Clinical Hematology International
Vol. **2**(**4**); December (2020), *pp.* 168–172
DOI: https://doi.org/10.2991/chi.k.200719.001; eISSN 2590-0048
https://www.atlantis-press.com/journals/chi/

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The Incidence and Timing of Blood Cultures in Multiple Myeloma – Results from a Retrospective, Single Center, Real-World Study

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ARTICLE INFO

Article History

Received 14 May 2020
Accepted 09 July 2020

Keywords

Blood cultures
multiple myeloma
infection
incidence
risk factor

1. INTRODUCTION

Multiple myeloma (MM) is a cancer of the immune system characterized by complex cellular and humoral immunodeficiency [1–3]. Patients with MM often have advanced age, increased comorbidity and are exposed to immunosuppressive drugs during therapy [4]. These factors contribute to markedly increased risk of infections, mainly pneumonia and sepsis [5–7]. These complications are responsible for a substantial part of early deaths in MM [7–9]. The incidence of bacterial infections peaks in the first six months after diagnosis [10,11]. We have previously reported the results of a retrospective, single-center, real-world study conducted at Vejle Hospital (a primary and secondary referral center receiving approximately 30 newly diagnosed cases of MM per year), in which we reviewed the clinical course of 303 patients with MM who initiated treatment from 2006 to 2016 [12]. The aims of the present study were to describe, in a single-center cohort of patients with MM, the results of blood cultures, to determine their incidence and timing, and to assess their associations with baseline clinical characteristics and treatment-related factors. Moreover, we assessed the use of immunoglobulin replacement therapy (IGRT) in the study population.

We collected blood culture results from the Danish microbiology register (MiBA [13]) of all hospitals where patients were treated. A 'blood culture day' (BCD) was defined as a day a patient had at least one blood culture performed. A positive BCD was defined as a day a patient had at least one positive blood culture result. Blood cultures were categorized as "negative", "positive" or "possible contamination" according to the guidelines for classification of hospital-acquired blood stream infections in the Danish Healthcare-associated Infections Database [14]. Blood cultures classified initially as "possible contamination" were reclassified as blood stream infections if the same microorganism was identified in the patient's blood cultures more than once in a period of 14 days. We assessed the time to first blood culture and first positive blood culture by the Kaplan–Meier method. We calculated BCDs over time as counts per 1000 patients. The number of BCDs was described with median, range and interquartile range (IQR). We investigated univariate and multivariate association of baseline patient characteristics and treatment-related factors, reported as hazard ratios with 95% confidence intervals, with time to BCDs by Cox regression. We included repeated events in the Cox regression model to take into account multiple blood cultures for the same patient. Blood culture data were available in 302 patients. Two hundred and eighty-two patients had at least one blood culture result and 113 patients had at least one positive blood culture result. We identified 4992 blood culture results: 4243 were negative and 249 were positive. Fifty-nine positive blood culture results were classified as possible contaminations. The most frequently cultured pathogenic microorganisms were *Enterobacterales* (31%; of these 75% *Escherichia coli*), *Streptococcus pneumoniae* (17%) and Coagulase-negative Staphylococci (11%). The full list of cultured microorganisms is shown in Table S1. The median number of blood cultures

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Peer review under responsibility of the International Academy for Clinical Hematology

per patient was six (IQR: 3; 11; range: 0; 43). The incidence of BCDs peaked in the month of diagnosis (>500/1000 patients/month) and was elevated in the first 6 months after diagnosis (Figure 1A). After this period, the incidence of BCDs was constantly below 200/1000 patients/month. Fifty-one percent, 67% and 74% of patients had a BCD 3, 6 and 12 months after diagnosis, respectively (Figure 1B). Besides the time of diagnosis, we found incidence peaks in BCDs in relation to initiation of both the first and later lines of therapy (>600/1000/month) and events of progressive disease (>700/1000/month), as shown in Figure 2.

