Risk factors for the development of bacterial infections in patients with multiple myeloma treated with two different vincristine-adriamycin-dexamethasone schedules

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Background and Objectives. We evaluated bacterial infections (BIs) in patients with multiple myeloma (MM) treated with two different schedules of vincristine-adriamycin-dexamethasone (VAD).

Design and Methods. Ninety-seven patients were studied during 340 VAD cycles. VAD was given by either continuous intravenous infusion (CII) to hospitalized patients or rapid intravenous infusion (RII) to outpatients. The characteristics of patients and VAD schedules were retrospectively analyzed to detect correlations with the incidence of BI.

Results. By analyzing each VAD cycle, we found that profound hypogammaglobulinemia (p=0.06) and post-treatment neutropenia (p=0.08) were associated with a trend for a higher risk of infection, while renal function impairment was significantly correlated with BI risk at both univariate (p<0.02) and multivariate (p<0.002) analyses. Evaluating only the first 4 months of therapy, characterized by a significantly higher incidence of BI than the later period (p<0.0001), previously untreated disease was significantly correlated with BI risk (p<0.04), while male sex (p=0.06), CII schedule (p=0.07), and profound hypogammaglobulinemia (p=0.1) were associated with a tendency to a higher risk of infection; however, at multivariate analysis the latter two parameters independently predicted BI probability (p<0.015 and p<0.03, respectively) as did previously untreated disease (p<0.025). The high probability of CII-related infection was demonstrated to depend on the frequent development of nosocomial infections.

Interpretation and Conclusions. Patients with profound hypogammaglobulinemia who receive VAD as first line treatment are at a major risk of BI up to the completion of the fourth month of therapy. In this setting hospitalization should be avoided and, if patients require admission, antibacterial prophylaxis with intravenous immunoglobulins could be appropriate and effective.

Key words: bacterial infection, multiple myeloma, VAD.

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Patients with multiple myeloma (MM) are at a high risk of developing bacterial infections (BIs) due to a variety of disease-related factors, such as decreased antibody responses, defects in both complement and granulocyte function and renal function impairment.[1-4] Other treatment-related factors, such as post-treatment neutropenia and corticosteroids, are likely to play a role in the observed sharp increase in the incidence of BI during the initial period of chemotherapy (CT) administration.[2,3] Combination chemotherapy with vincristine-adriamycin-dexamethasone (VAD) is widely used as induction treatment for MM patients undergoing transplantation procedures.[5-12] Bacterial infections require treatment, cause hospitalization-related costs, mortality, and may reduce the potential of disease control by delaying the planned programme of cytoreduction. Rapid intravenous (i.v.) infusion (RII) modalities of administering VAD, feasible in outpatients,[9,11,12] have been increasingly used as an alternative to the traditional continuous i.v. infusion (CII) schedule mostly requiring hospitalization[5-8,10] because of their easy delivery and reduced hospital-related costs. Although RII schedules have been associated with a lower infection rate than have the CII schedules,[9] no systematic comparison of the probability of infection has been made between different administration modalities.

The aims of our study were to evaluate infectious complications in 97 MM patients during 340 VAD cycles delivered by either CII in the hospital setting or RII in the outpatient setting, and to identify clinical and/or schedule-related variables associated with the probability of developing BIs during the course of therapy.

Design and Methods

Patients and VAD schedules

Ninety-seven patients (53 males, 44 females) with either MM (n=95) or osseous/extra-medullary (n=1/1) plasmacytoma, receiving a total of 340 VAD courses between May 1990 and December 2001, were included in the study (Table 1). In 52 hospitalized patients 194 courses of chemotherapy consisted in the CII of vincristine (0.4 mg days 1-4) and adriamycin (9 mg/m^2 days 1-4) and i.v. infusion of dexamethasone (40 mg days 1-4, 9-12, 17-20). In 45 outpatients 146 courses consisted in the RII of vincristine (2 mg day 1) and adriamycin (50 mg/m^2 day 1) and intramuscular administration of dexamethasone (40 mg days 1-4, 15-18). In

Table 1. Clinical characteristics of patients undergoing VAD chemotherapy.

