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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Procalcitonin as a biomarker to differentiate bacterial infections from engraftment syndrome following autologous hematopoietic stem cell transplantation for multiple myeloma

To the Editor:

Procalcitonin (PCT) is a hormokine. It is approved by the Food and Drug Agency as a biomarker for sepsis and has been found to be a useful prognostic biomarker in febrile neutropenic patients with documented infections.[1,2] Infectious complications are the major cause of morbidity and mortality in febrile neutropenic patients after ASCT. Fever is, therefore, frequently treated with antibiotics. However, unnecessary use of broad-spectrum antibiotic treatment harbors the risk of evolution of drug resistant bacteria and *Clostridium difficile* infection.

We previously reported the high resource utilization associated with late-onset fever and engraftment syndrome (ES) following autologous stem cell transplantation (ASCT).[3] The median hospital length-of-stay in patients who developed ES was 3 days longer than those without ES. These patients also incurred an average additional cost of $9825/patient/day. Patients with multiple myeloma (MM) are most at risk for the development of ES following ASCT. Up to 30% of these patients developed the complication and the high incidence has been attributed to the prior use of bortezomib and lenalidomide.[4] Due to associated hypogammaglobulinemia, MM patients are also at increased risk for infections. The ability to differentiate between fever from bacterial infection and fever from ES in MM patients is, therefore, greatly needed. Here, we set out to evaluate the utility of PCT as a biomarker to differentiate between bacterial infection and ES in MM patients following ASCT.

Between March 2017 and September 2018, PCT and C-reactive protein (CRP) levels were obtained in febrile patients after ASCT who met Spitzer or Maiolino criteria for ES.[4,5] PCT was measured using the Kryptor bioanalyser via an immunofluorescent assay with a lower detection limit of 0.15 ng/mL, with values >2.0 ng/mL being highly suggestive of systemic infection or a severe localized infection. Patient demographics, clinical and laboratory data, diagnosis, and treatment history were collected from their electronic medical records. The study was approved by the Institutional Review Board at New York Medical College/Westchester Medical Center.

Fifteen patients developed ES following ASCT. Their clinical characteristics are shown in Table 1. The median age was 62. Sixty-six percent were men. Autologous peripheral blood stem cells were mobilized using G-CSF (10 μg/kg/day) ± plerixafor (0.24 mg/kg). Transplant preparative regimen consisted in all cases of intravenous melphalan 200 mg/m^2. All patients received GM-CSF (500 μg/day) starting day +1 and prophylactic ciprofloxacin, fluconazole, and acyclovir during neutropenia. Symptom onset of ES occurred up to 2 days prior to 3 days following beginning neutrophil recovery, between the 6th to the 10th day post transplantation. Fever lasted 1-10 days (median 5). Work up for bacterial infection was negative in all but one patient at the time of engraftment. One patient had *Escherichia coli* bacteremia. No other bacterial infections were observed following engraftment until hospital discharge. While CRP levels were elevated in all patients (median 8.5; range 1.4-17; norm 0.0-0.5 mg/dL), PCT was elevated in the bacteremia patient only (6.39 ng/mL) and remained <2 ng/mL (median 0.48; range 0.10-1.97) in all other observations.