Univariate and multivariate analyses of risk factors for blood culture days are shown in Table S2. Among clinical baseline characteristics, low hemoglobin, high ionized calcium, high creatinine, low immunoglobulin (Ig) M, M-protein of IgA isotype, light-chain only disease and poor Eastern Cooperative Oncology Group (ECOG) performance status were independently associated with higher risk of BCDs. Among treatment-related factors, worse than very good partial response to the ongoing line of therapy, increasing number of prior lines of therapy and a recent event of progressive disease were independently associated with higher risk of BCDs. Among the assessed treatment regimens, high-dose melphalan (days 0–30), proteasome inhibitor-steroid doublets, chemotherapy-steroid doublets, daratumumab monotherapy and intensive combination regimens including five or more drugs were independently associated with such higher risk of BCDs. Two hundred and nine (69%) patients were exposed to immunoglobulin replacement therapy with a median time of 3.2 (IQR: 0.9; 22.3) months after diagnosis.

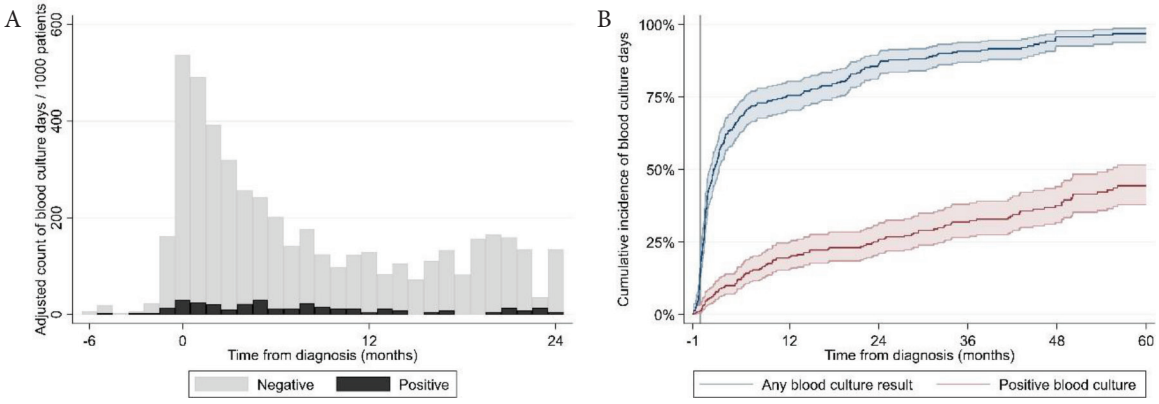

Figure 1 | (A) Adjusted incidence of blood culture positivity from the time of diagnosis. (B) Cumulative incidence of blood culture positivity from the month prior to diagnosis until death or follow up at 60 months.