Characteristics	*CII Schedule (n=52)*	*RII Schedule (n=45)*	*p value*
Age (Years)			0.04
Median	56	60	
Range	29-67	30-73	
Sex			0.30
Male	31 (60%)	22 (49%)	
Female	21 (40%)	23 (51%)	
Diagnosis			
Osseous/extra-medullary Plasmacytoma	1 (2%)/1 (2%)	0/0	
MM			0.64
Stage IA/IIA	7 (13.5%)/7(13.5%)	7 (16%)/5 (11%)	
Stage IIIA/IIIB	32 (61.5%)/4 (7.5%)	27 (60%)/6 (13%)	
Type of monoclonal component			
IgG	24 (46%)	26 (58%)	
IgA	11 (21%)	7 (16%)	
IgG plus IgA	0	1 (2%)	
IgD	1 (2%)	0	
Urinary light chain	13 (25%)	11 (24%)	
None*	3 (6%)	0	
Previous chemotherapy			0.026
No	39 (75%)	42 (93%)	
Yes	13 (25%)	3 (7%)	
Performance status (ECOG)			1.0
0-2	42 (81%)	35 (78%)	
3-4	10 (19%)	10 (22%)	
Polyclonal Serum Ig Reductions			0.46
0-1	13 (25%)	9 (20%)	
2-3	35 (67%)	32 (71%)	
Not evaluated	4 (8%)	4 (9%)	
Serum Creatinine (mg/dL)			0.66
Median	0.96	0.96	
Range	0.45-8.87	0.5-4.9	
Serum β2-microglobulin (ng/mL)			0.23
Median	3.59	2.8	
Range	1.35-21.1	0.45-16.2	
Disease Response			0.068
Complete remission	5 (10%)	1 (2.2%)	
Partial remission	19 (36.5%)	26 (57.8%)	
Refractory disease	12 (23%)	10 (22.2%)	
Progressive disease	10 (19%)	2 (4.5%)	
Not evaluated	6 (11.5%)	6 (13.3%)	

**One non-secreting MM and two plasmacytomas.*

both schedules, cycles were repeated every four weeks. The CII regimen was given to 11 patients until 1997, to 15 patients in 1997, to 13 patients in 1998, to 8 patients in 1999, and to 5 patients in 2000. The RII regimen was administered to 7 patients in 1999, to 20 patients in 2000, and to 18 patients in 2001.

The patients' performance status (PS) and response to VAD treatment were evaluated according to the ECOG criteria.[16] Patients who responded to the treatment or who had stable disease after three cycles were treated for a minimum of 3 more cycles. In the event of disease progression, treatment was suspended.

Classification of infection

Infections were classified by severity as follows: (A) major: infections requiring hospitalization and i.v. antimicrobials; (B) moderate: infections manageable in the outpatient setting; (C) minor: infections not necessarily requiring antimicrobials. The definition of bacterial, viral or fungal infection was based on clinical, radiological and laboratory evaluations. Infections responding to empiric antibiotic therapy were considered to be of bacterial origin.

Monitoring and treatment of infection

Patients were monitored for infections throughout the VAD program and during an almost one-month follow-up. Primary antimicrobial prophylaxis was not routinely administered. However, specific prophylaxis was given in cases of previous major or moderate fungal or viral infection. At the discretion of the treating physician, secondary antibacterial prophylaxis [oral trimethoprim-sulfamethoxazole 800 + 160 mg q 12 h and/or i.v. immunoglobulins (Ig) 250 mg/Kg q 4 wks] was administered for a prior life-threatening BI. Antimicrobials were delivered intravenously or orally according to empiric, clinical or microbiological indications.

