ONLINE SUPPLEMENTARY MATERIALS ONLY

A systematic literature review of the efficacy, effectiveness, and safety of filgrastim

Journal: *Supportive Care in Cancer*

Authors: David C. Dale,[1] Jeffrey Crawford,[2] Zandra Klippel,[3] Maureen Reiner,[4] Timothy Osslund,[5] Ellen Fan,[6] Phuong Khanh Morrow,[3] Kim Allcott,[7] Gary H. Lyman[1,8]

Affiliations: [1]Department of Medicine, University of Washington, Seattle, WA 98195, USA; [2]Duke Cancer Institute, Duke University Medical Center, Durham, NC 27710, USA; [3]Clinical Development, Amgen Inc., 1 Amgen Center Drive, Thousand Oaks, CA 91320, USA; [4]Global Biostatistical Sciences, Amgen Inc., 1 Amgen Center Drive, Thousand Oaks, CA 91320, USA; [5]Pre-Pivotal Drug Product Technologies, Amgen Inc., 1 Amgen Center Drive, Thousand Oaks, CA 91320, USA; [6]Global Scientific Affairs, Amgen Inc., 1 Amgen Center Drive, Thousand Oaks, CA 91320, USA; [7]Oxford PharmaGenesis Ltd, Tubney Warren Barn, Tubney, Oxford OX13 5QJ, UK; [8]Public Health Sciences Division and Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA

Corresponding author:

David C. Dale, MD

Department of Medicine, University of Washington

1959 NE Pacific St

Seattle, WA 98195, USA

Phone: +1 206-543-7215; Fax: 206-685-4458

Email: dcdale@uw.edu

Online Resource 1. Details of search strategy and results

Number	MEDLINE & MEDLINE InProcess Searches	Results
1	rhg-csf.mp.	1139
2	rhgcsf.mp.	19
3	rhg?csf.mp.	31
4	r-met-HuG-CSF.mp.	5
5	r-metHuG-CSF.mp.	85
6	rmet?HuG-CSF.mp.	8
7	recombinant human.mp.	35091
8	recombinant methionyl human.mp.	123
9	g-csf.mp.	12140
10	gcsf.mp.	418
11	granulocyte colony-stimulating factor.mp.	17537
12	1 or 2 or 3 or 4 or 5 or 6	1258
13	7 or 8	35192
14	9 or 10 or 11	20201
15	13 and 14	2059
16	filgrastim.mp.	2061
17	NEUPOGEN.mp.	144
18	12 or 15 or 16 or 17	4254
19	limit 18 to (English language and humans)	3406
	EMBASE Searches	
1	rhg-csf.mp.	1342
2	rhgcsf.mp.	37
3	rhg?csf.mp.	46
4	r-met-HuG-CSF.mp.	5

5	r-metHuG-CSF.mp.	100
6	rmet?HuG-CSF.mp.	10
7	recombinant human.mp.	43024
8	recombinant methionyl human.mp.	141
9	g-csf.mp.	18150
10	gcsf.mp.	1491
11	granulocyte colony-stimulating factor.mp.	46811
12	1 or 2 or 3 or 4 or 5 or 6	1487
13	7 or 8	43139
14	9 or 10 or 11	48580
15	13 and 14	2677
16	filgrastim.mp.	3643
17	NEUPOGEN.mp.	2276
18	12 or 15 or 16 or 17	7997
19	limit 18 to (human and English language)	5858
20	limit 18 to conference abstract	833
21	19 not 20	5248

Cochrane Library Searches

1	rhg-csf	172
2	rhgcsf	0
3	rhg*csf	2
4	r-met-HuG-CSF	2
5	r-metHuG-CSF	62
6	rmet*HuG-CSF	1
7	"recombinant human"	3718
8	"recombinant methionyl human"	41

9	g-csf	1718
10	gcsf	77
11	"granulocyte colony-stimulating factor"	2138
12	#1 or #2 or #3 or #4 or #5 or #6	235
13	#7 or #8	3758
14	#9 or #10 or #11	2776
15	#13 and #14	318
16	filgrastim	660
17	NEUPOGEN	51
18	#12 or #15 or #16 or #17	992

	Congress Searches[a]
1	Filgrastim
2	NEUPOGEN
3	rhG-CSF
4	r-met-HuG-CSG

[a]The 16 congresses searched include: Academy of Managed Care Pharmacy, American College of Clinical Pharmacy, American Society for Blood and Marrow Transplantation, American Society of Clinical Oncology, American Society of Hematology, American Society of Hospital Pharmacists, European Hematology Association, European Society for Blood and Marrow Transplantation, European Society for Medical Oncology; ISPOR (International Society for Pharmacoeconomics and Outcomes Research); including European, North American, and Latin American conferences, Multinational Association of Supportive Care in Cancer, and San Antonio Breast Cancer Symposium.

Online Resource 2: Studies included in the meta-analysis of data in CIN

Studies that had reported sufficient homogeneous data for incidence of FN, grade 3 and 4 neutropenia, or bone pain were identified, and meta-analysis was performed for these outcomes. Meta-analysis for incidence of FN included data from 9 of the 11 identified randomized controlled trials (RCTs) [4, 19-21, 23, 24, 26, 27, 29], meta-analysis for incidence of grade 3 or 4 neutropenia included data from 5 RCTs [4, 19, 20, 25, 27] and 1 nonrandomized clinical trial (NCT) [30], and meta-analysis for incidence of bone pain included data from 5 RCTs [4, 23, 25, 27, 28]. Data for patients enrolled in the RCT by Osby et al 2003 [27] were analyzed separately for the subgroup of patients with non-Hodgkin's lymphoma (NHL) who received cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) (filgrastim, n=101; no filgrastim, n=104) and those who received cyclophosphamide, mitoxantrone, vincristine, prednisone (CNOP) (filgrastim, n=103; no filgrastim, n=100) for incidence of FN, grade 3 or 4 neutropenia, and bone pain. Also data for patients enrolled in the NCT by Blayney et al 2005 [30] were analyzed separately for the subgroup of 33 patients with non-small cell lung cancer (NSCLC) (filgrastim, n=24; no filgrastim, n=9) and the subgroup of 15 patients with NHL (filgrastim, n=10; no filgrastim, n=5) who had received the 21-day standard chemotherapy regimens.

Online Resource 3: Details of search results

Part 1 of the search identified 9953 records. Of these 9646 were retrieved from the electronic databases. An additional 12 records where identified from reviewing bibliographies of 3 recent systematic review articles identified as part of the search–Cooper et al 2011 [13], Renner et al 2012 [14], and Sheppard et al 2012 [15]. Removal of 3364 duplicates and 1 record (Erduran et al 1994) that was not available for further assessment resulted in 6588 records. From these, 4934 records were excluded on the basis of title/abstract screening, leaving 1654 records. Full-text review of the 1654 records eliminated another 460, leaving 1194 publications in total that met the eligibility criteria for part 1 of the search.

In part 2 of this analysis, the 1194 publications selected in part 1 were screened to identify studies comparing originator filgrastim (NEUPOGEN®) to placebo or no treatment. Of these, 828 were excluded on the basis of title/abstract screening (Figure 1). Full-text review of the remaining 366 publications led to exclusion of 336 publications. An additional four publications were excluded on further review: two reported filgrastim use outside its US-approved indications (one in established FN [52] and the other for priming with filgrastim [53]), one reported results from a subset population of a phase 3 clinical trial in severe chronic neutropenia (SCN) [54], and another compared filgrastim to other hematopoietic growth factors with no placebo or no treatment comparator arm [55]. The remaining 26 publications consisted of 25 full articles and one abstract (He et al 2012) [19]. The 26 publications were from 25 separate studies; two publications, Heil et al 1997 [33] and Heil et al 2006 [39], were from 1 RCT that evaluated filgrastim as an adjunct to chemotherapy for adults with de novo acute myeloid leukemia. Heil et al 1997 [33] reported the primary safety and efficacy results, and Heil et al 2006 [39] reported long-term survival data from the trial.

Online Resource 4: Key characteristics of studies that compared filgrastim with placebo or no treatment by indication and study type

