Annals of Research in Oncology
Vol. 1(3), 185-91, 2021

REVIEW

THE USE OF GRANULOCYTIC COLONY-STIMULATING FACTORS IN PATIENTS RECEIVING CHEMOTHERAPY FOR GERM CELL TUMORS

S. Secondino[1,2], A. Ferrari[1], F. Pasi[1], B. Filippi[1,2], S. M. C. Borgetto[1,2], G. Rosti[1]

[1] Medical Oncology Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy
[2] Department of Internal Medicine and Medical Therapy, University of Pavia, Pavia, Italy

CORRESPONDING AUTHOR:

Giovanni Rosti
Medical Oncology, Fondazione IRCCS Policlinico San Matteo
viale Golgi Camillo 19
27100 Pavia, Italy
E-mail: rosti.giovanni@gmail.com
ORCID: 0000-0003-2097-2803

Doi: 10.48286/aro.2021.24

ABSTRACT

Germ cell tumors (GCT) are a relatively rare malignancy occurring in adolescent/young males in the vast majority of cases. With the advent of platinum containing regimens 4 decades ago, impressive cure rates have been achieved both in the adjuvant setting and in first line for advanced disease, with the vast majority of patients being cured. Moreover, 35 to 50% of patients with recurrent disease can be cured with conventional on high-dose chemotherapy programs. Neutropenia and its complications (mainly neutropenic fever) may be a limiting toxicity with the risk of reducing the planned curative doses or delaying intervals with potential impact on outcome. Granulocytic-hematopoietic growth factors (G-CSFs) by limiting neutropenia and neutropenic fever allow the delivery of curative chemotherapy in a safer manner to GCTs patients. We will present an overview of the use of G-CSF in this setting.

KEY WORDS

Granulocytic colony-stimulating factors; chemotherapy; germ cell tumors; G-CSF prophylaxis; bleomycin.

IMPACT STATEMENT

The proper delivery of chemotherapy in germ cell tumors is crucial to achieve excellent results in terms of cure. G-CSFs may allow the clinicians to deliver chemotherapy in a timely manner and to reduce the risk of severe neutropenia and neutropenic fever.

INTRODUCTION

Germ cell tumors (GCTs), represent a minority of solid tumors, and they are the most frequent occurring in men aged 15-40 years (1, 2). They are histologically divided into two major categories; seminoma and non-seminoma (3).

GCTs have been the first solid tumors to achieve impressive high cure rate with first line chemotherapy; but even in second and subsequent lines, the disease is often curable (4-6).

According to the recent IGCCCG Update Consortium report, patients with metastatic seminoma show 5-year overall survival (OS) of 95% and 88% in good and intermediate prognosis groups, respectively (7). These figures are better than those presented in the IGCCCG classification published in 1997 (8).

In non-seminoma, clinical improvement is even higher regarding poor prognosis patients: OS increasing from 48% to 67% in the last two decades, with a minor, but clear better outcome also for good (from 92% to 94%) and intermediate prognosis groups (from 80% to 89%) (9).

Such impressive cure rates are mainly related to the introduction of cisplatin-based chemotherapy at the end of the '70s. The combination of cisplatin, etoposide, bleomycin (BEP) has proved to be superior in terms of outcome and toxicity compared to PVB (cisplatin, vinblastine and bleomycin) (10). BEP still represents the backbone of first line therapy in metastatic GCT after nearly 35 years from its introduction.

The successful story in our ability to cure young patients with GCT, other than advances in systemic and local treatment modalities including expert surgery, derives from the promotion of multidisciplinary team-based care that ensures greater adherence to clinical guidelines and other components of quality of care, such as reducing treatment toxicity and minimizing delays in diagnosis and greater utilization of surveillance (4, 11).

Chemotherapy regimens employed in GCTs may induce non-negligible adverse effects which can compromise the high cure rates of the treatment itself. In order to minimise morbidity, mortality and to maintain this high-cure rate, neutropenia and related complications are hurdles to be removed on the pathway to cure.