Statistical analysis

Data are described by their median and range when continuous, and absolute and relative frequency when categorical. To compare baseline characteristics of the patients according to treatment schedule, the Mann Whitney U test and Fisher's exact test were used for continuous and categorical variables, respectively. Event rates (events per person-years) were compared according to time since diagnosis (cut-off 4 months) by the Mantel and Haenszel test. Time since diagnosis, absolute neutrophil counts (ANC) at nadir, serum creatinine levels, the reduction of polyclonal serum Ig levels, the presence of antibacterial prophylaxis, pre-treatment ANC, the presence of a central venous catheter (CVC) and the schedule were assessed as potential risk factors for BI development during each cycle. Sex, previously treated disease, schedule, reduction of baseline of polyclonal serum Ig levels, baseline serum creatinine levels, age, stage, type of paraprotein, history of previous bacterial infections, PS and remission status after the VAD program were assessed as potential risk factors for the development of BIs during the

early period at higher risk of infection. The impact of various factors on the development of infections was evaluated using logistic regression modelling. When needed, Huber-White robust standard errors were computed to account for intra-patient correlation over the period of courses. Continuous variables were categorized according to predefined cut-offs or to quantiles of their distribution. Odds ratios (OR) and 95% confidence intervals (CI) were calculated with respect to the reference (lowest) category. Variables with p values < 0.1 were introduced into a multivariate logistic model after checking for collinearity. Stata 7.0 software (StataCorp, College Station, TX, USA) was used for the computations. A 2-sided p value < 0.05 was considered statistically significant.

Results

Clinical characteristics of the patients

The median time from diagnosis was 4 (range, 1-151) months. Clinical and tumor-related characteristics of the patients, according to the treatment schedule, are summarized in Table 1. Fourteen patients in stage I were treated for a rapidly progressive tumor mass and/or the evidence of > 50% plasma cells in the bone marrow. Most patients received VAD as soon as the diagnosis was confirmed. Sixteen patients had refractory or progressive disease after a median of 9 (range, 1-25) previous CT cycles. Eight previously untreated patients had a history of BIs at a median of 2 (range, 1-6) months before diagnosis, and in other 2 patients BI developed at the moment of MM diagnosis. Median polyclonal serum IgG, IgA and IgM levels were 450 (range, 44-1,420) mg/dL, 31 (range, 0-175) mg/dL and 22 (range, 0-175) mg/dL, respectively (normal: 680-1,445, 70-373 and 50-248 mg/dL, respectively). In 59 cases (17.4%), serum creatinine levels > 1.2 mg/dL (upper limit of normal) were recorded. As shown in Table 1, the median age of patients receiving CII was significantly lower than that of patients receiving RII (56 vs 60 yrs, $p < 0.04$), and the proportion of previously treated patients was significantly higher in the CII group than in the RII group (25% vs 7%, $p < 0.026$); no other baseline characteristic differed significantly between the two groups. Patients received a median of 3 courses (range, 1-7) of VAD. Sixty-seven patients received at least three courses, 23 received two courses, and 7 received only one course. Weekly ANCs were recorded in 177 courses of therapy. The median neutrophil nadir was 2×10^9/L; the nadir fell below 1.0×10^9/L and 0.5×10^9/L in 32 (18.1%) and 15 courses (8%), respectively. The overall remission rate was 60%; non-responding patients showed refractory or progressive disease after a median of 4 (range, 2-6) CT courses. No difference was observed between the groups treated with the CII schedule or RII schedule as regards the proportion of patients achieving remission (52% vs 69%, $p = 0.068$).

Table 2. Episodes of BI occurring during 340 VAD courses.

Entity and site of infection	*Courses (%)*			
	CII Schedule (n=194)		*RII Schedule (n=146)*	
	Nosocomial	*Community acquired*	*Nosocomial*	*Community acquired*
Major				
Septicemia, meningoencephalitis, UTI	1 (0.5)	0	0	0
Septicemia, Pneumonia, UTI	1 (0.5)	0	0	0
Septicemia, CVC-related Infection, pneumonia	1 (0.5)	0	0	0
Pneumonia, UTI	1 (0.5)	0	0	0
Pneumonia	2 (1)	9 (4.6)	0	6 (4.1)
CVC-related infection, UTI	1 (0.5)	0	0	0
Pneumonia, CVC-related infection	1 (0.5)	0	0	0
Pyrexia of unknown origin	0	1 (0.5)	0	1 (0.7)
Total	8 (4)	10 (5.1)	0	7 (4.8)
Moderate				
Pyrexia of unknown origin	1 (0.5)	4 (2)	0	8 (5.5)
UTI	3 (1.5)	0	0	0
Acute bronchitis	0	0	0	1 (0.7)
Upper respiratory tract infection	0	1 (0.5)	0	0
Skin cellulitis	0	0	0	1 (0.7)
Total	4 (2)	5 (2.5)	0	10 (6.9)

UTI: urinary tract infection.