Author, Year	Country	Disease Type	Chemotherapy	Filgrastim Intervention: Patient Numbers, Dose, Route, Timing, and Treatment Duration	Age (years) Mean ± SD or Median (range)	Reported Outcomes	Follow-Up Time
Chemotherapy-induced neutropenia							
Randomized controlled trials							
Crawford et al, 1991 [4]	US	SCLC	CAE	N = 199 Filgrastim: n = 95 Placebo: n = 104 230 µg/m^2/day, SC; from day 4 to 17 after start of chemotherapy (21 days cycle); administered for a median of 13 days	Median (range) Filgrastim: 62 (31–78) Placebo: 63 (31–80)	Incidence of fever with neutropenia and ANC<0.5×10^9/L, mean absolute neutrophil nadir, duration of neutropenia, antibiotic use per cycle, duration of hospital stay per cycle, AEs	NR
Trillet-Lenoir et al, 1993 [23]	Europe (13 centers)	SCLC	CDE	N = 129 Filgrastim: n = 65 Placebo: n = 64 230 µg/m^2, SC, on day 4 for a maximum of 14 days during each cycle	Median (range) Filgrastim: 58 (NR) Placebo: 60 (NR)	Incidence of FN (primary outcome), duration and severity of neutropenia, antibiotic use, duration of hospitalization, tumor response rates, survival	NR
Zinzani et al, 1997 [25]	Italy	High-grade NHL	VNCOP	N = 149 Filgrastim: n = 77 No filgrastim: n = 72 5 mg/kg/day, SC; starting on day 3 of every week for 5 consecutive days	Median (range) Filgrastim: 69 (60–82) No filgrastim: 70 (60–80)	CR rate, RFS, PFS, OS, chemotherapy dose delay, RDI, incidence of infections, neutropenia	30 months
Pui et al, 1997 [29]	US	ALL	Remission-induction therapy (not specified)	N = 148 Filgrastim: n = 73 Placebo: n = 75 10 mg/kg/day, SC; administered for 15 days	Median (range) Filgrastim: 5.8 (0.2–17.9) Placebo: 5.7 (1.0–16.9)	FN, EFS, rate of hospitalization, severe infections, hospital stays	Event free survival at 3 years: 83% in both groups.
Larson et al, 1998 [28]	US	ALL	Intensive remission induction chemotherapy (not specified)	N = 198 Filgrastim: n = 102 Placebo: n = 96 5 µg/kg/day, SC Course 1: starting ~12 to 24 h after 3rd dose of daunorubicin Course 2: starting on day 2	Median age (range) 35 (16–79)	ANC and platelet recovery, duration of neutropenia and thrombocytopenia, duration of hospitalization and fever >38.5°C, DFS, OS, toxicity	Median (range), years 4.7 (2.0–6.4)
Fossa et al, 1998 [24]	Norway, UK, Hungary, The	Germ cell tumors	BEP, EP, BOP, VIP-B	N = 259	Median (range)	Neutropenic fever, grade 4 FN, DFS, OS, RDI	Not specified

Author, Year	Country	Disease Type	Chemotherapy	Filgrastim Intervention: Patient Numbers, Dose, Route, Timing, and Treatment Duration	Age (years) Mean ± SD or Median (range)	Reported Outcomes	Follow-Up Time
	Netherlands, Belgium			Filgrastim: n = 129 No filgrastim: n = 130 5 µg/kg, SC, QD; administered for a median of 14 days (BEP/EP) or 7 days (VIP)	28 (15-65)		
Doorduijn et al, 2003 [26]	The Netherlands, Belgium	NHL	CHOP	N = 389 Filgrastim: n = 197 No filgrastim: n = 192 300 µg, SC; on days 2 to 11; administer for a median of 9 days	Mean ± SD 73 ± 5	RDI, CR rate, OS, EFS, PFS, DFS	Median: 33 months Total: 3 years
Osby et al, 2003 [27]	Sweden, Norway, Denmark, Finland	NHL	CHOP, CNOP	N = 455 Filgrastim = 226 No filgrastim = 229 5 µg/kg, SC; starting on day 2 for a maximum of 14 days, discontinued if ANC >10×10^9/L on day 11 or later	Median (range) 71 (60–86)	TTF (primary outcome), CR rate, OS, DFS, RDI, incidence of granulocytopenia, infections requiring hospitalizations	Median (range), months: 57 (18–91)
Papaldo et al, 2003 [20]	Italy	Breast cancer	EC	N = 503 Filgrastim: n = 254 No filgrastim: n = 249 300 or 400 g/day, SC	Median (range) 45 (25–65)	DFS, OS, dose adjustments, dose intensity, toxicity and deaths or discontinuations due to toxicity	Median: 55 months
Del Giglio et al, 2008 [21]	Brazil, Romania, Germany, Belarus, Slovenia, South Africa, Chile, Russia, Lithuania, Poland	Breast cancer	Docetaxel, doxorubicin	N = 348 Filgrastim: n = 136 XM02: n = 140 Placebo/XM02: n = 72 Filgrastim or XM02: 5 µg/kg/day, SC; starting on day 1 after chemotherapy; administered for a median of 9 days	Median (range) Filgrastim: 51 (28–74) XM02: 51 (25–75) Placebo/XM02: 48 (28–74)	DSN in cycle 1 (defined as # of days with grade 4 neutropenia with an ANC<$0.5\text{x}10^9$/L), incidence of FN, depth of ANC nadir, time to ANC recovery, AEs	NR
He et al, 2012 [19]	China	Breast cancer	TEC	N = 107 PP filgrastim: n = 53 No PP filgrastim: n = 54 PP: 3 µg/kg/day on day 3 to 8 (n = 53); administered for a median of 5 days No PP: 5 µg/kg/day on day of grade 3/4 neutropenia,	NR	Neutropenic fever, neutropenia, side-effects, costs, scores on the EORTC QLQ-C30 questionnaires	NR

Author, Year	Country	Disease Type	Chemotherapy	Filgrastim Intervention: Patient Numbers, Dose, Route, Timing, and Treatment Duration	Age (years) Mean ± SD or Median (range)	Reported Outcomes	Follow-Up Time
				FN, and delayed recovery of ANC on day 21 until neutrophil recovery (N = 54)			
Nonrandomized clinical trial							
Blayney et al, 2005 [30]	US	NSCLC and NHL	NSCLC: etoposide, cisplatin NHL: CHOP	N = 104 NSCLC (n = 55): Filgrastim = 46 No filgrastim = 9 NHL (n = 49): Filgrastim = 44 No filgrastim = 5 NSCLC trial: 5 µg/kg/day starting on day 4 NHL trial: 5 µg/kg/day starting on day 2; administered for a median of 10 to 12 days	Median (range) NSCLC (n = 55): 59 (39-79) NHL (n = 49): 53 (28-73)	Blood counts and blood chemistry, physical examinations, concomitant medications, AEs	NR
Observational studies							
Gilad et al, 1999 [31]	Israel	Breast cancer, lung cancer, NHL, Hodgkin's disease, and others	Various	N = 209 (1079 cycles) Cycles with PP filgrastim = 66 Cycles with no PP = 1013 3–5 µm/kg of body weight; within 48 hours of chemotherapy	Median (range) 55 (19–88)	Incidence of FN, infection, infection-related hospitalization, mortality	NR
Hershman et al, 2009 [32]	US	Breast cancer, lung cancer, ovarian cancer, colon cancer, lymphoma	Various	N = 3123 PP G-CSF (filgrastim or pegfilgrastim) = 822 No PP G-CSF (delayed filgrastim or pegfilgrastim = 1523 or no G-CSF = 778)	<65 years: 61% in PP vs 58% in no G-CSF >65 years: 38% in PP vs 41.2% in no G-CSF	Risk of FN, patient characteristics associated with increased risk of FN	NR
Altwairgi et al, 2013 [18]	Canada	Breast cancer	Adjuvant treatment (taxane regimens ± anthracyclines)	N = 239 PP G-CSF (filgrastim or pegfilgrastim) = 145 No PP G-CSF (secondary G-CSF or no G-CSF) = 94 Filgrastim QD for 7 days; pegfilgrastim, single dose, 24 h after chemotherapy;	Median (range) 55 (32–80)	Use of filgrastim or pegfilgratim as primary prophylaxis, subsequent dose reductions, chemotherapy delays, treatment discontinuation, RDI, FN events	NR

Author, Year	Country	Disease Type	Chemotherapy	Filgrastim Intervention: Patient Numbers, Dose, Route, Timing, and Treatment Duration	Age (years) Mean ± SD or Median (range)	Reported Outcomes	Follow-Up Time
				administered for a median of 7 days			
Acute myeloid leukemia							
Randomized controlled trials							
Heil et al, 1997 [33][a]	Germany Spain Belgium Portugal Sweden Austria UK Italy Australia	AML	Induction and consolidation chemotherapy with daunorubicin, cytarabine, and etoposide	N = 521 Filgrastim: n = 259 No filgrastim: n = 262 5 µg/kg/day, SC; from 24 hours after last chemotherapy dose until ANC ≥1.0x10^9/L for 3 consecutive days or ≥10x10^9/L for 1 day; administered for a median of 13 days	Median (range) Filgrastim: 54 (16–89) Placebo: 54 (16–88)	Incidence and duration of fever, duration of neutropenia, incidence of infections, requirement for parenteral anti-infectives, duration of hospitalization, AEs, CR rate, DFS, OS	Median (range), months 24 (5–40)
Godwin et al, 1998 [35]	US	AML	Induction with cytarabine, daunorubicin	N = 211 Filgrastim: n = 106 Placebo: n = 105 400 µg/m^2, IV; from day 11, QD until ANC 1000 µL	Median (range) 68 (56–88)	Treatment failures, toxicity criteria, duration of neutropenia, duration of thrombocytopenia, number of febrile days, antibiotic days, numbers and types of infection, number of hospital days	≤3 years
Harousseau et al, 2000 [37]	France	AML	Consolidation with either high-dose cytarabine plus mitoxantrone or 2 amsacrine plus etoposide	N = 194 Filgrastim: n = 100 No filgrastim: n = 94 5 µg/kg, SC; from 1 day after ICC, QD until granulocytes >1x10^9/L or >0.5x10^9/L on 3 consecutive days; administered for a median of 8.4 days	Median (range) Filgrastim: 47.5 (16–60) No filgrastim: 45 (15–60)	Duration of neutropenia (primary endpoint), incidence of septicemia and toxic deaths, duration of antibacterial and antifungal therapy, duration of hospitalization, # of confirmed infections, # of days of fever, thrombocytopenia, number of RBCs and platelet transfusions	Median: 26 months
Usuki et al, 2002 [36]	Japan	de novo AML	Induction chemotherapy not specified	N = 245 Filgrastim: n = 120 No filgrastim: n = 125 200 µg/m^2; from 48 h after completion of chemotherapy until ANC >1.5×10^9/L	Median (range) Filgrastim: 48.5 (15–75) No filgrastim: 49.7 (15–87)	OS, hematological recovery, fever and infection, CR rate	Median: 20 months
Heil et al, 2006 [39][a]	Germany, Spain, Austria,	AML	Standard induction and	N = 521 Filgrastim: n = 259	Median (range): Filgrastim: 54 (16–89)	OS, DFS, time to death	Median (range),

