

- Adiga GU, Elkadi D, Malik SK, Fitzpatrick JD, Madajewicz S. Abdominal aortitis after use of granulocyte colony-stimulating factor. *Clin Drug Investig*. 2009;29(12):821-825.
- Sato Y, Kaji S, Ueda H, Tomii K. Thoracic aortitis and aortic dissection following pegfilgrastim administration. *Eur J Cardiothorac Surg*. 2017;52:993-994.
- Darie C, Boutalba S, Fichter P, et al. Aortitis after G-CSF injections. *Rev Med Interne*. 2004;25:225-229.
- D'Souza A, Jaiyesimi I, Trainor L, Venuturumili P. Granulocyte colony-stimulating factor administration: adverse events. *Transfus Med Rev*. 2008;22(4):280-290.
- Miller EB, Grosu R, Landau Z. Isolated abdominal aortitis following administration of granulocyte colony stimulating factor (G-CSF). *Clin Rheumatol*. 2016;35:1655-1657.
- Neulasta (Pegfilgrastim) Labeling. Full Prescribing Information*. Thousand Oaks, CA: Amgen Inc; June 18, 2018.

Received: 27 June 2018 | Revised: 11 July 2018 | Accepted: 16 July 2018

DOI: 10.1002/ajh.25221

Late-onset fever and engraftment syndrome following autologous stem cell transplant: Impact on resource utilization

To the Editor:

Despite being first reported more than 20 years ago,¹ engraftment syndrome (ES) remains a variably defined complication following hematopoietic progenitor cell transplant (HPCT).²⁻⁴ ES is typically characterized by the occurrence of a new noninfectious fever that coincides with neutrophil engraftment. The fever may be associated with a skin rash, diarrhea, pulmonary infiltrates, or hepatic dysfunction. Although most cases of ES are self-limiting, some can be prolonged and cause severe symptoms, necessitating the use of corticosteroids. The underlying pathophysiology associated with ES remains poorly understood. Based on the Lewis rat syngeneic and autologous HPCT model,⁵ ES is generally believed to have arisen due to the interplay between pro-inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF) α , and interferon (IFN) γ associated with hematopoietic recovery in a setting with a deficiency of T_{reg} cells.

Many studies have examined the factors predisposing patients to ES. Despite ES being associated with significant transplant-related morbidities, there has been a paucity of study examining its impact on health resource utilization. Here, we set out to determine, in a retrospective study, how ES following autologous HPCT affects the post-transplant length-of-stay (PT-LOS) in the hospital, use of intravenous antimicrobials, additional radiologic examination, and financial costs to the transplant. Patient demographics, clinical data, diagnosis, and treatment history were collected from their electronic medical

records. Costs of care during transplant were obtained from the accounts department of the medical center. This study was approved by the Institutional Review Board at New York Medical College/Westchester Medical Center.

All transplants were carried out on an inpatient basis in high efficiency particulate air filtered single rooms using autologous peripheral blood stem cells. Autologous peripheral blood stem cells were mobilized using G-CSF (10 μ g/kg/day) \pm plerixafor (0.24 mg/kg) \pm chemotherapy. All patients received GM-CSF (500 μ g/day) starting Day +1 and prophylactic ciprofloxacin, fluconazole, and acyclovir when their absolute neutrophil counts dropped to less than 500/mm³. Weekly surveillance Cytomegalovirus detection by PCR was performed in all patients (detection threshold <137 IU/mL or < 2.14 Log₁₀ IU/mL).

We defined fever as an oral temperature of 100.5°F or above. Fever that occurred from Day +1 to Day +8 was considered early-onset fever, and new fever that occurred from Day +9 to day of discharge was considered late-onset fever. Neutrophil engraftment was defined as the attainment of an absolute neutrophil count of 500/mm³ or more for three consecutive days.

Seventy-five consecutive patients who underwent peripheral blood HPCT for hematologic malignancies between April 2014 and December 2017 were identified. There were 46 males and 39 females. Their median age was 59 years (range: 24-72). Most common diagnosis was multiple myeloma (53, 71%), followed by non-Hodgkin's lymphoma (17, 22%), and Hodgkin's disease (5, 7%). Forty-six (61%) patients received a bortezomib-containing regimen prior to transplant. Preparative regimens used for HPCT were: Melphalan 200 mg/m² (53, 71%), Rituxan (375 mg/m² on Day 1)/BCNU (300 mg/m² on Day 1)/Etoposide (400 mg/m²/day on Days 2-5)/ARA-C (400 mg/m²/day on Days 2-5) and melphalan (140 mg/m² on Day 6) (R-BEAM) (12, 16%), and BEAM (10, 13%). The patients were divided into three groups according to the occurrence of fever: Group 1—No post-transplant fever; Group 2—Early-onset fever; Group 3—Late-onset fever. No statistical differences were found among these three groups in age, sex distribution, dose of CD34+ cells infused, underlying diagnosis, prior use of bortezomib, transplant preparative regimen, and dose of GM-CSF per kg body weight. All patients with early-onset fever did not show any evidence of neutrophil engraftment within 72 h of developing fever.