Prevalence, severity and type of infections

Patients were evaluated for infections for a median of 5 (range, 2-36) months after CT initiation. The total observation time amounted to 100.7 person-years. Eleven patients (11.3%) had non life-threatening viral or fungal infections [moderate: localized herpes zoster (n=4); minor: localized herpes simplex (n=3), and oral candidiasis (n=4)]. Forty-four episodes of BI were recorded in 32 patients (33%), for an overall incidence of 0.42 per person-years. The incidence of BI was significantly higher during cycles delivered within the first 4 months of treatment than during later cycles (1.3 vs 0.2 per person-years, $p < 0.0001$). Twenty-seven and 17 episodes of BI were recorded in 18 (35%) and 14 (31%) patients in the CII and RII schedule, respectively. The distribution of BI according to the administration modality is summarized in Table 2. Episodes of pneumonia accounted for 72% of major infections. All the infections in outpatients receiving VAD by RII were community-acquired. In contrast, 12 out of 27 episodes of BI (44.4%) observed in patients treated with the CII schedule were nosocomial, as judged by the time of onset of signs/symptoms and the microbiological characteristics of the infection. In 6 out of 12 cases of nosocomial infection (50%), ≥ 2 distinct sites of infection were recorded. BI recurrence was registered in 7 (13.5%) and 2 (4.4%) patients receiving CII and RII, respectively.

Microbiology and outcome of BIs

Microbiologically documented bacterial infection occurred in 13 cases. *Pseudomonas aeruginosa*, *Listeria monocytogenes* and *Staphylococcus epidermidis* septicemias were observed in association with pneumonia, meningoencephalitis with brain abscesses, and CVC-related infection plus pneumonia, respectively. *Staphylococcus epidermidis* was further isolated from 2 CVC-related infections (one with and one without pneumonia). Positive sputum and urine cultures were also recorded in a case of pneumonia (*Klebsiella pneumoniae* and *Staphylococcus aureus*) and in 7 urinary tract infections (UTI) (*Escherichia coli* n=3, *Pseudomonas aeruginosa* n=2, *Staphylococcus epidermidis* n=2). In the remaining cases, the definition of bacterial infection was based on the clinical picture and the response to empiric antibiotics.

There were no deaths due to infection. The median time of response to antibacterials was 8 days (range, 5-50). Pyrexia of unknown origin responded to a first-line single antibiotic, whereas in 6 cases (20%) of clinically or microbiologically documented BI, a second- or third-line antibiotic was required. In 5 out of 27 cases requiring i.v. antibacterials (18.5%), carbapenems were administred because of resistance of the infection to the most commonly used antibiotics. Major infections caused a median treatment delay of 19 (range, 4 to 75) days in 18 cases, and prevented further therapy after the first or second course of treatment in 5 cases.

Prognostic indicators for BIs

Tables 3 and 4 show the relative risk (OR) of BI development together with the 95% CI for a series of potential risk factors, and the *p*-values of the univariate and multivariate logistic models. Evaluating each VAD cycle, at univariate analysis ≥ 2 polyclonal serum Ig reductions (p=0.06) and post-treatment neutropenia (p=0.08) were associated with a tendency to higher risk of infection, while serum creatinine levels > 1.2 mg/dL were significantly correlated with a higher risk of BI (p<0.02). The latter was the only parameter independently predicting an increased probability of infection in the multivariate analysis (p<0.002)(Table 3). By evaluating the first 4 months of treatment, the period characterized by a higher risk of infection than later periods, the univariate analysis revealed that previously untreated disease significantly correlated with BI risk (p<0.04), while male sex (p=0.06), CII schedule (p=0.07), and ≥ 2 polyclonal serum Ig reductions (p=0.1) were associated with a tendency to an increased risk of infection. However, multivariate analysis showed that the latter two parameters independently predicted the probability of BI (p<0.015 and p<0.03, respectively) as did previously untreated disease (p<0.025) (Table 4). Male gender strictly correlated with smoking habits (p<0.002). By dividing the probability of early infection into tertiles of its distribution, the multivariate model allowed the identification of three groups of risk: (A) low risk (<33%): patients with ≤ 2 polyclonal serum Ig reductions mainly enrolled in the RII schedule and previously treated; (B) intermediate risk (33-65%): previously untreated patients mainly males, enrolled in the CII schedule and with 2 polyclonal serum Ig reductions; (c) high risk (≥66%): previously untreated patients with the