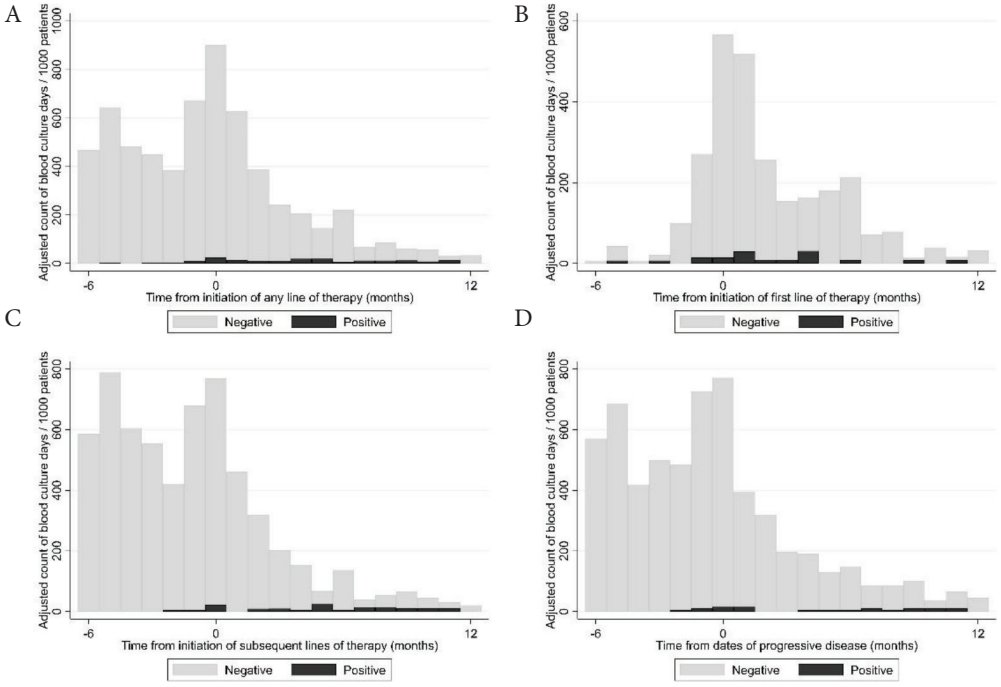

Figure 2 | (A) Adjusted incidence of blood culture days in relation to initiation of any line of therapy. (B) Adjusted incidence of blood culture days in relation to the date of initiation of the first line of therapy. (C) Adjusted incidence of blood culture days in relation to the date of initiation of any subsequent line of therapy. (D) Adjusted incidence of blood culture days in relation to the dates of progressive disease.

In conclusion, the burden of infections in our cohort of MM patients was high. Blood stream infections were mainly caused by Gram-negative bacteria. Patients were especially susceptible to infections at the time of diagnosis and in situations of insufficient disease control. Certain anti-myeloma regimens, such as proteasome inhibitor-steroid doublets, chemotherapy-steroid doublets, daratumumab monotherapy and combination regimens including five or more drugs may require increased attention to infectious complications.

CONFLICTS OF INTEREST

AGS: consulting for Janssen; TP: consulting for Janssen, Celgene, Takeda, Abbvie, Genmab; KFI: no conflicts of interest; SM: no conflicts of interest; FSR: no conflicts of interest.

AUTHORS' CONTRIBUTION

AGS designed the study, created the study database, conducted patient chart review, wrote the manuscript and designed the figures. KFI conducted patient chart review and contributed to writing the manuscript. SM carried out data analysis and statistics and contributed to writing the manuscript. FSR reviewed and categorized the blood culture results and contributed to writing the manuscript. TP supervised the study, contributed to writing the manuscript and designing the figures.

FUNDING

The authors received no financial support for the research, authorship or publication of this article.

ACKNOWLEDGMENTS

We thank the Department of Internal Medicine and the Hematological Clinical Research Unit at Vejle Hospital for providing the financial and logistical background for this study. Data management for this project was carried out by Open Patient Data Exploratory Network, University of Southern Denmark.

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SUPPLEMENTARY MATERIALS

Table S1 | Microorganisms cultured on positive blood culture days

Pathogenic microorganism	*n*	Percentage (%)
*Enterobacterales**	59	31
Streptococcus pneumoniae	33	17
Coagulase-negative Staphylococci	21	11
Staphylococcus aureus	14	7
Anaerobic bacteria	14	7
Enterococci	13	7
Viridans streptococci	7	4
Listeria monocytogenes	6	3
Pseudomonas aeruginosa	6	3
Candida	6	3
Beta-hemolytic streptococci	6	3
Other bacteria	5	3
Total (pathogenic microorganisms)	190	
Possible contaminations	59	
Total (positive)	249	

*44 (75%) *Escherichia coli*. A positive BCD was defined as a day a patient had at least one positive blood culture result.

Table S2 | Univariate and multivariate analysis of risk factors for blood culture days