Fourteen (19%) patients did not develop any fever during the peri-transplant period. Sixty-one patients developed a post-transplant fever: 19 (25%) patients developed early-onset fever and 42 (56%) late-onset fever; 11 microbial organisms were isolated from 11 of these 61 patients with fever. Toxigenic *C. difficile* was the commonest ($n = 3$), followed by vancomycin-resistant enterococci ($n = 2$), cytomegalovirus ($n = 2$, viremia), Coronavirus ($n = 1$), *S. epidermidis* ($n = 1$), *Staph. aureus* ($n = 1$), and *Corynebacterium jeikeium* ($n = 1$). It is likely the *S. epidermidis* was from contamination. All bacterial isolates were obtained from blood cultures, except for toxigenic *C. difficile* that was detected by PCR on diarrheal stool. There was no difference in the likelihood of a positive microbial isolate between the two groups of patients with fever; two from the group of 19 patients with early-onset fever and 11 from 42 patients with late-onset fever ($P = 0.31$).

Patients who developed fever had a significantly longer PT-LOS (HR 2.59; 95% CI 1.1-7.6) ($P < .001$) when compared with those who

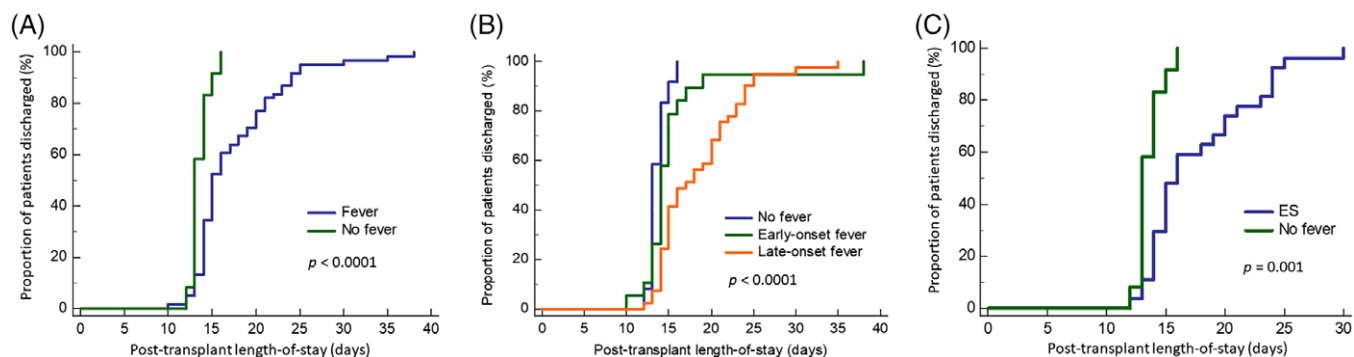


FIGURE 1 Effects of fever and engraftment syndrome on post-transplant length-of-stay in the hospital. A, Patients who developed fever during the peri-transplant periods had significantly longer post-transplant length-of-stay when compared with those who did not develop any fever. B, The impact on post-transplant fever on length-of-stay in the hospital was caused primarily by those who developed late-onset fever, rather than those with early-onset fever. C, ES resulted in significantly longer post-transplant length-of-stay when compared with those who did not develop any fever

did not develop any post-transplant fever (Figure 1A). The median PT-LOS was 13 days (range 12-16; 95% CI 13-14) in the group without fever but 15 days (range 12-38; 95% CI 15-17) in the group with fever ($P = 0.01$). The third quartile PT-LOS in the group without fever was 14 days and with fever 20 days ($P = 0.004$). The difference in the PT-LOS between the two groups was predominantly due to the increased PT-LOS in those with late-onset fever (Figure 1B). There was no statistical difference in the PT-LOS between the group without fever and the group with early-onset fever. However, the median PT-LOS for late-onset fever was significantly longer when compared with those without fever (17 days vs. 13 days; HR 3.3; 95% CI 1.3-8.7; $P = 0.002$) and those with early onset fever (17 vs. 14; HR 1.7; 95% CI 0.9-3; $P = 0.048$).