Author, Year	Country	Disease Type	Chemotherapy	Filgrastim Intervention: Patient Numbers, Dose, Route, Timing, and Treatment Duration	Age (years) Mean ± SD or Median (range)	Reported Outcomes	Follow-Up Time
	UK, Belgium, Portugal, Sweden, Italy, Australia		consolidation chemotherapy (not specified)	Placebo: n = 262 5 µg/kg/day, SC; from 24 hours after last chemotherapy dose until ANC ≥1.0x10^9/L for 3 consecutive days or ≥10x10^9/L for 1 day	Placebo: 54 (16–88)		years 7 (0.5–8.3)
Beksac et al, 2011 [34]	Turkey	AML	De novo AML induction therapy cytarabine and idarubicin	N = 260 Filgrastim: n = 123 No filgrastim: n = 137 5 µg/kg IV; from day 8 of chemotherapy until ANC >0.5×10^9/L for 2 consecutive day	Median (SD) Filgrastim: 38.9 (13.5) No filgrastim: 38.3 (14.0)	Duration of fever, use of antibacterial, antifungal, and antiviral therapies, duration of hospitalization, WBC recovery, severity and duration of leukopenia, need for RBC or platelet transfusions, survival, mortality rates and AEs, response to chemotherapy	3 years
Nonrandomized clinical trial							
Moore et al, 1997 [38]	US	AML	Consolidation with diaziquone, mitoxantrone	N = 123 Filgrastim: n = 61 No filgrastim: n = 62 5 µg/kg; from day 4 of the chemotherapy course and continued until granulocyte ≥500/µL on 2 successive days	Median (range) 41 (16–59)	Granulocyte recovery (defined as the number of days from the date granulocytes decreased below 500/mL to the date of recovery of granulocytes ≥500/mL for 2 successive days), platelet recovery (defined as recovery to a post-nadir platelet count of ≥20000/µL on 2 consecutive days without transfusions and evidence that platelet counts were stable or rising), survival time, duration of CR, duration of hospitalization and antibiotic use	Median 63 months
Severe chronic neutropenia							
Randomized controlled trial							
Dale et al, 1993 [6]	US	Severe chronic neutropenia	NA	N = 123 Filgrastim: n = 63 4-month observation + filgrastim: n = 60 Total who received filgrastim = 120 Idiopathic neutropenia: 3.45 µg/kg/d BID, SC Cyclic neutropenia: 5.75 µg/kg/d BID, SC	Median (range) 12.1 (0.6–75.7)	Complete blood counts, bone marrow aspirates, physical examinations, concomitant medications, incidence and duration of infections, antibiotic use and hospitalizations, AEs	≤4 months

Author, Year	Country	Disease Type	Chemotherapy	Filgrastim Intervention: Patient Numbers, Dose, Route, Timing, and Treatment Duration	Age (years) Mean ± SD or Median (range)	Reported Outcomes	Follow-Up Time
				Congenital neutropenia: 11.50 µg/kg/d BID, SC. Dose was adjusted to maintain a median monthly ANC of 1.5–10.0×10^9/L			
Observational study							
Yilmaz et al, 2007 [40]	Turkey	Idiopathic SN, n = 31 Congenital SN, n = 3 Familial SN, n = 3 Auto immune SN, n = 2	NA	N = 39 Filgrastim: n = 16 No filgrastim: n = 23 5 µg/kg/day; depending on response, the dose was gradually decreased to twice a week, then once a week, and eventually stopped if the ANC continued to be >1x10^9/L	Median (range) 15 months (3 months to 17 years)	Neutropenia resolved, neutropenia persisted	≤57 months
Bone marrow transplantation							
Randomized controlled trial							
Gonzalez-Vicent et al, 2004 [41]	Spain	Acute leukemia, lymphoma, solid tumor	NA	N = 117 Filgrastim: n = 51 No filgrastim: n = 66 10 µg/kg/day, SC; starting on day +5 until ANC was >0.5x10^9 /L	Median (range) Filgrastim: 8 (1–18) No filgrastim: 8 (1–18)	Neutrophil engraftment, engraftment kinetics, duration of hospitalization, supportive care and treatment costs	NR
Observational study							
Gertz et al, 2011 [42]	US	Multiple myeloma	NA	N = 664 Filgrastim: n = 498 No filgrastim: n = 166 5 µg/kg/day post-transplant day + 6 and until neutrophil engraftment was established	Median (range): Filgrastim: 8 (1–18) No filgrastim: 8 (1–18)	Neutrophil engraftment, duration of hospitalization, frequency of bacteremia, AEs	NR

Note: filgrastim = originator filgrastim (NEUPOGEN®).

[a]The two publications Heil et al 1997 [33] and Heil et al 2006 [39] are from the same study.

Chemotherapy regimens: BEP = cisplatin, etoposide, bleomycin; BOP = bleomycin, vincristine, cisplatin; CAE = cyclophosphamide, doxorubicin, etoposide; CDE = cyclophosphamide, doxorubicin, etoposide; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone; EC = epirubicin, cyclophosphamide; EP = BEP without bleomycin; VIP-B = cisplatin, ifosfamide, etoposide, bleomycin; TEC = docetaxel, epirubicin, cyclophosphamide; VNCOP = cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin, prednisone

AE = adverse event; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; ANC = absolute neutrophil count; BID = twice a day; CR = complete response; DFS = disease-free survival; DSN = duration of severe neutropenia; EFS = event-free survival; EORTC = European Organization for Research and Treatment of Cancer; FN = febrile neutropenia; G-CSF = granulocyte colony-stimulating factor; ICC = intensive consolidation chemotherapy; IV = intravenous; NA = not applicable; NHL = non-Hodgkin's lymphoma; NR = not reported; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; PP = primary prophylaxis; QD = daily; QLQ = quality of life questionnaire;; SC = subcutaneous; SCLC = small cell lung cancer; SD = standard deviation; SN = severe neutropenia; RBC = red blood cell; RDI = relative dose intensity; RFS = relapse-free survival; TTF = time to treatment failure; WBC = white blood cell.

Online Resource 5: Filgrastim dose, timing, and duration

In chemotherapy-induced neutropenia (CIN), filgrastim dose was reported in the 11 RCTs [4, 19-21, 23-29], 1 NCT [30], and 1 observational study [31], but was not reported in 2 observational studies [18, 32] (Online Resource 4). Filgrastim dose was not consistent across the 13 studies, with studies reporting filgrastim doses of 300 μg [26], 230 μg/m^2/day [4, 23], 3–5 μg/kg/day [19, 21, 24, 27, 28, 30], 3–5 μm/kg [31], 5–10 mg/kg/day [25, 29], and 300 or 400 g/day [20]. Similarly, timing of filgrastim administration with respect to chemotherapy administration, reported in 10 studies, was not consistent across the studies, with filgrastim administered within 12-24 hours after the third dose of chemotherapy [28], within 2 days of chemotherapy [31], and on day 1 [21], day 2 [26, 27], day 3 [19, 25], or day 4 after start of chemotherapy [4, 23], and on day 4 in NSCLC or day 2 in NHL [30] after start of chemotherapy. Duration of filgrastim administration, reported in 10 studies [4, 19, 21, 23-27, 29, 30], varied across the studies, from a maximum of 5 days to a median of 14 days.

In AML, filgrastim dosing was reported in the 5 RCTs [33-37] and 1 NCT [38] (Online Resource 4). Filgrastim dose was not consistent across the 6 studies, with studies reporting filgrastim doses of 200–400 μg/m^2/day [35, 36] or 5 μg/kg/day [33, 34, 37, 38]. Similarly, timing of filgrastim administration with respect to chemotherapy administration was not consistent across the 6 studies, with filgrastim administered 24 hours after last chemotherapy dose [33], from day 1 after intensive consolidation chemotherapy [ICC] [37], from day 2 after completion of chemotherapy [36], and from day 4 [38], day 8 [34], and day 11 [31] of the chemotherapy course. Duration of filgrastim administration was reported in the 6 studies and was maintained for varying periods, targeting different pre-specified absolute neutrophil count (ANC) levels.

In SCN, filgrastim dose was reported as 3.5-11.5 μg/kg/day in the RCT [6] and 5 μg/kg/day in the observational study [40] and was adjusted as needed in both studies to maintain a pre-specified ANC level. In bone marrow transplantation (BMT), filgrastim dose was reported as 10 μg/kg/day in the RCT [41], started at post-transplant day +5, and dosed until

ANC was >0.5 x 10^9/L; whereas it was started at 5 μg/kg/day in the observational study [42], started at post-transplant day +6, and dosed until neutrophil engraftment was established.