Variable	Number of observations	Univariate analysis	*p*	Multivariate analysis	*p*
		HR (95% CI)		HR (95% CI)	
Demographics					
Age					
<50	14	Reference		Reference	
50–60	36	0.94 (0.77; 1.15)	0.567	0.67 (0.53; 0.85)	0.001
60–70	106	1.07 (0.90; 1.28)	0.434	0.67 (0.54; 0.83)	<0.001
>70	146	1.01 (0.84; 1.21)	0.939	0.61 (0.49; 0.75)	<0.001
Sex					
Male	175	Reference		Reference	
Female	127	0.85 (0.79; 0.93)	<0.001	0.93 (0.85; 1.03)	0.154
CRAB features					
Hemoglobin <6.2 mmol/L	102	0.85 (0.82; 0.88)	<0.001	0.91 (0.86; 0.95)	<0.001
Ionized calcium >1.345 mmol/L	79	1.65 (1.36; 2.01)	<0.001	1.38 (1.09; 1.76)	0.008
Creatinine >177 μmol/L	57	1.00 (1.00; 1.00)	<0.001	1.00 (1.00; 1.00)	0.005
Osteolytic lesion on either skeletal X-ray or WBLDCT not present	97	Reference		Reference	
Osteolytic lesion on either skeletal X-ray or WBLDCT present	205	0.85 (0.78; 0.93)	<0.001	0.75 (0.68; 0.83)	<0.001
Immunoglobulins					
IgA ≥ 0.7 g/L (excluding patients with IgA M-protein isotype)	133	Reference		Reference	
IgA < 0.7 g/L (excluding patients with IgA M-protein isotype)	169	1.05 (0.97; 1.14)	0.213	0.91 (0.80; 1.04)	0.180
IgG ≥ 6.1 g/L (excluding patients with IgG M-protein isotype)	190	Reference		Reference	
IgG < 6.1 g/L (excluding patients with IgG M-protein isotype)	112	1.33 (1.23; 1.45)	<0.001	0.61 (0.49; 0.75)	<0.001
IgM ≥ 0.4 g/L	50	Reference		Reference	
IgM < 0.4 g/L	252	1.90 (1.67; 2.17)	<0.001	1.77 (1.48; 2.11)	<0.001
M-protein isotype					
IgA	59	1.44 (1.30; 1.60)	<0.001	1.52 (1.18; 1.94)	0.001
IgG	168	Reference		Reference	
Light-chain only	54	1.02 (0.91; 1.14)	0.789	1.37 (1.11; 1.69)	0.004
Non-secretory	6	0.76 (0.55; 1.04)	0.088	1.06 (0.72; 1.56)	0.779
Other	2	2.71 (1.68; 4.39)	<0.001	4.15 (2.34; 7.34)	<0.001
Myeloma risk profile					
ISS I	88	Reference		Reference	
ISS II	92	1.11 (1.00; 1.23)	0.043	1.01 (0.89; 1.14)	0.848
ISS III	72	1.55 (1.39; 1.73)	<0.001	0.87 (0.75; 1.01)	0.076

(*Continued*)

Table S2 | Univariate and multivariate analysis of risk factors for blood culture days—*Continued*

