not statistically significant. | Pegfilgrastim is not inferior to filgrastim in hematological reconstitution and represents an effective alternative after HDC and PBSC. |
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</table>
| Gerds 2010   | RCT              | To assess pegfilgrastim versus filgrastim after autologous peripheral blood stem cell transplantation | **Study population:** Adults undergoing APBSCT for multiple myeloma, lymphoma, testicular cancer, or ovarian cancer. Adequate CD34+ cells collected for transplant.  
**Intervention:**  
Filgrastim after APBSCT  
Filgrastim given daily, s.c., 5 mcg/kg, from day +1 until sustained engraftment or through day +25 posttransplant  
Vs  
Pegfilgrastim after APBSCT  
Pegfilgrastim given as single 6 mg s.c. injection on day +1 posttransplant  
**Sample size:** 78 (39 in each arm) | Median time to neutrophil engraftment: 12 days in both groups  
Reached the cytokine discontinuation engraftment endpoint of ANC 5 X 10^9/L X 3 days or 10 X 10^9/L X 1 day:  
Filgrastim: 95%  
Pegfilgrastim: 44%  
Secondary outcomes that were similar in two groups: platelet engraftment, platelet transfusions, positive cultures for bacterial pathogens, days of fever, deaths prior to engraftment, duration of hospital stay | This phase III study failed to demonstrate a difference in time to neutrophil engraftment or any clinical sequelae between pegfilgrastim and filgrastim when given post-APBSCT, with pegfilgrastim achieving a cost savings over filgrastim. |
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</table>
| Engert 2009<sup>61</sup> | RCT | To investigate XM02, in comparison to filgrastim in terms of safety and efficacy in the prevention of chemotherapy-induced neutropenia in NHL. | **Study population:** Adults with aggressive NHL who planned to receive CHOP and were chemotherapy naïve.  
**Intervention:** XM02 Vs Filgrastim  
**Sample size:** 92 (63 in XM02 group and 29 in filgrastim group. | Mean duration of severe neutropenia (days), cycle 1  
XM02: 0.5  
Filgrastim: 0.9  
p=0.1055  
Incidence of FN, cycle 1  
XM02: 11.1%  
Filgrastim: 20.7%  
p=0.1232  
Mean ANC nadir [10⁹/L], cycle 1  
XM02: 1.7  
Filgrastim: 1.1  
p=0.1531  
Mean time to ANC recovery (days), cycle 1  
XM02: 6.0  
Filgrastim: 6.7  
p=0.4939  
AE profile was similar between the XM02 and filgrastim groups | Treatment with XM02 is as beneficial as filgrastim in ameliorating severe neutropenia and FN in patients with NHL receiving chemotherapy. XM02 is safe and well tolerated in the doses applied in this study. |
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</thead>
</table>
| Engert 2009⁶² | Meta-analysis    | To XM02 with filgrastim in terms of its prophylactic effect on the development of febrile neutropenia (FN) during the first chemotherapy cycle in relation to the myelotoxic potency of the applied chemotherapy regimen | Adults with high-risk stage II, III, or IV breast cancer, small cell or advanced non-small cell lung cancer, or aggressive NHL. 3 Phase III trials. Included a total of 608 patients (363 in XM02 group and 245 in filgrastim group). | Incidence of FN in cycle 1  
Breast cancer  
XM02: 12.1%  
Filgrastim: 12.5%  
XM02 minus filgrastim= -0.4%, 95% CI -8.3% to 7.5%  
Lung cancer  
XM02: 15.0%  
Filgrastim: 8.8%  
XM02 minus filgrastim= 6.3%, 95% CI -3.2% to 14.0%  
NHL  
XM02: 11.1%  
Filgrastim: 20.7%  
XM02 minus filgrastim= -9.6%, 95% CI -28.2% to 5.2%  
Adjusted estimate, XM02 minus filgrastim= 1.7%, 95% CI -3.8% to 7.1% | XM02 demonstrated to be non-inferior to filgrastim regarding the incidence of FN, irrespective of the myelotoxicity of the chemotherapy regimen. |
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</table>
| Fox 2009*                | RCT  | To compare the effectiveness, tolerance, and pharmacokinetics of a single dose of pegfilgrastim to daily filgrastim in children and young adults with sarcomas treated with dose-intensive combination chemotherapy | **Study population:** Patients ages <26 y with Ewing sarcoma family of tumors, alveolar rhabdomyosarcoma, stage 3 or 4 embryonal rhabdomyosarcoma, and unresectable or metastatic malignant peripheral nerve sheath tumor or synovial sarcoma  
**Intervention:**  
Pegfilgrastim 100 mcg/kg s.c. as a single dose 24 to 36 h after completion of each cycle of chemotherapy  
Vs  
Filgrastim 5 mcg/kg/d s.c., daily starting 24 h and continuing until the postnadir neutrophil count was ≥10,000/mcL after each cycle of chemotherapy  
**Sample size:**  
Arm 1: 17  
Arm 2: 17 | Median duration of severe neutropenia during first two chemotherapy cycles  
Arm 1: 5.5  
Arm 2: 6.0  
p=0.76  
Median duration of severe neutropenia during second two chemotherapy cycles  
Arm 1: 1.5  
Arm 2: 3.75  
p=0.11  