Online Resource 6: Efficacy, effectiveness, and safety of filgrastim compared with placebo or no treatment in CIN

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Grade 3 or Grade 4 Neutropenia	Incidence of Infection/Antibiotic Use	Incidence/Duration of Hospitalizations	RDI, Dose Delays, or Dose Reductions	Survival/ Mortality	Incidence of G-CSF-Related AEs n (%)[a]
Randomized controlled trials										
Solid tumors										
Crawford et al, 1991 [4]	SCLC	N = 199 Filgrastim = 95 Placebo = 104	–	FN incidence in cycle 1 28% vs 57% *P* <0.001 FN incidence across 6 cycles 40% vs 77% *P* <0.001 Median duration (days) in cycle 1 4 vs 5 NS	Grade 4 neutropenia incidence in cycle 1 84% vs 98% *P* = 0.001 Median duration (days) in cycle 1 3 vs 6 *P* <0.001 Median duration (days) across 6 cycles 1 vs 6	Infection rate across 6 cycles 6.5% vs 13.3% G-CSF vs placebo: 51% reduction/cycle Mean days of antibiotic use/cycle 1.2 vs 2.3 RR (placebo vs filgrastim) 1.9, 95% CI: 1.44-2.51	Mean days of hospitalization/cycle) 2.3 vs 4.2 Relative risk (placebo vs filgrastim) 1.55, 95% CI: 1.26-1.91	NR	Median OS (months) 11.4 vs 12.2	Mild to moderate bone pain 20% vs 0% Mild rashes or Itching 6% vs 6% AE leading to withdrawal request (abdominal pain, diffuse aches and pains, preexisting eczema flare-up) 3 (3%) vs 0 (0%)
Trillet-Lenoir et al, 1993 [23]	SCLC	N =129 Filgrastim = 65 Placebo = 64	–	FN incidence 26% vs 53% *P* = 0.002	Median duration (days) of neutropenia over 6 cycles: 6 vs 15	Infection rate 20% vs 33% *P* = 0.101 Infection-related deaths 1 vs 3 IV antibiotics use 37% vs 58% *P* < 0.02	Infection-related hospitalization 39% vs 58% *P* < 0.04	Dose reduction ≥15% over all cycles 29% vs 61% *P* < 0.001 Dose delay ≥2 days in ≥1 cycles 29% vs 47%	Median survival (months) Extensive disease 8.9 vs 9.5 Limited disease 13.9 vs 12.8	Incidence 15% vs 9% Musculoskeletal pain, alopecia, nausea, vomiting, stomatitis, diarrhea

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Grade 3 or Grade 4 Neutropenia	Incidence of Infection/Antibiotic Use	Incidence/Duration of Hospitalizations	RDI, Dose Delays, or Dose Reductions	Survival/ Mortality	Incidence of G-CSF-Related AEs n (%)[a]
Papaldo et al, 2003 [20]	Breast Cancer	N = 503 Filgrastim = 254 No filgrastim = 249	–	FN incidence 1.2% vs 6.6% *P* = 0.004	Grade 3/4 Neutropenia 28.6% vs 81.6% *P* < 0.00001	NR	NR	Dose reduction 1.4% vs 3.6% *P* = 0.002 Dose delay 3.6% vs 10% *P* < 0.0001 Dose intensity 98.1% vs 95.5% NS	5-year OS 80.6% vs 79.6% NS DFS 67.2% vs 72.9% NS	Bone pain (grade 1 to 3) 42.5% Fever (grade 1/2) 16.3%
Del Giglio et al, 2008 [21]	Breast cancer	N = 348 Filgrastim = 136 XM02 = 140 Placebo/XM02 = 72	–	FN incidence 20.7% vs 22.1% vs 41.7%	Mean duration (days) of severe neutropenia Cycle 1 1.1 vs 1.1 vs 3.8 Cycle 4 0.7 vs 0.7 vs 0.6	NR	NR	NR	3 deaths in cycle 1 1 sepsis and 1 cardiorespiratory arrest in placebo; 1 ischemic stroke in XM02	Most commonly reported drug-related AEs bone pain (10.3%) asthenia (7.8%) myalgia (6.3%) diarrhea (5.2%)
He et al, 2012 [19]	Breast cancer	N = 107 PP filgrastim = 53 No PP filgrastim = 54	–	FN incidence 6.94% vs 15.32% *P* = 0.0482	Grade 3/4 neutropenia 12.2% vs 52.3% *P* < 0.001	NR	NR	NR	NR	Grade 3/4 neutropenia 12.2 vs 52.3 *P* < 0.001 Reduced in filgrastim vs no filgrastim: anemia, asthenia, stomatitis, anorexia, myalgia, dysgeusia
Fossa et al, 1998 [24]	Germ cell tumors	N = 259 Filgrastim = 129 No filgrastim = 130	–	FN incidence 20% vs 30% *P* < 0.052	NR	Blood culture proven sepsis 6.3% vs 7.8%	NR	Received ≥6 chemotherapy cycles 86% vs 71% *P* = 0.003	1-year survival 83% (78–91) vs 75% (67–82)	n, (%) BEP/EP and BOP/VIP-B WBC

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Grade 3 or Grade 4 Neutropenia	Incidence of Infection/Antibiotic Use	Incidence/Duration of Hospitalizations	RDI, Dose Delays, or Dose Reductions	Survival/ Mortality	Incidence of G-CSF-Related AEs n (%)[a]
								Dose intensity: Significantly higher dose intensities with filgrastim	Death due to toxicities 5 vs 15	Grade 3: 7 (11)/12 (18) and 23 (36)/24 (37) Grade 4: 8 (13)/12 (18) and 8 (13)/32 (49) Platelet count Grade 3: 14 (22)/15 (23) and 4 (6)/10 (15) Grade 4: 13 (21)/25 (38) and 6 (9)/22 (33) Neutropenic fever 9 (14)/16 (25) and 8 (13)/30 (46) Blood culture proven sepsis 4 (6)/4 (6) and 3 (5)/7 (11) Mucosal toxicity Grade 3: 4 (6)/4 (6) and 2 (3)/3 (5) Grade 4: 0 (0)/0 (0) and 0 (0)/3 (5) Pulmonary toxicity Grade 1/2: 16 (25)/11

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Grade 3 or Grade 4 Neutropenia	Incidence of Infection/Antibiotic Use	Incidence/Duration of Hospitalizations	RDI, Dose Delays, or Dose Reductions	Survival/ Mortality	Incidence of G-CSF-Related AEs n (%)[a]
										(17) and 10 (16)/9 (14) Grade 3: 0 (0)/3 (5) and 2 (3)/1 (2) Grade 4: 2 (3)/1 (2) and 0 (0)/3 (5)
NHL										
Zinzani et al, 1997 [25]	High-grade NHL	N = 149 Filgrastim = 77 No filgrastim = 72	–	NR	Grade 4 neutropenia incidence 23.0% vs 55.5% *P* = 0.00005	Infections 4/77 pts (5%) vs 15/72 pts (21%) *P* = 0.004 Antibiotic use For filgrastim, 4 pts with minor infections required symptomatic treatments and/or oral antibiotics vs For control, 5 pts with major infections and 10 pts with minor infections required parenteral antibiotics and/or hospitalization	NR	Average RDI 95% vs 85% NS	OS at 30 months 64% vs 62%	Musculoskeletal pain 2 (3%) vs 0 (0%)
Doorduijn et al, 2003 [26]	NHL	N = 389 Filgrastim = 197 No filgrastim = 192	–	FN incidence 72 pts (36.5%) vs 86 pts (44.8%) Median (range) days 2 (1–14) vs 3 (1–32) *P* = 0.04	NR	Infections 8% vs 12% *P* = 0.004 Severe infections 3% vs 3% *P* = 0.82 Median antibiotic use, days (range) 0 (0–126) vs 6 (0–180) *P* = 0.006	Days (range) hospitalization 5 [0–157] vs 6 [0–111] *P* = 0.40	Median (range) RDI 95.1% (39.4–110) vs 93.4% (47.7–109) *P* = 0.12	OS at 5 years 24% vs 22% *P* = 0.76	Grade 3/4 AEs Neurotoxicity 13 (1%) vs 33 (3%) Nausea/vomiting 15 (1%) vs 18 (2%) Diarrhea 8 (1%) vs 2 (<1%)

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Grade 3 or Grade 4 Neutropenia	Incidence of Infection/Antibiotic Use	Incidence/Duration of Hospitalizations	RDI, Dose Delays, or Dose Reductions	Survival/ Mortality	Incidence of G-CSF-Related AEs n (%)[a]
										Oral toxicity 2 (<1%) vs 4 (<1%) Cardiac toxicity 9 (1%) vs 6 (1%) Hemorrhage NR vs 1 (<1%) Liver toxicity NR vs 1 (<1%) Bone pain 3 (<1%) vs NR Other 23 (2%) vs 30 (3%)
Osby et al, 2003 [27]	NHL	N = 455 Filgrastim = 226 No filgrastim = 229	–	Granulocytopenic fever (<0.5x10^9/L) CHOP arms 34% vs 50% CNOP arms 32% vs 50%	Granulocytopenia (<0.5x10^9/L) CHOP arms 55% vs 89% CNOP arms 64% vs 86%	NR	Granulocytopenic fever requiring hospitalization (0.5×10^9/L): 33% vs 50% *P* = 0.001	RDI ≥90% during 8 courses 44% vs 34% *P* < 0.05	OS rates CHOP ± filgrastim 61% vs 51% CNOP ± filgrastim 33% vs 33%	CHOP + filgrastim vs CHOP Mucositis 5% vs 4% GI toxicity 15% vs 10% Alopecia 80% vs 81% Cardiac toxicity 5% vs 3% Musculoskeletal pain 10% vs 2% CNOP + filgrastim vs CNOP Mucositis 3% vs 2% GI toxicity 8% vs 5% Alopecia