We will comment on the role of these complications in the treatment of GCT and the role of granulocyte colony-stimulating factors (G-CSFs).

FEBRILE NEUTROPENIA IN GERM CELL CANCER PATIENTS

Febrile neutropenia (FN) is defined as an oral temperature of > 38.3 °C or two consecutive readings of > 38.0 °C for 2 hrs and an absolute neutrophil count (ANC) of < 0.5×10^9/l, or expected to fall below 0.5×10^9/l (12); it may be a life-threatening complication of platinum-based chemotherapy (13).

Although the occurrence of FN depends on several factors including chemotherapy regimen, dose intensity, host performance status, previous treatment(s) and bone marrow function, it is difficult to predict exactly the risk for a certain schedule in a single patient. Scoring systems have been published to identify such risk and they may be helpful to the clinicians in order to evaluate the prognosis of an infectious event during febrile neutropenia (14).

The impact of FN from the socio-economic aspect is also to be taken into consideration in terms of lengths of hospitalization and burden of costs (15, 16).

As most GCT patients are young, with adequate bone marrow function and few comorbidities, the risk of neutropenia largely depends on the chemotherapy schedule itself in this population.

Chemotherapy for advanced disease in germ cell patients has a curative intent in most cases and toxicity-related changes in the planned dose and schedule may have a detrimental effect on outcome (17).

In the early trails with BEP or PVB, grade 4 neutropenia was recorded in nearly 60% of patients, and 2.5 % developed fatal sepsis (10).

While BEP is the standard upfront chemotherapy regimen, second and subsequent lines, often given with curative intent, include cisplatin plus ifosfamide and/or paclitaxel and/or vinblastine, and even high-dose chemotherapy with stem cell support (5, 6, 18). All these regimens have a potential high rate of neutropenic fever (19, 20).

In the pre- G-CSF era a retrospective study in the UK (21) evaluated the incidence of neutropenic fever in 88 patients undergoing 240 courses of BEP or CEB (carboplatin replacing cisplatin) and receiving or not receiving prophylactic ciprofloxacin at the dose of 250 mg bid at the onset of neutropenia grade 3. Neutropenic fever was recorded in 5% of patients receiving ciprofloxacin compared to 15% of those not receiving prophylaxis. Neutropenia grade 3 or 4 was recorded among patients receiving BEP in 65%.

In a series from Graz University (22) FN was reported in nearly 17% of 413 consecutive patients; in a multivariate analysis, adjusted for age and risk classification, revealed that poor performance status, seminomatous histology and prior radiation therapy were associated with an increased risk of FN.
The advent of G-CSFs has given us a formidable tool for reducing the risk of NF and its consequences in the treatment of solid tumors (23).
Currently available G-CSFs include short-term G-CSF preparations (filgrastim, lenograstim), requiring daily administrations, and long-acting preparations that they only need to be administered once following chemotherapy (pegfilgrastim and lipegfilgrastim). Both originators and biosimilars have the same efficacy in reducing the risk of FN and related complications (24, 25).