Variable	Number of observations	Univariate analysis	*p*	Multivariate analysis	*p*
		HR (95% CI)		HR (95% CI)	
ISS not determined	47	1.16 (1.02; 1.32)	0.024	0.92 (0.79; 1.08)	0.300
High risk cytogenetics [t(4;14), t(14;16) or del(17p)] by FISH not present	254	Reference		Reference	
High risk cytogenetics [t(4;14), t(14;16) or del(17p)] by FISH present	48	1.18 (1.06; 1.32)	0.003	0.99 (0.87; 1.13)	0.875
ECOG Performance status					
0	111	Reference		Reference	
1	116	1.41 (1.28; 1.54)	<0.001	1.41 (1.27; 1.56)	<0.001
2	45	1.25 (1.09; 1.43)	0.001	1.12 (0.97; 1.30)	0.129
3	26	1.47 (1.27; 1.69)	<0.001	1.40 (1.17; 1.66)	<0.001
Best response to ongoing line of therapy	§				
sCR/CR/VGPR	1050	Reference		Reference	
PR/MR	1136	1.23 (1.13; 1.35)	<0.001	1.45 (1.29; 1.63)	<0.001
SD/PD	442	1.42 (1.26; 1.60)	<0.001	1.46 (1.24; 1.71)	<0.001
Number of prior lines of therapy	§				
1	873	Reference		Reference	
2	519	0.95 (0.85; 1.07)	0.415	1.15 (1.00; 1.33)	0.051
3	400	1.10 (0.97; 1.26)	0.131	1.27 (1.07; 1.50)	0.006
4	314	1.30 (1.13; 1.50)	<0.001	1.42 (1.16; 1.74)	0.001
5	191	0.94 (0.80; 1.12)	0.513	0.91 (0.72; 1.15)	0.429
6	212	1.60 (1.35; 1.90)	<0.001	1.83 (1.43; 2.33)	<0.001
7+	276	1.05 (0.89; 1.23)	0.566	1.45 (1.14; 1.84)	0.002
Ongoing line of therapy by regimen	§				
Melphalan 200 mg/m^2 days 0–30	434	1.19 (1.04; 1.37)	0.012	1.28 (1.07; 1.53)	0.006
IMID ± steroid	487	Reference		Reference	
PI ± steroid	280	1.72 (1.46; 2.02)	<0.001	1.80 (1.50; 2.15)	<0.001
CH ± steroid	201	2.01 (1.68; 2.40)	<0.001	1.79 (1.48; 2.18)	<0.001
IMID + PI ± steroid	224	1.29 (1.08; 1.53)	0.004	1.19 (0.99; 1.44)	0.067
PI + CH ± steroid	173	1.48 (1.23; 1.78)	<0.001	0.94 (0.76; 1.16)	0.547
IMID + CH ± steroid	301	1.46 (1.24; 1.70)	<0.001	1.14 (0.95; 1.36)	0.165
Daratumumab ± steroid	147	1.15 (0.93; 1.42)	0.192	1.29 (1.02; 1.63)	0.033
Daratumumab + PI ± steroid	37	0.60 (0.41; 0.89)	0.011	0.90 (0.59; 1.37)	0.624
Daratumumab + IMID ± steroid	171	1.26 (1.04; 1.53)	0.020	1.21 (0.97; 1.51)	0.094
Daratumumab + PI + IMID ± steroid	3	0.79 (0.25; 2.45)	0.677	0.85 (0.26; 2.82)	0.791
Five or more drugs	294	2.18 (1.87; 2.54)	<0.001	1.79 (1.50; 2.14)	<0.001
Other	33	2.31 (1.50; 3.55)	<0.001	1.02 (0.63; 1.63)	0.949
Time from diagnosis	§				
0–91 days after	77	Reference		Reference	
92–183 days after	472	0.53 (0.45; 0.63)	<0.001	0.52 (0.42; 0.65)	<0.001
183–365 days after	278	0.61 (0.51; 0.72)	<0.001	0.44 (0.34; 0.56)	<0.001
365–730 days after	270	0.40 (0.34; 0.47)	<0.001	0.26 (0.20; 0.32)	<0.001
More than 730 days after	404	0.26 (0.23; 0.30)	<0.001	0.12 (0.10; 0.16)	<0.001
Time from initiation of immunoglobulin replacement therapy	§				
Before	524	Reference		Reference	
0–91 days after	335	2.34 (2.02; 2.71)	<0.001	2.06 (1.75; 2.43)	<0.001
92–183 days after	179	1.57 (1.31; 1.88)	<0.001	1.26 (1.02; 1.56)	0.033
184–365 days after	249	2.39 (2.03; 2.82)	<0.001	2.05 (1.69; 2.48)	<0.001
Time from dates of progressive disease	§				
Before	1315	Reference		Reference	
0–91 days after	281	1.13 (0.98; 1.30)	0.087	1.17 (1.00; 1.37)	0.051
92–183 days after	33	0.95 (0.65; 1.40)	0.810	0.91 (0.59; 1.41)	0.682
184–365 days after	20	0.61 (0.37; 1.01)	0.054	0.71 (0.39; 1.29)	0.260

§, the same patient is taken into account multiple times. CH, chemotherapy (cyclophosphamide/low-dose melphalan/bendamustine/doxorubicine/liposomal doxorubicine/melflufen); CR, complete response; FISH, fluorescence in situ hybridisation; IMID, immunomodulatory agent (thalidomide/lenalidomide/pomalidomide); ISS, international staging system; sCR, stringent complete response; MR, minimal response; PD, progressive disease; PI, proteasome inhibitor (bortezomib/carfilzomib/ixazomib); PR, partial response; SD, stable disease; VGPR, very good partial response; WBLDCT, whole-body low-dose computer tomography.