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Grade 3 or Grade 4 Neutropenia	Incidence of Infection/Antibiotic Use	Incidence/Duration of Hospitalizations	RDI, Dose Delays, or Dose Reductions	Survival/ Mortality	Incidence of G-CSF-Related AEs n (%)[a]
										47 vs 41 Cardiac toxicity 3 vs 1 Musculoskeletal pain
ALL										
Pui et al, 1997 [29]	ALL	N = 148 Filgrastim = 73 Placebo = 75	ANC recovery Median days (range) for recovery to $0.5x10^9$ 5.3 vs 12.7 Platelets recovery ($x10^{-3}/mm^3$) 14 (2–330) vs 18 (3–120) <75000/mm^3 8.9 vs 8.3	Median (range) days with fever 2 (0–36) vs 2 (0–27)	NR	All infections 12 pts (16%) vs 27 (36%) *P* = 0.009 Grade 3/4 infections 5 pts (7%) vs 6 pts (8%) IV antibiotics use 42 pts vs 51 pts Median days (range) duration of IV antibiotic use 6 (2–36) vs 9 (2–30)	Incidence of FN-related hospitalization 42 pts (58%) vs 52 pts (68%) *P* = 0.23 Median days (range) duration hospital stay for FN 6 (1–37) vs 10 (1–30) *P* = 0.011	NR	EFS at 3 years, 83% (both groups)	Grade 3/4 Pneumonia 3 vs 2 Bacteremia 1 vs 3 Disseminated fungal infection 0 vs 1 Typhlitis 1 vs 0 AML incidence 5.1% vs 3.9% *P* = 0.39
Larson et al, 1998 [28]	ALL	N = 198 Filgrastim = 102 Placebo = 96	Median days (IQR) to ANC recovery (>1000/μL) Course I 16 (15–18) vs 22 (19–29) *P* < 0.001 Course IIA 20 (6–25) vs 29 (22–31) *P* < 0.001 Course IIB 25 (15–32) vs 31 (27–39) *P* < 0.001	NR	Median (IQ3) Neutropenia (ANC <1000/μL), days: Course I 13 (10–16) vs 20 (15–27) *P* < 0.001 Course IIA 5 (0–12) vs 13 (6–18) *P* < 0.001 Course IIB 11 (4–17) vs 14 (10–25) *P* = 0.001	Infections 78% vs 87% *P* = 0.13	Median (IQ3) hospital stay, days: Course I 22 (18–29) vs 28 (22–33) *P* = 0.02 Course IIA 7 (0–17) vs 3 (0–14) *P* = 0.32 Course IIB 4 (0–21) vs 2 (0–15) *P* = 0.17	NR	Estimated median overall survival after 4.7 years follow-up (years) 2.4 vs 1.8 *P* = 0.25 Died during induction, n (%): All enrolled pts 5 (5) vs 11 (11) All eligible pts	Grade 3/4/5 toxicity Pain, 21% vs 14%, *P* = 0.026 All other AEs were not significantly different Infection, 78% vs 87% Malaise/fatigue (PS >2), 16% vs 25%

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Grade 3 or Grade 4 Neutropenia	Incidence of Infection/Antibiotic Use	Incidence/Duration of Hospitalizations	RDI, Dose Delays, or Dose Reductions	Survival/ Mortality	Incidence of G-CSF-Related AEs n (%)[a]
			Median (IQR) days to platelet recovery (>50000/μL): Course I 16 (14–20) vs 19 (15–23) *P* = 0.003 Course IIA 20 (17–22) vs 20 (18–22) *P* = 0.53 Course IIB 24 (21–31) vs 22 (0–28) *P* = 0.03						4 (4) vs 10 (11) Died in complete remission, n (%): 8 (8) vs 5 (5) Alive in continuous complete remission, n (%): 35 (41) vs 22 (31)	Hemoglobin (<6.5 g/dL), 93% vs 86% Hypofibrinogenemia (<0.5 x normal), 26% vs 18% Bilirubin (>1.5 x normal), 44% vs 51% Nausea, 23% vs 28% Motor neuropathy, 18% vs 22% WBC (<1000/μL), 98% vs 97% Platelets (<25000/μL), 97% vs 95% Hyperglycemia (>250 mg/dL), 33% vs 35% Transaminases (>5 x normal), 35% vs 35%
Nonrandomized clinical trial										
Blayney et al, 2005 [30]	NSCLC and NHL	NSCLC (n = 55): Filgrastim = 46 No filgrastim = 9 NHL (n = 49): Filgrastim = 44 No filgrastim = 5	–	NR	Grade 3 and grade 4 neutropenia: 62% and 77% lower with filgrastim[b] Median duration of grade 3 and grade 4 neutropenia: 81% and 94% lower[b]	NR	Mean (SD) days in hospital NSCLC 12.8 (13.1) vs 15.1 (17.5)[b] NHL 4.7 (8.4) vs 2.4 (3.3)[b]	NSCLC Dose reduction 3% vs 12%[b] Dose delay 12% vs 38%[b] NHL Dose reduction 12% vs 0%[b]	NR	AEs reported not specific to G-CSF

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Grade 3 or Grade 4 Neutropenia	Incidence of Infection/Antibiotic Use	Incidence/Duration of Hospitalizations	RDI, Dose Delays, or Dose Reductions	Survival/ Mortality	Incidence of G-CSF-Related AEs n (%)[a]
								Dose delay 6% vs 12%[b]		
Observational studies										
Gilad et al, 1999 [31]	Breast cancer, lung cancer, NHL, Hodgkin's disease, and others	N = 209 (1079 cycles) Cycles with PP filgrastim = 66 Cycles with no PP = 1013	–	FN incidence 4.5% vs 3.7% *P* = 0.441	NR	Infections 1.5% vs 1.0% *P* = 0.781	Hospitalized pts 6.0% vs 4.5% *P* = 0.958	NR	Deaths: 1 pt vs 1 pt, none from infectious complication	AEs during induction 1 Rash 3 vs 2 Musculoskeletal pain 2 vs 1
Hershman et al, 2009 [32]	Breast cancer, lung cancer, ovarian cancer, colon cancer, lymphoma	N = 3123 PP G-CSF (filgrastim or pegfilgrastim) = 822 No PP G-CSF (delayed filgrastim or pegfilgrastim = 1523 or no G-CSF = 778)	–	PP G-CSF vs no PP G-CSF 4.5% vs 7.5% OR 0.49, 95% CI: 0.34–0.71 *P* < 0.001	NR	NR	NR	NR		NR
Altwairgi et al, 2013 [18]	Breast cancer	N = 239 PP G-CSF (filgrastim or pegfilgrastim) = 145 No PP G-CSF (secondary G-CSF or no G-CSF) = 94	–	PP G-CSF vs no PP G-CSF 14% vs 31% *P* = 0.002	NR	NR	NR	RDI (range) for pts who received the FEC/D regimen 98% (75%–117%) vs 95% (60%–100%) *P* = 0.05 Achievement of RDI >85% for pts who received the FEC/D regimen 97% vs 92% *P* = 0.118 Dose delay 17% vs 27%	NR	NR

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Grade 3 or Grade 4 Neutropenia	Incidence of Infection/Antibiotic Use	Incidence/Duration of Hospitalizations	RDI, Dose Delays, or Dose Reductions	Survival/ Mortality	Incidence of G-CSF-Related AEs n (%)[a]
								P = 0.060 Dose reduction 19% vs 25% *P* = 0.28		

Note: filgrastim = originator filgrastim (NEUPOGEN®).
[a]AEs considered to be related to G-CSF include bone pain, nausea/vomiting, diarrhea, leukocytosis, thrombocytopenia, allergic reactions, splenic rupture, acute respiratory distress syndrome, dyspnea, and alveolar hemorrhage and hemoptysis. Additionally, any AEs that were compared for the filgrastim vs no filgrastim arms in any of the studies were collected as these AEs were presumed to be filgrastim-related.
[b]Data reported are for the subgroup of 33 pts with NSCLC and the subgroup of 15 pts with NHL who received the standard 21-day chemotherapy regimens.
Chemotherapy regimens: BEP = cisplatin, etoposide, bleomycin; BOP = bleomycin, vincristine, cisplatin; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone; EP = BEP without bleomycin; VIP-B = cisplatin, ifosfamide, etoposide, bleomycin.
AE = adverse event;; ALL = acute lymphoblastic leukemia; CI = confidence interval; DFS = disease-free survival; E = adverse event; ANC = absolute neutrophil count; CIN = chemotherapy-induced neutropenia; EFS = event-free survival; FN = febrile neutropenia; G-CSF = granulocyte colony-stimulating factor; IQ3 = interquartile 3; IQR = interquartile range; IV = intravenous; NHL = non-Hodgkin's lymphoma; NR = not reported; NS = not significant; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; PP = primary prophylaxis; pts = patients; RDI = relative dose intensity; SD = standard deviation; WBC = white blood cell.