Table 3. Analysis of the risk of developing BIs during 340 VAD courses.

		Univariate		*Multivariate (p Value < 0.009)*	
Variable	*No. of events (courses at risk)*	*Odds ratio (95% CI)*	*p value*	*Odds Ratio (95% CI)*	*p value*
Months since diagnosis	17 (157)		0.26		–
> 4	27 (183)	1.51 (0.74-3.10)		–	
≤ 4					
ANCs at Nadir (×10⁹/L)			0.08		0.14
≥ 1	25 (145)				
< 1	10 (32)	2.18 (0.91-5.22)		2.04 (0.78-5.28)	
Serum creatinine (mg/dL)			0.02		0.002
≤ 1.2	31 (281)				
> 1.2	13 (59)	2.28 (1.09-4.75)		3.60 (1.61-8.07)	
Polyclonal serum Ig Reductions			0.06		0.85
≤ 1	4 (68)				
2	23 (173)	2.45 (0.80-7.53)		1.34 (0.40-4.50)	
3	15 (73)	4.14 (1.29-13.28)		1.37 (0.42-4.51)	
Antibacterial prophylaxis			0.24		–
Yes	3 (44)				
No	41 (296)	2.01 (0.62-6.49)		–	
Pre-treatment ANC (×10⁹/L)			0.88		–
≤ 3.5	21 (156)				
>3.5	21 (149)	1.05 (0.52-2.13)		–	
CVC			0.16		–
Absent	38 (312)				
Present	6 (28)	2.49 (0.70-8.87)		–	
Schedule			0.59		–
RII	17 (146)				
CII	27 (194)	1.23 (0.58-2.58)			–

Table 4. Analysis of pretreatment risk factors for BI development during the first 4 months of VAD treatment in 97 MM patients.

		Univariate		*Multivariate (p value < 0.002)*	
Variable	*No. of events (Patients at risk)*	*Odds Ratio (95% CI)*	*p Value*	*Odds Ratio (95% CI)*	*p Value*
Sex			0.06		0.18
Female	9 (44)				
Male	21 (53)	2.34 (0.96-5.72)		2.02 (0.72-5.72)	
Previously treated disease			0.04		0.025
Yes	1 (16)				
No	29 (81)	4.20 (0.89-19.77)		6.80 (1.26-36.51)	
Schedule			0.07		0.015
RII	10 (45)				
CII	20 (52)	2.24 (0.93-5.41)		3.66 (1.28-10.55)	
Polyclonal Serum Ig reductions			0.10		0.03
≤ 1	4 (22)				
2	16 (52)	2.38 (0.69-8.17)		3.51 (0.93-13.30)	
3	8 (15)	5.14 (1.16-22.88)		8.46 (1.66-43.25)	
Serum creatinine (mg/dL)			0.45		–
≤ 1.2	23 (80)				
> 1.2	7 (17)	1.51 (0.52-4.43)		–	
Age (years)			0.66		–
≤ 56	12 (51)				
> 56	18 (46)	1.21 (0.52-2.82)		–	
Stage			0.71		–
I	5 (14)				
II	3 (12)	0.50 (0.09-2.64)		–	
III	22 (69)	0.75 (0.24-2.36)		–	
Type of monoclonal component			0.36		
IgG	15 (50)				
IgA	4 (18)	0.92 (0.28-3.05)		–	
Urinary light chain	11 (24)	1.92 (0.73-5.06)		–	
Previous BIs			0.83		–
No	27 (87)				
Yes	3 (10)	1.18 (0.26-5.28)			
Performance status (ECOG)			0.22		–
0-2	22 (77)				
3-4	8 (20)	1.89 (1.69-5.17)		–	
Disease remission			0.39		–
Yes	15 (51)			–	
No	12 (34)	1.66 (0.52-5.29)			

reduction of 3 uninvolved serum Igs enrolled in the CII schedule.