TABLE 1 Clinical characteristics of patients

Gender, age	Underlying malignancy	Cell dose	Palifermin	Symptom onset in relation to day of beginning ANC recovery/ (day from transplant)	Duration of fever (d)	Imaging data	Microbiological data	PCT (ng/mL)	CRP (mg/dL)	Infection (Y/N)
60 M	MM	5.14 × 10/g/kg	60 mcg/kg	+3 (d + 10)	4	CT a/p CXR LE Doppler US	BCx UCx C-diff toxin PCR Multiplex PCR	1.49	8.6	Y (non-bacterial, CMV viremia)
53 M	MM	4.33 × 10/6/kg	60 mcg/kg	+3 (d + 9)	1	CXR	BCx UCx Multiplex PCR	0.39	8.5	N
68 F	MM	3.94 × 10/6/kg	60 mcg/kg	+1 (d + 8)	6	CT c/a/p	BCx UCx C-diff toxin PCR Multiplex PCR	0.73	6	Y (non-bacterial, coronavirus 229E)
62 M	MM	4.44 × 10/6/kg	60 mcg/kg	-1 (d + 7)	9	CT c/a/p	BCx UCx C-diff toxin PCR Multiplex PCR	0.66	16	N
65 M	MM	8.92 × 10/6/kg	60 mcg/kg	−2 (d + 8)	7	CT c/a/p	BCx UCx C-diff toxin PCR	0.93	17	N
62 F	MM	5.5 × 10/6/kg	60 mcg/kg	−1 (d + 8)	7	CXR	BCx UCx C-diff toxin PCR	0.30	10	N
58 F	MM	6.20 × 10/6/kg	60 mcg/kg	−1 (d + 8)	7	CXR LE Doppler	BCx UCx	0.15	5	N
68 M	MM	6.25 × 10/6/kg	60 mcg/kg	0 (d + 8)	4	CXR	BCx UCx C-diff toxin PCR	0.71	12	N
56 M	MM	7.4 × 10/6/kg	60 mcg/kg	−1 (d + 8)	10	CT c/a/p	BCx UCx C-diff toxin PCR	0.58	1.4	N
67 M	MM	2.57 × 10/6/kg	60 mcg/kg	−2 (d + 8)	5	CXR	BCx UCx	1.97	15	N
61 F	MM	4.96 × 10/6/kg	60 mcg/kg	−1 (d + 10)	4	CXR	BCx UCx C-diff toxin PCR Multiplex PCR	0.22	8.3	N
57 M	MM	3.7 × 10/6/kg	60 mcg/kg	−2 (d + 7)	5	NA	BCx UCx C-diff toxin PCR Multiplex PCR	0.24	8.5	N
61 F	MM	5.03 × 10/6/kg	60 mcg/kg	−2 (d + 8)	5	CT c/a/p	BCx UCx C-diff toxin PCR Multiplex PCR	0.16	2.8	N
65 M	MM	7.29 × 10/6/kg	60 mcg/kg	−2 (d + 7)	4	CXR	BCx UCx C-diff toxin PCR	6.39	4.4	Y (*E. coli* bacteremia)
64 M	MM	9.18 × 10/6/kg	60 mcg/kg	−2 (d + 6)	5	CXR ABD US	BCx UCx C-diff toxin PCR	0.10	5	N

Abbreviations: M, male; F, female; mcg, microgram; kg, kilogram; mg, milligram; ng, nanogram; dL, deciliter; PCT, procalcitonin; CRP, C-reactive protein; d, day; ANC, absolute neutrophil count; CT, computed tomography; c, chest; a, abdomen; p, pelvis; CXR, chest X-ray; LE, lower extremity; US, ultrasound; ABD, abdominal; BCx, blood culture; UCx, urine culture; C-diff, clostridium difficile; PCR, polymerase chain reaction; Y, yes; N, No; NA, non-applicable.

PCT with a cutoff of <2 ng/mL might be an adjunctive biomarker in identifying patients suffering from non-infectious fever associated with ES following ASCT. A PCT guided algorithm may limit the duration of antibiotics, reduce adverse events and prevent the emergence of antimicrobial resistance. Large randomized controlled trials comparing PCT guided antimicrobial therapy *vs.* standard of care to limit unnecessary exposure to antimicrobials in immunocompromised ASCT recipients are warranted.

CONFLICT OF INTEREST

Nothing to report.

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Drug-induced thrombocytopenia: 2019 Update of clinical and laboratory data

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To the Editor:

Thrombocytopenia caused by drug-dependent antibodies occurs suddenly, is typically severe, is often misdiagnosed and therefore commonly recurs. To document drugs (and also beverages, foods and food supplements) that have definite clinical evidence for causing immune-mediated thrombocytopenia, we have systematically reviewed all published reports of drug-induced thrombocytopenia (DITP) since 1998.[1] We established a web site that lists all reports of thrombocytopenia attributed to drugs, beverages, foods and food supplements with their level of evidence for a causal association (www.ouhsc.edu/platelets/ditp). Our web site also includes the experience of the BloodCenter of Wisconsin with identification of drug-dependent, platelet-reactive antibodies in patients with suspected DITP.[2] We have defined definite evidence for a causal association of a drug with thrombocytopenia as recurrent acute thrombocytopenia with recurrent drug exposure and/or documentation of drug-dependent, platelet-reactive antibodies. This combination methodology provides strong support for clinicians who are considering the diagnosis of DITP.

This report describes our current search of 8 databases for articles published January, 2015-November, 2018 (Supporting Information Table S1) to identify reports describing definite evidence for a causal association of the drug with thrombocytopenia. Fifty-two articles reported evaluable data for 61 individual patients with thrombocytopenia attributed to 46 drugs and 1 food supplement. Definite clinical evidence for a causal association was described for 18 drugs and the food supplement; 10 drugs and the food supplement had not been previously described with definite evidence. Nine articles reported evaluable group data; only one report of quinine treatment described definite evidence for a causal association and quinine has been previously reported with definite evidence.[1] Supporting Information Table S2 summarizes the data for the 61 evaluable reported patients and the 9 articles reporting evaluable group data. These new data from our systematic literature review together with the new data from the BloodCenter of Wisconsin are merged with the previously reported data on our updated web site.

Table 1A lists the 10 drugs plus 1 food supplement that have not been previously reported with definite evidence for a causal association with thrombocytopenia. Three of the 10 drugs (dexamethasone,