Online Resource 7: Efficacy, effectiveness, and safety of filgrastim compared with placebo or no treatment in AML

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Neutropenia	Incidence/ Duration of Infections	Incidence/ Duration of Antibiotic Use	Incidence/ Duration of Hospitalization	Overall Survival	Incidence of G-CSF-Related AEs[a]
Randomized controlled trials										
Heil et al, 1997[b] [33]	AML	N = 521 Filgrastim: n = 259 No filgrastim: n = 262	Time to ANC recovery[c] Kaplan-Meier median (95% CI) days for induction 1 20 (19–20) vs 25 (24–27) *P* = 0.0001	Fever incidence Induction 1 91% vs 92% *P* = 0.50 Induction 2 80% vs 75) *P* = 0.47 Consolidation 1 49% vs 63% *P* = 0.014	Median (range) duration of neutropenia, days Induction 2: 10 (0–38) vs 14 (0–43) *P* = 0.015 Consolidation 1: 4 (0–46) vs 11 (0–22) *P* = 0.0001	Infection rate in induction 1 37% vs 36% *P* = 0.85	Use of antibacterials: Induction 1: 95% vs 96% Use of anti-infectives Induction 1: 95% vs 96% *P* = 0.81	Median (range) hospital stay, days Induction therapy: 23 (2–104) vs 29 (7–93) *P* = 0.0001 Induction and consolidation: 42 (15–140) vs 55 (23–114) *P* = 0.0001	Median survival (95% CI), months DFS: 10.1 (8.2–11.4) vs 9.4 (8.2–11.1) *P* = 0.99 OS: 12.5 (10.9–14.4) vs 14.0 (12.2–15.6) *P* = 0.83 Deaths in induction phase: 21 pts (8.1%) vs 25 pts (9.5%)	AEs in induction 1 Rash: 3% vs 2% Musculoskeletal pain: 2% vs 1%
Godwin et al, 1998 [35]	AML	N = 211 Filgrastim: n = 106 Placebo: n = 105	ANC recovery (time from chemotherapy start until neutrophil count >500/μl, days: 24 (75/104 pts recovered) vs 27 (74/103 pts recovered)	NR	15% (95% CI: 3–27) shorter neutropenia duration with filgrastim *P* = 0.014 No difference in thrombocytopenia	Number of ≥3 culture confirmed infections 21% vs 21% *P* = 0.82 one-tailed	Median (range) days on antibiotics 22 (0–128) vs 26 (0–69) *P* = 0.053 one-tailed	Median (range) length of first hospitalization, days 29 (4–155) vs 29 (3–106) Median (range) # of febrile days during the first hospitalization: 8 (0–79) vs 10 (0–34) *P* = 0.091 one-tailed	Median survival (95% CI) months 6 (3–8) vs 9 (7–10) *P* = 0.71 RFS, months 8 (4-10) vs 9 (7–10) *P* = 0.38	Bone pain: 1 pt (1%) vs 5 pts (5%) Fatal induction toxicities 20% (21/104 pts) vs 19% (20/103 pts)

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Neutropenia	Incidence/ Duration of Infections	Incidence/ Duration of Antibiotic Use	Incidence/ Duration of Hospitalization	Overall Survival	Incidence of G-CSF-Related AEs[a]
Haroussseau et al, 2000 [37]	AML	N = 194 Filgrastim: n = 100 No filgrastim: n = 94	NR	Fever duration (association with neutropenia not specified), days: ICC1: 5 (0–23) vs 6 (0–25) *P* = 0.35 ICC2: 5 (0–31) vs 6 (0–100) *P* = 0.70	Grade 4 neutropenia duration, days ICC1: 12 (5–45) vs 19 (9–39) *P* < 0.001 ICC2: 20 (7–56) vs 28 (10–100) *P* < 0.001	Documented infections: ICC1: 55% vs 66% *P* = 0.16 ICC2: 40.5% vs 55.5% *P* = 0.07 Episodes of septicemias: ICC1: 40% vs 48%, *P* = 0.34 ICC2: 25% vs 31%, *P* = 0.05	Median (range) duration of IV antibiotics, days: ICC1: 13 (0–34) vs 15 (0–51) *P* = 0.02 ICC2: 15 (0–47) vs 22 (0–100) *P* = 0.04	Median (range) time of hospital stay, days: ICC1 24 (17–100) vs 27 (16–61) *P* < 0.001 ICC2: 29 (19–62) vs 34 (21–100) *P* < 0.001	Deaths: 27 pts (27%) vs 31 pts (33%) 2-year OS (SD): 64% (6%) vs 63% (6%)	NR
Usuki et al, 2002 [36]	de novo AML	N = 245 Filgrastim: n = 120 No filgrastim: n = 125	Median (95% CI) time to ANC recovery to $1x10^9$/L, days 14 (13.9–16.0) vs 22 (19.7–22.7) *P* < 0.0001 Median (95% CI) time to ANC recovery to $0.5x10^9$/L, days 12 (1.7–13.5) vs 18 (17.2–20.1 *P* < 0.0001	Incidence of fever 76.7% vs 76.0% *P* = 1.000 Median (range) duration of FN, days 3 (3.1–4.4) vs 4 (4.1–5.6) *P* < 0.0001	NR	Rate of infection 83.3% vs 91.2% *P* = 0.083 Median (95% CI) duration of infection, days 11 (8.3) vs 13 (14.0) *P* = 0.2320	Rate of IV antibiotic use 81.7% vs 87.2% *P* = 0.100 IV antibiotics use, days (range) 16.5 (0–49) vs 17 (0–70) *P* = 0.7039	NR	Median DFS, months 14.0 vs 12.5 DFS probability (95% CI) at 5 years: 34.5% (23.8–43.7%) vs 33.6% (23.3–43.9%) *P* = 0.9407 Median OS, months 20.8 vs 18.8 OS probability (95% CI) at 5 years 42.7% (31.4–52.9) vs 35.6% (25.9–45.2) *P* = 0.5918	G-CSF-related: Mild musculoskeletal pain (3 pts), fever (1 pt), severe skin rash (1 pt) G-CSF association unknown: Sweet's disease (1 pt), chest pain (1 pt), generalized pruritus, and skin rash (1 pt)
Heil et al, 2006[a] [39]	AML	N = 521 Filgrastim: n = 259 Placebo: n = 262	NR	NR	NR	NR	NR	NR	3-year OS (95% CI) 23% (18–29) vs 21% (16–26) 5 year OS (95% CI)	NR

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness						Safety	
			Time to ANC or Platelet Recovery	Incidence/ Duration of FN	Incidence/Duration of Neutropenia	Incidence/ Duration of Infections	Incidence/ Duration of Antibiotic Use	Incidence/ Duration of Hospitalization	Overall Survival	Incidence of G-CSF-Related AEs[a]
									19 (15–24) vs 17 (12–22)	
Beksac et al, 2011 [34]	AML	N = 260 Filgrastim: n = 123 No filgrastim: n = 137	NR	Duration of fever, days 8 (1.0–27) vs 8.5 (0.0–28) P = 0.96	NR	NR	Antibacterial therapy 91.6% vs 92.4% *P* = 0.82 Antifungal therapy 63.0% vs 61.8% *P* = 0.85 Antiviral therapy: 8.4% vs 5.3% *P* = 0.34	Median duration (range) of hospitalization, days 31 (9.0–72.0) vs 35 (3.0–80.0) *P* = 0.18	Median OS duration (SD), days 239 (81) vs 184 (65) *P* = 0.38 3-year OS (SD) 31.8% (5.6) vs 25.6% (5.1)	Frequent AEs in both arms: rash, musculoskeletal pain, and fever
Nonrandomized clinical trial										
Moore et al, 1997 [38]	AML	N = 123 Filgrastim: n = 61 No filgrastim: n = 62	Median days to recovery (95% CI) ANC ≥500/μL 20.5 (19–24) vs 31.1 (31–36) *P* < 0.001 Platelets ≥20000/μL 23.4 (19–31) vs 30.2 (26–38)	NR	NR	Grade ≥3 infections: 58% and 47% vs 71% and 75%	NR	Incidence of hospitalization 47 pts (85%) vs 56 pts (97%) *P* = 0.05 Duration of hospitalization 24 (6-44) and 20 (1-58) vs 40 (11-91) and 30 (2-80)	Median survival of pts who received third intensification course, years 3.4 vs 2.4 Death 3 pts vs 3 pts	NR

Note: filgrastim = originator filgrastim (NEUPOGEN®).

[a]AEs considered to be related to G-CSF include bone pain, nausea/vomiting, diarrhea, leukocytosis, thrombocytopenia, allergic reactions, splenic rupture, acute respiratory distress syndrome, dyspnea, and alveolar hemorrhage and hemoptysis. Additionally, any AEs that were compared for the filgrastim vs no filgrastim arms in any of the studies were collected as these AEs were presumed to be filgrastim-related.

[b]The two publications Heil et al 1997 and Heil et al 2006 are from the same RCT

[c]ANC recovery was defined as number of days from first day of chemotherapy to first 3 days with an ANC >$0.5x10^9$/L

AEs = adverse events; AML = acute myeloid leukemia; ANC = absolute neutrophil count; CI = confidence interval; DFS = disease-free survival; FN = febrile neutropenia; G-CSF = granulocyte colony-stimulating factor; ICC = intensive consolidation chemotherapy; IV = intravenous; NR = not reported; OS = overall survival; pts = patients; RCT = randomized controlled trial; RFS = relapse-free survival.