G-CSF PROPHYLAXIS FOR CHEMOTHERAPY-RELATED NEUTROPENIA IN GERM CELL TUMORS

In a randomized EORTC study including 120 poor-prognosis advanced testicular cancer treated with standard BEP or intensified BOP/VIP, G-CSF primary prophylaxis improved the delivery of planned treatment schedule, and reduced the toxic death rate in the intensification arm (19).
In a nationwide retrospective analysis conducted by the National Cancer Institute in Slovakia the use of primary prophylaxis with G-CSF in patients receiving BEP showed statistically significant reduction in the rate of febrile neutropenia (10% with G-CSF *vs* 32% in patients not receiving G-CSF) (26).
Major international guidelines recommend the use of G-CSFs as primary prophylaxis in patients undergoing chemotherapy with a predictive risk of febrile neutropenia around 20% and above (27).
Several of the most employed regimens in the treatment of advanced GCTs have such a potential (24), so the use of G-CSF is highly advisable with the aims of avoiding prolonged and profound neutropenia as well as maintaining dose intensity and timing. In fact, as these tumors are curable with standard multiple-drug regimens, less myelosuppressive agents/regimens are not available with the same efficacy (**table I**).
In second or subsequent chemotherapy lines the incidence of hematologic complications is high.
In a reported series from Memorial Sloan-Kettering Cancer Centre 46 patients were treated in second line (32) with four courses of TIP (paclitaxel, ifosfamide and cisplatin); all received G-CSF 5 ug/kg daily from day 7 until day 18. The rate of febrile neutropenia was high (48%) and the progression free survival at more than 5 years was 65%.
One of the more recent schedules employed in third line is TPG (paclitaxel, cisplatin and gemcitabine) (33) developed at the NCI in Milan with the three drugs administered a week apart (day 1 and 8). G-CSF was

AUTHOR (REFERENCE)		CHEMOTHERAPY REGIMEN	PRIMARY G-CSF PROPHYLAXIS	FEBRILE NEUTROPENIA	GRADE IV NEUTROPENIA
Williams SD, 1987	(10)	PVB/BEP	No	NR	59%
Fosså SD, 1998	(19)	BOP/VIP-B	No Yes	46% 25%	49% 18%
De Wit R, 1998	(28)	VIP	No	11%	26%
Bathia S, 2000	(29)	HDCT	Yes	51%	100%
Hinton S, 2003	(30)	VIP	No	8%	70%*
Kondagunta GV, 2005	(5)	TIP	No	48%	130**
Culine S, 2007	(31)	3 BEP 4 EP	36% 29%	7% 5%	72% 90%
Kondagunta GV, 2007	(32)	HDCT	Yes	67%	100%
Necchi A, 2014	(33)	TPG	No	7%	29%
Terbuch A, 2018	(22)	Mainly BEP	14.9%	16.9%	NR

Table I. *Risk of neutropenia and febrile neutropenia of different chemotherapy regimens in germ cell tumors.*
PVB: cisplatin, vinblastine, bleomycin; BEP, bleomycin, etoposide, cisplatin; NR, not reported; BOP/VIP, bleomycin, vincristine, cisplatin/vinblastine, ifosfamide, cisplatin; HCDT, high dose chemotherapy; TIP, paclitaxel, ifosfamide, cisplatin; EP, etoposide, cisplatin; TPG: paclitaxel, gemcitabine, cisplatin.
*Grade IV hematologic toxicity; **median neutrophils count at nadir/microliter.

planned daily on day 9. Febrile neutropenia was recorded in 7% of the courses and nearly 30% of the patients developed grade IV neutropenia.

High-dose chemotherapy

In the last three decades high-dose chemotherapy (HDC) supported by peripheral blood progenitor cells have become an option for recurrent GCTs. Curves plateauing around 40% have been published even in third line (4, 15) and many guidelines suggest this therapy as a possible option (27, 34).
G-CSFs are crucial in the mobilization phase of peripheral blood progenitor cells (usually at 10 ug/kg daily). In the event of poor mobilization new agent plerixafor has been added to G-CSF with excellent results (35).
G-CSF reduces the length of neutropenia allowing faster recovery following HDC; in this setting single dose of pegfilgrastim can be used replacing several injections of daily G-CSF filgrastim (36).

SPECIFIC SETTINGS

Elderly patients

As mentioned before, GCTs are diseases of adolescents and young adults and the incidence after the age of 50 or 60 years is rare, with only 5-8% of patients included in this age category (37, 38).
Incidence of hematologic complication, in particular FN, in this older population is higher compared to the younger counterpart (33).
The use of G-CSF has been suggested to be mandatory as primary prophylaxis in this population, as 44 percent of the patients developed > 1 episode of NF (39). In the previously cited study by Terbuch *et al.* (22) G-CSF was recommended in patients over 50 years of age due to higher risk of neutropenia-related complications.
In the very few patients older than 75 years reported in the literature, full dose BEP can be safely delivered with G-CSF prophylaxis (40) as reported in other more common diseases (41).