We next determined the impact of ES on PT-LOS. We first used the following criteria for ES: The occurrence of a new fever, not associated with any microbial isolate or infection, that occurred 72 hours before or after neutrophil engraftment, and associated with a skin rash, pulmonary infiltrates, diarrhea, or new abnormal liver function tests. Twenty (27%) cases of ES occurred in this cohort of patients. However, when we included the eight patients with noninfectious fever whose fever was probably due to ES even though the fever was not associated with any rash, diarrhea, pulmonary infiltrate, or abnormal liver function tests, the incidence of ES went up to 37%. By far, ES was the commonest cause for new fever that occurred after Day +8, being responsible for 67% of all late-onset fevers. ES resulted in significantly longer PT-LOS when compared with those without fever ($P = 0.0001$; HR 2.9; 95% CI 1.1-7.2; Figure 1C). The median PT-LOS in patients with ES was 16 days (95% CI 15-20), when compared with 13 days (95% CI 13-14) in those without fever ($P = 0.004$).

Finally, we examined the impact of ES on intravenous antimicrobial usage, additional radiologic examinations, and financial costs to the transplant. We used the PT-LOS incurred by the group of patients without fever as the point of reference for cutoff and determined the resource utilization above the cutoff that was incurred by patients who developed ES. In addition to longer PT-LOS, ES led to an increase of 202 intravenous antimicrobial days (averaging 7.2 days/ES patient). Furthermore, 47 additional chest X-ray examinations (averaging 1.7/ES patient), and three computer-assisted tomographic scans of chest, abdomen, and pelvis were carried out

among the 28 patients who developed ES. The total expenditure incurred by ES in 27 of these 28 patients for whom billing records were available was \$1 980 402 (averaging \$9825/patient with ES/day).

In conclusion, ES occurs frequently after autologous HPCT. ES not only increases transplant-related morbidities but also resource utilization. Identification of biomarkers that can be used to help diagnose ES is highly desirable so that these patients do not have to undergo unnecessary investigations and additional antimicrobial therapy that consequently result in longer PT-LOS and higher transplant costs. Elevation of C-reactive protein (CRP) has been found to be associated with ES.⁶ However, CRP is highly nonspecific and is also elevated in sepsis, the very complication that requires aggressive antimicrobial therapy in this group of immunocompromised patients. Serum procalcitonin is a robust biomarker for sepsis. Future studies may examine the combination of CRP and procalcitonin in the diagnosis of ES and exclusion of sepsis, so patients with a low procalcitonin that accompanies an elevated CRP be confidently diagnosed ES and be spared the additional investigations and prolonged courses of intravenous antimicrobial therapy for the symptoms associated with ES.

ORCID

Amandeep Aujla <http://orcid.org/0000-0003-1449-7794>

Seah H. Lim <http://orcid.org/0000-0002-4135-5989>

Jibrán Ahmed
Michael Karass
Amandeep Aujla
Patricia McHale
Patricia Kretschmer
Amítabhā Mazumder
Karen Seiter
Tauseef Ahmed
Seah H. Lim
Bettina M. Knoll

Blood and Marrow Transplant Program, Westchester Medical Center,
New York Medical College, Hawthorne, New York

Correspondence

Seah H. Lim, Westchester Medical Center Cancer Institute, 19 Bradhurst Avenue, Suite 2575S, Hawthorne, NY 10532. Email: seah.lim@wmchealth.org

REFERENCES

1. Lee C-K, Gingrich RJ, Hohl RJ, Ajram KA. Engraftment syndrome in autologous marrow and peripheral stem cell transplantation. *Bone Marrow Transplant.* 1995;16:175-182.
2. Maiolino A, Biasoli I, Lima J, Portugal AC, Pulcheri W, Nucci M. Engraftment syndrome following autologous hematopoietic stem cell transplantation: definition of diagnostic criteria. *Bone Marrow Transplant.* 2003;31:393-397.
3. Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2001;27:893-898.
4. Capizzi SA, Kumar S, Huneke NE, et al. Periengraftment respiratory distress syndrome during autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2001;27:1299-1303.
5. Hess AD, Horwitz L, Beschoner WE, Santos GW. Development of graft-vs.-host disease-like syndrome in cyclosporine-treated rats after syngeneic bone marrow transplantation. I. Development of cytotoxic T lymphocytes with apparent polyclonal anti-Ia specificity, including auto-reactivity. *J Exp Med.* 1985;161:718-730.
6. Fassas AB, Miceli MH, Grazzutti M, Dong L, Barlogie B, Anaissie E. Serial measurement of serum C-reactive protein levels can identify patients at risk for severe complications following autologous stem cell transplantation. *Leuk Lymphoma.* 2005;46:1159-1161.