Online Resource 8: Efficacy, effectiveness, and safety of filgrastim compared with placebo or no treatment in SCN

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness			Safety	
			Median ANC	Incidence of Infection/ Antibiotic Use	Incidence/ Duration of Hospitalization	Survival/ Mortality	Incidence of G-CSF-Related AEs[a]
Randomized controlled trial							
Dale et al, 1993 [6]	Severe chronic neutropenia	N = 123 Filgrastim: n = 63 4-month observation + filgrastim: n = 60 Total who received filgrastim = 120	Median ANC ($1x10^9$ cells/L) (min-max) All diagnoses filgrastim-treated vs observed for 4 months: 6.10 (0.03–19.44) vs 0.21 (0.00–1.55) *P* ≤ 0.001 >16-fold increase in ANC for filgrastim-treated vs untreated pts *P* ≤ 0.001 90% of 120 filgrastim-treated pts achieved ANC of $1.5x10^9$ cells/L	~50% reductions in incidence and duration of infection-related events *P* < 0.05 ~70% reduction in duration of antibiotic use	Low median incidence and median duration of hospitalizations	NR	Exposure-adjusted AEs for pts after receiving filgrastim vs before receiving filgrastim[b]: Headache, 35% vs 24% General musculoskeletal pain, 25% vs 10% Transient bone pain, 17% vs 6% Rash, 10% vs 4% Palpable splenomegaly after vs before receiving filgrastim, n/N (%): 29/120 (24%) vs 18/123 (14%)
Observational study							
Yilmaz et al, 2007 [40]	Idiopathic SN, n = 31 Congenital SN, n = 3 Familial SN, n = 3 Autoimmune SN, n = 2	N = 39 Filgrastim: n = 16 No filgrastim: n = 23	Median ANC at presentation ($1x10^9$/L) (range) 0.12 (0–0.35) vs 0.21 (0–0.46) Median ANC at follow-up ($1x10^9$/L) (range) 0.16 (0–0.22) vs 0.22 (0.06–0.37) Median duration of neutropenia that resolved, months (range)	At presentation / at follow-up, n (%) Recurrent upper airway infections 8 (61.6) / 4 (30.8) vs 5 (25.7) / 3 (16.6) Skin infection/ abscess 7 (53.9) / 4 (30.8) vs 6 (33.3) / 1 (5.5) Recurrent otitis media 4 (30.8) / 4 (30.8) vs 7 (38.8) / 6 (33.3) Pneumonia 3 (23.1) / 0 (0) vs 2 (11.1) / 2 (11.1)	9 pts required hospitalization at time of diagnosis 3 pts were hospitalized during follow-up. None of the pts were on prophylactic antibiotics at the time of admission. Indications for hospitalization: pulmonary infection with respiratory distress, sepsis, fluid resuscitation, vomiting,	NR	NR

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness			Safety	
			Median ANC	Incidence of Infection/ Antibiotic Use	Incidence/ Duration of Hospitalization	Survival/ Mortality	Incidence of G-CSF-Related AEs[a]
			9 (5–15) vs 15 (5–36) NS	Diarrhea 2 (15.4) / 3 (23.1) vs 1 (5.5) / 2 (11.1) Stomatitis/oral ulcers 3 (23.1) / 3 (23.1) vs 2 (11.1) / 0 (0) Brain abscess 1 (7.7) 0 (0) vs 0 (0) / 0 (0) Periorbital cellulitis 1 (7.7) / 0 (0) vs 0 (0) / 0 (0) Submandibular abscess 1 (7.7) / 0 (0) vs 0 (0) / 0 (0) Exanthema gangrenosum 1 (7.7) / 0 (0) vs 0 (0) / 0 (0) Septic shock 0 (0) / 1 (7.7) vs 0 (0) / 0 (0) Bacteremia 0 (0) / 0 (0) vs 1 (5.5) / 0 (0)	dehydration, and unstable vital functions 9 (29%) of pts had hospitalization history at presentation		

Note: filgrastim = originator filgrastim (NEUPOGEN®).

[a]AEs considered to be related to G-CSF include bone pain, nausea/vomiting, diarrhea, leukocytosis, thrombocytopenia, allergic reactions, splenic rupture, acute respiratory distress syndrome, dyspnea, and alveolar hemorrhage and hemoptysis. Additionally, any AEs that were compared for the filgrastim vs no filgrastim arms in any of the studies were collected as these AEs were presumed to be filgrastim-related.

[b]Exposure-adjusted AEs reported are the total number of events divided by the total study exposure in pt months.

AEs = adverse events; ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor; max = maximum; min = minimum; n/N = number of pts experiencing event divided by total population evaluated or that event; NR = not reported; NS = not significant; pts = patients; SCN = severe chronic neutropenia; SN = severe neutropenia.

Online Resource 9: Efficacy, effectiveness, and safety of filgrastim compared with placebo or no treatment in BMT

Author, Year	Disease Type	Filgrastim Intervention and Patient Numbers	Efficacy and Effectiveness			Safety	
			Time to Neutrophil/ Platelet Recovery	Incidence of Infection/ Antibiotic Use	Incidence/ Duration of Hospitalization	Survival/Mortality	Incidence of G-CSF-Related AEs[a]
Randomized controlled trials							
Gonzalez-Vicent et al, 2004 [41]	ALL, solid tumor	N = 117 Filgrastim: n = 51 No filgrastim: n = 66	Median days (range) to achieve >0.5x10^9/L neutrophil count 10 (7–14) vs 11 (8–21) *P* < 0.009 Median days (range) to achieve >50x10^9/L platelets 15 (9–100) vs 14 (11–71) *P* < 0.005	Median days (range) antibiotic use 8 (0–50) vs 8 (0–36) *P* = 0.32	Median days (range) hospital stay 16 (10–72) vs 17 (6–60) *P* = 0.46	NR	NR
Observational study							
Gertz et al, 2011 [42]	Multiple myeloma	N = 664 Filgrastim: n = 498 No filgrastim: n = 166	Median days for neutrophil recovery 12.5 vs 13.5 *P* < 0.001 Median days to engraftment of 50000 platelets/mL 14.5 vs 14.5 *P* = 0.12	Bacteremia: 39% vs 27% *P* = 0.005	Never hospitalized 38% vs 52% Median hospital stay (days) 3.5 vs 0 *P* < 0.001 Mean hospital stay (days) 7 vs 4.1 *P* < 0.001	All-cause mortality before day +100 10 pts (2%) vs 3 pts (2%)	NR

Note: filgrastim = originator filgrastim (NEUPOGEN®).
[a]AEs considered to be related to G-CSF include bone pain, nausea/vomiting, diarrhea, leukocytosis, thrombocytopenia, allergic reactions, splenic rupture, acute respiratory distress syndrome, dyspnea, and alveolar hemorrhage and hemoptysis. Additionally, any AEs that were compared for the filgrastim vs no filgrastim arms in any of the studies were collected as these AEs were presumed to be filgrastim-related.
AEs = adverse events; ALL = acute lymphoblastic leukemia; BMT = bone marrow transplantation; G-CSF = granulocyte colony-stimulating factor; NR = not reported; pts = patients.

REFERENCES

1. Bodey GP, Powell RD, Jr., Hersh EM, Yeterian A, Freireich EJ. Pulmonary complications of acute leukemia. *Cancer* 1966;19:781-93.
2. Crawford J, Dale DC, Kuderer NM, Culakova E, Poniewierski MS, Wolff D, et al. Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice. *J Natl Compr Canc Netw* 2008;6:109-18.
3. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. *Cancer* 2004;100:228-37.
4. Crawford J, Ozer H, Stoller R, Johnson D, Lyman G, Tabbara I, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med* 1991;325:164-70.
5. Dale DC. Update on the management of neutropenia. *Clin Adv Hematol Oncol* 2006;4:187-9.
6. Dale DC, Bonilla MA, Davis MW, Nakanishi AM, Hammond WP, Kurtzberg J, et al. A randomized controlled phase III trial of recombinant human granulocyte colony-stimulating factor (filgrastim) for treatment of severe chronic neutropenia. *Blood* 1993;81:2496-502.
7. Chang J. Chemotherapy dose reduction and delay in clinical practice. evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer. *Eur J Cancer* 2000;36(Suppl 1):S11-4.
8. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. *J Clin Oncol* 2003;21:4524-31.

9. Chatta GS, Price TH, Allen RC, Dale DC. Effects of in vivo recombinant methionyl human granulocyte colony-stimulating factor on the neutrophil response and peripheral blood colony-forming cells in healthy young and elderly adult volunteers. *Blood* 1994;84:2923-9.
10. Price TH, Chatta GS, Dale DC. Effect of recombinant granulocyte colony-stimulating factor on neutrophil kinetics in normal young and elderly humans. *Blood* 1996;88:335-40.
11. NEUPOGEN® (filgrastim) [prescribing information]: Thousand Oaks, CA: Amgen Inc.
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
13. Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. *BMC Cancer* 2011;11:404.
14. Renner P, Milazzo S, Liu JP, Zwahlen M, Birkmann J, Horneber M. Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients. *Cochrane Database Syst Rev* 2012;10:CD007913.
15. Sheppard D, Bredeson C, Allan D, Tay J. Systematic review of randomized controlled trials of hematopoietic stem cell mobilization strategies for autologous transplantation for hematologic malignancies. *Biol Blood Marrow Transplant* 2012;18:1191-203.
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015;45:139-45.
18. Altwairgi AK, Hopman WM, Mates M. Real-world impact of granulocyte-colony stimulating factor on febrile neutropenia. *Curr Oncol* 2013;20:e171-9.
19. He M., Huang S, Yu L, et al. Evaluation of the quality of life and economic burden with granulocyte-colony stimulating factor in Chinese breast cancer patients receiving docetaxel, epirubicin and cyclophosphamide. Ann Oncol (2012) 23 (suppl 9): ix499-ix527.

doi: 10.1093/annonc/mds416This article appears in:Abstract Book of the 37th ESMO Congress Vienna, Austria, 28 September – 2 October 2012.