Bleomycin and G-CSF

Bleomycin is still nowadays a cornerstone of first line regimen in germ cell tumors. It is well known that the administration on this drug can result in the serious complication of pulmonary fibrosis probably due to the lack of the enzyme bleomycin hydroxylase in the lungs. The incidence of this event has been reported as high as 8% in patients exposed to > 300 IU with a mortality rate of 1% to 3% (42).
As standard BEP for four courses includes 90 IU each cycle, a careful pre and on therapy check of respiratory function tests is highly advisable.
Early studies with bleomycin and G-CSF did not suggest that G-CSF is causally related to an increase in bleomycin pulmonary toxicity also in patients treated for Hodgkin disease (43).
What is important is a possible development of renal damage due to cisplatin which can lead to increased bleomycin lung toxicity.
In a retrospective series of 212 patients treated at the Peter McCallum Cancer Center in Melbourne, the rate of bleomycin inducing pneumonitis was 34%, the majority being asymptomatic (only radiological findings).
In this series the use of G-CSFs (either daily G-CSF or pegfilgrastim) was not randomized. The use of G-CSFs did not have a significant effect on the severity of bleomycin lung damage (44).
A recent Canadian report (45) on 88 patients, treated with germ cell tumors and Hodgkin disease with or without filgrastim (in a not randomized fashion), adds further evidence that the concomitant use of filgrastim does not increase the risk of pulmonary toxicity of bleomycin (45).
Another topic regards the best timing for G-CSF administration in BEP schedule**.**
BEP regimen includes a second and third administration of bleomycin (30 IU) on days 1, 8 and 15 or 2, 9 and 16.
As G-CSFs have not to be administered within the 24-hour period prior to chemotherapy due to the schedule of this regimen, G-CSFs can be started on day 6, but soon interrupted, despite the fact that bleomycin is not a myelotoxic drug.
Possibilities to overcome this hurdle is to deliver peg-G-CSF either on the day 6 anticipating the second dose of bleomycin on the day 5 or starting daily G-CSFs on day 10 until day 15. Another option developed at the European Institute of Oncology in Milan is to deliver bleomycin 15IU as an intravenous push on day 1 and 10 IU i.v. continuous infusion over 12 hours on days 1 to 3. In their experience on 182 patients the efficacy of this modified BEP regimen was comparable to standard BEP (46), allowing G-CSFs to be administered after completion of CT until neutrophil recovery.

CONCLUSIONS

Due to high cure rate of GCTs, it is mandatory to deliver the planned treatment schedule of chemotherapy. For this reason, primary and secondary G-CSF prophylaxis should be considered, in accordance with the recommendations of the main scientific societies, for patients with GCTs undergoing chemotherapy both at conventional doses (*i.e.*, ifosfamide-containing) and within intensified/HDC programs.

In selected clinical situation, including fragile/elderly patient, G-CSF should also be given when chemotherapy is administered with a curative intent.

CONFLICT OF INTERESTS

The authors have declared no conflict of interests.