Twelve of 17 patients on the pegfilgrastim arm experienced 18 episodes (29% of cycles) of grade 3 fever and neutropenia requiring hospitalization during the first four cycles of chemotherapy compared with 15 of 17 patients and 32 episodes (47% of cycles) on the filgrastim arm. | A single dose per cycle of pegfilgrastim was well tolerated and may be as effective as daily filgrastim based on the duration of severe neutropenia and number of episodes of febrile neutropenia and documented infections after dose-intensive treatment with VDC and IE. |
<table>
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</table>
| Gatzemeier   | RCT              | To show that a new granulocyte colony-stimulating factor, XM02, is as safe and effective as filgrastim in the treatment of chemotherapy-induced neutropenia in patients with small cell or non-small cell lung cancer |                                                                                                                                            | Mean duration severe neutropenia, cycle 1 (days)  
XM02: 0.5  
Filgrastim: 0.3  
Mean ANC nadir, cycle 1  
XM02: 2.1  
Filgrastim: 2.9  
Mean time to ANC recovery, cycle 1 (days)  
XM02: 6.3  
Filgrastim: 4.5  
Incidence of FN, cycle 1  
XM02: 15.0%  
Filgrastim: 8.8%  
p=0.2347  
AE profile similar between XM02 and Neupogen. | XM02 demonstrated similar efficacy and safety profile as filgrastim in cycle 1.                                                        |
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</table>
| del Giglio 2008⁶⁴ | RCT | To compare XM02, and with filgrastim after myelotoxic chemotherapy in breast cancer (BC) patients. | **Study population:** Male and female patients ≥ 18 years of age with breast cancer high risk stage II, III or IV, chemotherapy-naïve  
**Intervention:**  
XM02 sc for at least five days starting day after chemotherapy  
Vs  
Filgrastim sc for at least five days starting day after chemotherapy  
**Sample size:**  
Arm 1: 140 (XM02)  
Arm 2: 136 (Filgrastim)  
Arm 3: 72 (placebo) | Mean duration of severe neutropenia, cycle 1  
XM02: 1.1 days  
Filgrastim: 1.1 days  
Placebo: 3.8 days  
Mean ANC nadir, cycle 1  
XM02: 0.7  
Filgrastim: 0.7  
Placebo: 0.2  
Mean time to ANC recovery, cycle 1  
XM02: 8.0 days  
Filgrastim: 7.8 days  
Placebo: 14.0 days  
Incidence of FN, cycle 1  
XM02: 12.1%  
Filgrastim: 12.5%  
Placebo: 36.1% | XM02 was superior to placebo and equivalent to filgrastim in reducing duration of severe neutropenia after myelotoxic chemotherapy  
Immunogenicity was low in all treatment groups.  
Few patients developed binding anti-G-CSF antibodies in all treatment groups whereas no confirmed plausible neutralizing antibodies were detected. |
<table>
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</thead>
<tbody>
<tr>
<td>Pinto 2007</td>
<td>Meta-analysis</td>
<td>To obtain a pooled estimate of the effect of pegfilgrastim compared with filgrastim on incidence of febrile neutropenia (FN), and related outcomes among patients with solid tumors and malignant lymphomas receiving myelosuppressive chemotherapy.</td>
<td>RCTs, including phase II and phase III trials, of adults with non-myeloid cancer 5 RCTS included in the meta-analysis. Total of 617 patients.</td>
<td>FN Pooled RR favors pegfilgrastim RR=0.64, 95% CI 0.43 to 0.97 Differences between study groups in grade IV neutropenia and time to ANC recovery were not statistically significant. Incidence of bone pain was similar in the two study groups.</td>
<td>A single dose of pegfilgrastim performed better than a median of 10-14 days of filgrastim in reducing FN rates for patients undergoing myelosuppressive chemotherapy.</td>
</tr>
<tr>
<td>Author, year</td>
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</table>
| Martino 2006\textsuperscript{46} | RCT | To compare pegfilgrastim vs. filgrastim after high-dose melphalan and autologous peripheral blood stem cell transplantation (APBSCT) in multiple myeloma (MM) patients | **Study population:** de novo diagnosis of multiple myeloma, stages II-III Durie Salmon classification  
**Intervention:** Pegfilgrastim on day +1 after stem cell infusion. Single s.c. injection, 6 mg. Vs Filgrastim starting on day +5 after stem cell infusion and continuing until neutrophil engraftment. 5 mcg/kg/day  
**Sample size:** 37 (18 in pegfilgrastim group and 19 in filgrastim group) | Duration of grade 4 neutropenia (days)  
Pegfilgrastim: 5  
Filgrastim: 6  
p=NS  
Incidence of FN  
Pegfilgrastim: 61.1%  
Filgrastim: 100%  
p=0.003  
Duration of FN (days)  
Pegfilgrastim: 1.5  
Filgrastim: 4  
p=0.005  
Time to platelet engraftment, number of red blood cell or platelet transfusions, and days of hospitalization were similar in the two study groups.  
Incidence of bone pain  
Pegfilgrastim: 10%  
Filgrastim: 12%  
p=NS | Pegfilgrastim can be used with safety and efficacy similar to those provided by daily injections of filgrastim, and is associated with a decreased incidence of infectious events after APBSCT in MM patients |
## Clinical Question 12, Radiation Injury