Received: 25 June 2018 | Revised: 11 July 2018 | Accepted: 16 July 2018
DOI: 10.1002/ajh.25222

Daily alternating deferasirox and deferiprone therapy successfully controls iron accumulation in untreatable transfusion-dependent thalassemia patients

To the Editor:

Chelation therapy to treat iron overload has beneficial impact on the prognosis of patients with transfusion-dependent thalassemia (TDT). Three different chelating agents are currently available: deferoxamine (DFO) which is given subcutaneously, and two oral agents, deferasirox (DFX) and deferiprone (DFP).

Combination of two different iron chelators is common practice in patients with severe iron burden, or for those in which monotherapy is not adequately effective. Combination of DFO and DFP is well established as a treatment for severe iron overload in heart dysfunction.¹ More recently, the combination of DFO and DFX has been

shown to be safe and efficacious in treating iron overload in TDT patients nonresponder to standard treatment regimens.² Successful combination therapy with DFX and DFP has been reported previously,³ as being effective in reducing iron overload and superior in improving cardiac T2*, compliance and patient satisfaction compared with the deferoxamine/deferiprone combination.⁴ The use of combination therapy to address intolerance to monotherapy is not common practice, due to the expectations that patients will continue to exhibit similar or worse lack of tolerance. Some TDT patients do not tolerate either mono or combined therapy, resulting in worsening iron overload and in poor prognosis in term of life expectancy. The main described side effects are persistent proteinuria (deferasirox) or gastro-intestinal symptoms (deferasirox or deferiprone). These TDT patients are at high risk to develop life-threatening complications related to iron overload. We previously reported safe and effective treatment of two TDT patients treated with alternating regimens of DFP and DFX over 1 year.⁵ We have subsequently extended this daily alternating approach to other six previously untreatable TDT subjects. Patients were defined as intolerant due to the presence of the following side effects during monotherapies or classical combined therapy: significant proteinuria persistent after re-challenge; arthralgia with functional limitation; neutropenia resolved after DFP discontinuation; gastrointestinal intolerance; systemic reactions. A total of eight TDT patients (4 males and 4 females) have been placed so far on DFP (starting dose 75 mg/kg/day, three doses/day) combined with DFX (starting dose 25 mg/kg/day) administered as alternating chelation therapy. Patients' mean age was 28 years (ranging from 17 to 36). Figure 1A reports the demographic, clinical conditions of TDT patients on daily alternating chelation therapy and the doses of chelators.

The median adherence, calculated as the percentage of drug taken in respect to the one issued, was 90%. Median iron intake from blood transfusions was 9.9 mg/year. Mean follow-up was 52 months (ranging from 12 to 104). The mean value of serum ferritin was 1632 at baseline and 1045 ng/mL at follow-up ($P = .2$). Figure 1C reports the evaluations of serum ferritin during the follow-up. Figure 1B,C reports the performed MRI-T2* evaluations (1.5 T GE HDxt scanner) of liver, heart and pancreas during the follow-up for seven patients; one patient was excluded from analysis due to lack of MRI follow-up. The mean value of cardiac MRI-T2* was 27 and 37 millisecond (ms) at baseline and follow-up, respectively ($P = .21$). Three patients showed cardiac iron overload at baseline (1 pt with $T2^* < 10$ ms, 2 pts with $T2^* > 10$ and < 20 ms) that disappeared at follow-up (Figure 1B). Mean values of liver MRI-T2* were 5.8 and 12.8 ms at baseline and follow-up, respectively ($P = 0.19$). Five patients showed liver iron overload at baseline (1 moderate-severe, 4 mild) which is almost disappeared at the follow-up (Figure 1B). Mean values of the MRI-T2* of pancreas were 12.6 and 17 ms at baseline and follow-up, respectively ($P = .47$). None of the patients' developed iron overload in liver and heart during alternate-combined iron chelation therapy. None of the patients experienced any of the safety problems previously experienced with daily monotherapy with either DFO, DFX, or DFP alone or combined.

The alternating-combined iron chelation therapy was designed to improve patient tolerance and achieve the desired therapeutic efficacy by allowing continued exposure to iron chelator and efficient iron clearance coverage. In our case series, daily alternating regimen of DFP and DFX was effective in removing iron from heart and liver as well as in