REFERENCES

1. Smith ZL, Werntz RP, Eggener SE. Testicular cancer: epidemiology, diagnosis, management. Med Clin North Am 2018;102: 251-64.
2. Znaor A, Skakkebaek NE, Rajpert-De Meyrs E, et al. Testicular cancer incidence predictions in Europe 2010-2015: a rising burden despite population ageing. In J Cancer 2020;147:820-8.
3. Moch H, Cubilla AL, Humphrey PA, et al. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs- Part A: Renal, and Testicular Tumours. Eur J Urol 2016; 70: 93-105
4. Albany C, Adra N, Snavely AC, et al. Multidisciplinary clinic approach improves overall survival outcomes of patients with metastastic germ-cell tumors. Ann Oncol 2018;29:341-6.
5. Kondagunta GV, Bacik J, Donadio A, et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol 2005;20:6549-55.
6. Necchi A, Lanza F, Rosti G, et al. High-dose chemotherapy for germ cell tumors. Do we have a model? Exp Opin Biol Ther 2015;1:33-44.
7. Beyer J, Collette L, Sauvé N, et al. Survival and New Prognosticators in Metastatic Seminoma: Results from the IGCCCG-Update Consortium. J Clin Oncol 2021;39:1553-2.
8. Mead GM. International Germ Cell Consensus Classification: A prognostic factor-based staging system for metastatic germ cell cancers. J Clin oncol1997;15:594-603.
9. Gillessen S, Sauvè N, Collette L, et al. Predicting Outcomes in Men with Metastatic Non-seminomatous Germ Cell Tumors (NSGCT): Results from the IGCCCG Update Consortium J Clin Oncol 2021;39:1563-74.
10. Williams SD, Birch B, Einhorn LH, et al. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide N Engl J Med 1987;316:1435-40.
11. Huang MM, Cheaib JC, Su ZT, et al. Assessing quality of care in the diagnosis and treatment of early-stage testicular cancer: A critical review and summary. Urol Oncol 10.1016/j.urolonc.2021.02.001.
12. Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines Ann Oncol 2016; 27(5):v111-8).
13. Zimmer AJ, and Freifeld AG. Optimal Management of Neutropenic Fever in Patients with Cancer. J Oncol Pract 2019;15:19-24.
14. Klastersky, M Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 2000;18 3038-51.
15. Dulisse B, Li X, Gayl JA, et al. A retrospective study of the clinical and economic burden during hospitalizations among cancer patients with febrile neutropenia J Med Econ 2013;16:720-35.
16. Kuderer NM, Dale DC, Crawford J, et al. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106:2258-66.
17. Grimison PS, Stockler MR, Thomson DB, et al. Comparison of two standard chemotherapy regimens for good-prognosis germ cell tumors: updated analysis of a randomized trial. J Natl Cancer Inst 2010;102:1253-62.
18. Pedrazzoli P, Rosti G, Secondino S, et al. High-dose chemotherapy with autologous hematopoietic stem cell support for solid tumors in adults. Semin Hematol 2007;44:286-95.
19. Fosså SD, Kaye SB, Mead GM, 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.
20. Motzer RJ, Sheinfeld J, Mazumdar M, et al. Etoposide and cisplatin adjuvant therapy for patients with pathologic stage II germ cell tumors. J Clin Oncol 1995;13:2700-4.
21. Counsell R, Pratt J, Williams MV. Chemotherapy for germ cell tumours: prophylactic ciprofloxacin reduces the incidence of neutropenic fever. Clin Oncol (R Coll Radiol) 1994;6:232-6.
22. Terbuch A, Posch F, Partl R, et al. Risk stratification for febrile neutropenia in patients with testicular germ cell tumors. Cancer Med 2018;7:508-14.
23. Locatelli F, Pedrazzoli P. Recombinant human G-CSF: how wide is the field of clinical applicability? Haematologica 1995;80:199-205.