20. Papaldo P, Lopez M, Cortesi E, Cammilluzzi E, Antimi M, Terzoli E, et al. Addition of either lonidamine or granulocyte colony-stimulating factor does not improve survival in early breast cancer patients treated with high-dose epirubicin and cyclophosphamide. *J Clin Oncol* 2003;21:3462-8.
21. del Giglio A, Eniu A, Ganea-Motan D, Topuzov E, Lubenau H. 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* 2008;8:332.
22. Welte K, Platzer E, Lu L, Gabrilove JL, Levi E, Mertelsmann R, et al. Purification and biochemical characterization of human pluripotent hematopoietic colony-stimulating factor. *Proc Natl Acad Sci U S A* 1985;82:1526-30.
23. Trillet-Lenoir V, Green J, Manegold C, Von Pawel J, Gatzemeier U, Lebeau B, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer* 1993;29A:319-24.
24. Fossa SD, Kaye SB, Mead GM, Cullen M, de Wit R, Bodrogi I, et al. Filgrastim during combination chemotherapy of patients with poor-prognosis metastatic germ cell malignancy. European Organization for Research and Treatment of Cancer, Genito-Urinary Group, and the Medical Research Council Testicular Cancer Working Party, Cambridge, United Kingdom. *J Clin Oncol* 1998;16:716-24.
25. Zinzani PL, Pavone E, Storti S, Moretti L, Fattori PP, Guardigni L, et al. Randomized trial with or without granulocyte colony-stimulating factor as adjunct to induction VNCOP-B treatment of elderly high-grade non-Hodgkin's lymphoma. *Blood* 1997;89:3974-9.

26. Doorduijn JK, van der Holt B, van Imhoff GW, van der Hem KG, Kramer MH, van Oers MH, et al. CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 2003;21:3041-50.
27. Osby E, Hagberg H, Kvaloy S, Teerenhovi L, Anderson H, Cavallin-Stahl E, et al. CHOP is superior to CNOP in elderly patients with aggressive lymphoma while outcome is unaffected by filgrastim treatment: results of a Nordic Lymphoma Group randomized trial. *Blood* 2003;101:3840-8.
28. Larson RA, Dodge RK, Linker CA, Stone RM, Powell BL, Lee EJ, et al. A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. *Blood* 1998;92:1556-64.
29. Pui CH, Boyett JM, Hughes WT, Rivera GK, Hancock ML, Sandlund JT, et al. Human granulocyte colony-stimulating factor after induction chemotherapy in children with acute lymphoblastic leukemia. *N Engl J Med* 1997;336:1781-7.
30. Blayney DW, McGuire BW, Cruickshank SE, Johnson DH. Increasing chemotherapy dose density and intensity: phase I trials in non-small cell lung cancer and non-Hodgkin's lymphoma. *Oncologist* 2005;10:138-49.
31. Gilad J, Riesenberg K, Mermershtain W, Borer A, Porath A, Schlaeffer F. Granulocyte-colony stimulating factor for the prevention of chemotherapy-induced febrile neutropenia in the adult cancer patient population of Southern Israel. *Support Care Cancer* 1999;7:260-4.
32. Hershman D, Hurley D, Wong M, Morrison VA, Malin JL. Impact of primary prophylaxis on febrile neutropenia within community practices in the US. *J Med Econ* 2009;12:203-10.
33. Heil G, Hoelzer D, Sanz MA, Lechner K, Liu Yin JA, Papa G, et al. A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia. The International Acute Myeloid Leukemia Study Group. *Blood* 1997;90:4710-8.

34. Beksac M, Ali R, Ozcelik T, Ozcan M, Ozcebe O, Bayik M, et al. Short and long term effects of granulocyte colony-stimulating factor during induction therapy in acute myeloid leukemia patients younger than 65: results of a randomized multicenter phase III trial. *Leuk Res* 2011;35:340-5.

35. Godwin JE, Kopecky KJ, Head DR, Willman CL, Leith CP, Hynes HE, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest oncology group study (9031). *Blood* 1998;91:3607-15.

36. Usuki K, Urabe A, Masaoka T, Ohno R, Mizoguchi H, Hamajima N, et al. Efficacy of granulocyte colony-stimulating factor in the treatment of acute myelogenous leukaemia: a multicentre randomized study. *Br J Haematol* 2002;116:103-12.

37. Harousseau JL, Witz B, Lioure B, Hunault-Berger M, Desablens B, Delain M, et al. Granulocyte colony-stimulating factor after intensive consolidation chemotherapy in acute myeloid leukemia: results of a randomized trial of the Groupe Ouest-Est Leucemies Aigues Myeloblastiques. *J Clin Oncol* 2000;18:780-7.

38. Moore JO, Dodge RK, Amrein PC, Kolitz J, Lee EJ, Powell B, et al. Granulocyte-colony stimulating factor (filgrastim) accelerates granulocyte recovery after intensive postremission chemotherapy for acute myeloid leukemia with aziridinyl benzoquinone and mitoxantrone: Cancer and Leukemia Group B study 9022. *Blood* 1997;89:780-8.

39. Heil G, Hoelzer D, Sanz MA, Lechner K, Noens L, Szer J, et al. Long-term survival data from a phase 3 study of Filgrastim as an adjunct to chemotherapy in adults with de novo acute myeloid leukemia. *Leukemia* 2006;20:404-9.

40. Yilmaz D, Ritchey AK. Severe neutropenia in children: a single institutional experience. *J Pediatr Hematol Oncol* 2007;29:513-8.

41. Gonzalez-Vicent M, Madero L, Sevilla J, Ramirez M, Diaz MA. A prospective randomized study of clinical and economic consequences of using G-CSF following autologous

peripheral blood progenitor cell (PBPC) transplantation in children. *Bone Marrow Transplant* 2004;34:1077-81.

42. Gertz MA, Gastineau DA, Lacy MQ, Dispenzieri A, Hayman SR, Kumar SK, et al. SCT without growth factor in multiple myeloma: engraftment kinetics, bacteremia and hospitalization. *Bone Marrow Transplant* 2011;46:956-61.
43. Schmitz N, Dreger P, Zander AR, Ehninger G, Wandt H, Fauser AA, et al. Results of a randomised, controlled, multicentre study of recombinant human granulocyte colony-stimulating factor (filgrastim) in patients with Hodgkin's disease and non-Hodgkin's lymphoma undergoing autologous bone marrow transplantation. *Bone Marrow Transplant* 1995;15:261-6.
44. Stahel RA, Jost LM, Cerny T, Pichert G, Honegger H, Tobler A, et al. Randomized study of recombinant human granulocyte colony-stimulating factor after high-dose chemotherapy and autologous bone marrow transplantation for high-risk lymphoid malignancies. *J Clin Oncol* 1994;12:1931-8.
45. Lyman GH, Reiner M, Morrow PK, Crawford J. The effect of filgrastim or pegfilgrastim on survival outcomes of patients with cancer receiving myelosuppressive chemotherapy. *Ann Oncol* 2015;26:1452-8.
46. Wildiers H, Reiser M. Relative dose intensity of chemotherapy and its impact on outcomes in patients with early breast cancer or aggressive lymphoma. *Crit Rev Oncol Hematol* 2011;77:221-40.
47. Balducci L, Mo M, Abella E, Saven A. Retrospective analysis of relative dose intensity in patients with non-Hodgkin lymphoma receiving CHOP-based chemotherapy and pegfilgrastim. *Am J Clin Oncol* 2014;37:603-10.
48. Denduluri N, Patt DA, Wang Y, Bhor M, Li X, Favret AM, et al. Dose Delays, Dose Reductions, and Relative Dose Intensity in Patients With Cancer Who Received Adjuvant

or Neoadjuvant Chemotherapy in Community Oncology Practices. *J Natl Compr Canc Netw* 2015;13:1383-93.

49. Havrilesky LJ, Reiner M, Morrow PK, Watson H, Crawford J. A review of relative dose intensity and survival in patients with metastatic solid tumors. *Crit Rev Oncol Hematol* 2015;93:203-10.
50. Dale DC, Cottle TE, Fier CJ, Bolyard AA, Bonilla MA, Boxer LA, et al. Severe chronic neutropenia: treatment and follow-up of patients in the Severe Chronic Neutropenia International Registry. *Am J Hematol* 2003;72:82-93.
51. Hwang WYK, Poon Z, Bari S. Improving the efficacy and availability of stem cell transplant therapies for hematopoietic stem cell transplantation. *J Stem Cell Res Ther* 2014;4:214. Available at: http://dx.doi.org/10.4172/2157-7633.1000214.
52. Maher DW, Lieschke GJ, Green M, Bishop J, Stuart-Harris R, Wolf M, et al. Filgrastim in patients with chemotherapy-induced febrile neutropenia. A double-blind, placebo-controlled trial. *Ann Intern Med* 1994;121:492-501.
53. Pabst T, Vellenga E, van Putten W, Schouten HC, Graux C, Vekemans MC, et al. Favorable effect of priming with granulocyte colony-stimulating factor in remission induction of acute myeloid leukemia restricted to dose escalation of cytarabine. *Blood* 2012;119:5367-73.
54. Boxer LA, Hutchinson R, Emerson S. Recombinant human granulocyte-colony-stimulating factor in the treatment of patients with neutropenia. *Clin Immunol Immunopathol* 1992;62:S39-46.
55. Linker C, Anderlini P, Herzig R, Christiansen N, Somlo G, Bensinger W, et al. Recombinant human thrombopoietin augments mobilization of peripheral blood progenitor cells for autologous transplantation. *Biol Blood Marrow Transplant* 2003;9:405-13.