<table>
<thead>
<tr>
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<th>Methods</th>
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</thead>
<tbody>
<tr>
<td>Dainiak 2011&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Consensus statement</td>
<td>To develop evidence-based management of the hematopoietic syndrome resulting from exposure to ionizing radiation</td>
<td>Published case series and case reports of individuals with HS, published randomized controlled trials of relevant interventions used to treat nonirradiated individuals, reports of studies in irradiated animals, and prior recommendations of subject matter experts were selected.</td>
<td>A strong recommendation was made for the administration of granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor and a weak recommendation was made for the use of erythropoiesis-stimulating agents or hematopoietic stem cell transplantation</td>
<td>Assessment of therapeutic interventions for hematopoietic syndrome in humans exposed to nontherapeutic radiation is difficult because of the limits of the evidence</td>
</tr>
</tbody>
</table>
## Data Supplement 2: Additional Evidence Tables: Quality Results for RCTs

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<tr>
<th>Author</th>
<th>Adequate Randomization</th>
<th>Sufficient Sample Size</th>
<th>Similar Groups</th>
<th>Blinded</th>
<th>Validated and Reliable Measures</th>
<th>Adequate Follow-up</th>
<th>Intent-to-treat Analysis</th>
<th>Insignificant Conflicts of Interest</th>
<th>OVERALL RISK OF BIAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aarts 2013&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>Arun 2011&lt;sup&gt;25&lt;/sup&gt;</td>
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<td>Balducci 2007&lt;sup&gt;13&lt;/sup&gt;</td>
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<td>Cunningham 2013&lt;sup&gt;21&lt;/sup&gt;</td>
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58. Skarlos DV, Timotheadou E, Galani E, et al: Pegfilgrastim administered on the same day with dose-dense adjuvant chemotherapy for breast cancer is associated with a higher incidence of febrile neutropenia as compared to conventional growth factor support: matched case-control study of the Hellenic Cooperative Oncology Group. Oncology 77:107-12, 2009
64. del Giglio A, Eniu A, Ganea-Motan D, et al: XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer 8:332, 2008
DATA SUPPLEMENT 3. Search Strategy String and Dates

Computerized literature searches of MEDLINE and the Cochrane Collaboration Library were performed. The searches of the English-language literature published from October 1, 2005 to September 30, 2014 combined terms for colony-stimulating factors, study designs of interest, cancer, and stem cell transplantation. Results of the database searches were supplemented with contributions from Update Committee members’ personal files.

**CSF**


**Cancer**


**Stem cell transplantation**

"stem cell transplantation"[MeSH] or "stem cell transplantation"[TIAB]

**Randomized trial search**

"Clinical Trials, Phase III as Topic"[Mesh] OR "Clinical Trial, Phase III" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type]

**Combined search**

CSF AND randomized trials AND (cancer OR stem-cell transplantation)

OR

CSF AND systematic[sb]
562 potentially relevant abstracts identified

10 papers identified through expert consultation

84 papers selected for full-text review

18 papers were excluded. Primary reason for exclusion:
- 8 not outcome of interest
- 10 not study design of interest

66 papers met selection criteria
Data Supplement 5: Clinical Questions

1. Among adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians consider when selecting patients for primary prophylaxis of febrile neutropenia with a CSF?

2. Among adults treated with chemotherapy for a solid tumor or lymphoma, what factors should clinicians use to select patients for secondary prophylaxis of febrile neutropenia with a CSF?

3. Are there circumstances in which CSFs should be considered for the treatment of neutropenia among adults with cancer?

4. In what settings should CSFs be used in order to increase chemotherapy dose-density?

5. What is the role of CSFs as adjuncts to progenitor-cell transplantation?

6. What is the role of CSFs in the setting of acute leukemia or myelodysplastic syndromes?

7. Should CSFs be avoided in patients receiving concomitant chemotherapy and radiation therapy?

8. Are there CSF recommendations that apply specifically to older adults, and that differ from recommendations in younger adults?

9. How should CSFs be used in the pediatric population?

10. What are recommendations for the initiation, duration, dosing, and administration of CSFs?

11. Do CSFs differ in efficacy?

12. What is the role of CSFs in the treatment of radiation injury?