24. Gilligan T, Lin DW, Aggarwal R, et al. NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2020;17:1529-54.
25. Botteri EA, Krendyukov G, Curigliano G. Comparing granulocyte colony-stimulating factor filgrastim and pegfilgrastim to its biosimilars in terms of efficacy and safety: A meta-analysis of randomised clinical trials in breast cancer patients Eur J Cancer 2018;89:49-55.
26. Hapakova N, Chavonec M, Rejlekova K, et al. The effect of primary granulocyte-colony stimulating factors prophylaxis on incidence of febrile neutropenia in patients with testicular germ cell tumors. ASCO 2020, abst. 17056.
27. Honecker F, Aparicio J, Berney D, et al. ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. Ann Oncol 2018;29:1658-86.
28. de Wit R, Stoter G, Sleijfer DTh, et al. Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. B J Cancer 1998;78:828-32.
29. Bhatia S, R. Abonour, P. Porcu, et al. High-Dose Chemotherapy as Initial Salvage Chemotherapy in Patients with Relapsed Testicular Cancer. J Clin Oncol 2000;18:3346-52.
30. Hinton S, Catalano PJ, Einhorn LH, et al. Cisplatin, Etoposide and either Bleomycin or Ifosfamide in the treatment of disseminated germ ell tumors. Cancer 2003;97:1869-75.
31. Culine S, Kerbrat P. Kramar A, et al. Refining the optimal chemotherapy regimen for good-risk metastatic nonseminomatous germ-cell tumors: a randomized trial of the Genito-Urinary Group of the French Federation of Cancer Centers (GETUG T93BP). Ann Oncol 2007;18:917-24.
32. Kondagunta GV, Bacik J, Sheinfeld J, et al. Paclitaxel plus Ifosfamide followed by high-dose carboplatin plus etoposide in previously treated germ cell tumors. J Clin Oncol 2007;25:85-90.
33. Necchi A, Nicolai N, mariani L, et al. Combination of paclitaxel, cisplatin, and gemcitabine (TPG) for multiple relapses or platinum-resistant germ cell tumors: long-term outcomes. Clin Genitourin Cancer 2014; 12:63-9.
34. Linee Guida Tumori del testicolo, 2018. Available from www.AIOM.it.
35. Horwitz ME, Long G, Holman P, et al. Efficacy and safety of hematopoietic stem cell remobilization with plerixafor+G-CSF in adult patients with germ cell tumors. Bone Mar 2012;47:1283-86.
36. Castagna L, Bramanti S, Levis A, et al. Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. Ann Oncol 2010;21:1482-85.
37. Berney DM, Warren AY, Verma M, et al. Malignant germ cell tumours in the elderly: a histopathological review of 50 cases in men aged 60 years or over. Modern Pathol 2008;21:54-9.
38. Ghazarian AA, Rusner C, Trabert B, et al Testicular cancer among UF men aged 50 years and older. Cancer Epidemiol 2018;55:68-72.
39. Feldman DR, Voss MH, Jacobsen EP, et al.. Clinical features, presentation, and tolerance of platinum-bases chemotherapy in germ cell tumor patients 50 years of age and older. Cancer 2013;119:2574-81.
40. Rosti G, Carminati O, Soresini E, et al. Testicular germ cell cancer in the elderly: a case report. Arg Geriat Oncol 2021;6:38-41.
41. Falandry C, Krakowski I, Curè H, et al. Granulocyte-colony-stimulating factors in elderly patients receiving chemotherapy for breast cancer and gynaecological cancers: results of a French survey. Anticancer Res 2014;34:5007-15.
42. O'Sullivan JM, Huddart RA, Norman AR, et al. Predicting the risk of bleomycin lung toxicity in patients with germ cell tumours. Ann Oncol 2003;14:91-6.
43. Bastion Y and Coiffier B. Pulmonary toxicity of bleomycin: is G-CSF a risk factor? The Lancet 1994;344: 474.
44. Kwan EM, Beck S, Amir E, et al. Impact of Granulocyte-colony Stimulating Factor on Bleomycin- induced Pneumonitis in Chemotherapy-treated Germ Cell Tumors. Clin Genitourinary Cancer 2017;16: e193-9.
45. Laprise-Lechance M, Lemieux P, Grègoire J-P. Risk of pulmonary toxicity of bleomycin and filgrastim. J of Oncol Pharmacy Practice 2018;25:1638-44.
46. Aurilio G, Verri E, Frassoni S, et al. Modified-BEP Chemotherapy in Patients with Germ-Cell Tumors Treated at a Comprehensive Cancer Center. Am J Clin Oncol 2020;43:381-7.
47. Necchi A, Nicolai N, Mariani L, et al. Combination of Paclitaxel, Cisplatin, and Gemcitabine (TPG) for Multiple Relapses or Platinum-resistant germ Cell Tumors: Long-Term Outcomes. Clin Genitourinary Cancer 2014;12:63.9.