Discussion

Although efforts to improve the prevention and/or the early identification of BIs could both greatly reduce the medical/economic burden of such complications and allow a more successful disease outcome, systematic investigation of VAD-associated infections is still lacking. In correlation with the evidence that cellular immunity is rarely compromised in MM,[1] we detected a very low frequency of viral and/or fungal infections. Their level of severity was insignificant, and specific secondary prophylaxis probably prevented recurrence. However, occasionally described life-threatening viral or mycobacterial processes[5,9] and our reported *Listeria monocytogenes*-related meningoencephalitis, suggest that inhibition of T-cell function related to high doses of dexamethasone might sporadically play a crucial role in the development of a major infection. As previ-

ously observed,[5,8-10] more than half of the infections in our series were of bacterial etiology. It could not be demonstrated that secondary antibacterial prophylaxis against BIs had a statistically significant protective role. However, the control of BI probability in 11 out of 13 patients receiving i.v. immunoglobulins and/or antibiotics for previous major infection encourages the identification of clinical settings in which prophylactic strategies could be successfully used. Previously untreated MM patients receiving a variety of chemotherapy schemes had a high risk of BI during the first 2 months of treatment, and a lower rate of infection during the period of response. This seems to reflect a correlation between disease burden and probability of infection.[2-4,13] A newly diagnosed disease was confirmed to be an independent risk factor for BI during this early period of therapy. The disease response to the overall treatment course did not influence development of BI. However, since patients with progressive MM were withdrawn early from therapy, the drastic decline in the incidence of BI after the initial observation period probably indicates that almost four cycles are required to obtain a parallel reduction of tumor load and infection risk in patients responsive to VAD schemes. The impaired immunoglobulin synthesis frequently observed in MM is considered the most important variable predisposing patients to BIs.[1] Savage *et al.*[4] identified non-myeloma serum immunoglobulin reduction as an independent prognostic factor for infections caused by Gram-positive microorganisms, and in another two studies the correlation between impaired humoral immune response and BIs was confirmed.[2,3] Similarly, the reduction of ≥ 2 polyclonal immunoglobulin significantly predicted early development of BI. This variable was not, however, found to predict infections independently during single cycles, indicating a key role of other factors in determining the infection risk throughout the overall treatment course.

Renal function impairment is well recognized to be correlated with BI occurrence in uremic patients, because of a variety of acquired immune deficiencies.[17,18] Savage *et al.*[4] showed a close relationship between increased serum urea levels and Gram-negative BIs in MM. Similarly to others[2] we could not predict an early infection from baseline serum creatinine level. However, when assessed in each course of therapy, the latter was identified as the only risk factor independently associated with BIs, confirming the previous suggestion that renal function impairment does not necessarily parallel the behavior of tumor burden in predisposing to BIs.[4] A great interpatient variability in frequency and degree of VAD-induced myelosuppression is likely to reflect different pre-treatment characteristics of the patients and/or susceptibility to chemotherapeutic agents.[7] As observed in MM patients receiving either VAD or non-VAD schemes[2,4,7] no relationship was found between neutropenia and septicemia. Nevertheless, a correlation between neutrophil suppression and BIs was confirmed.[4] Therefore, patients' blood cell counts should be strictly monitored after treatment and, if neutropenia occurs, empiric antibiotics should be promptly administered at the first signs and/or symptoms of infection. The previously suggested higher infection-related morbidity in patients receiving VAD by CII than in those receiving VAD by RII[9] was confirmed. Indeed, in our study, the group receiving the CII schedule experienced a relevant number of recurrent, multiple site and/or major infections, and a significantly higher rate of early infections than did the RII schedule group. Although the high risk of BI associated with the CII schedule was suggested to depend on the frequent requirement for CVC in this group,[9] the presence of a central catheter did not correlate with probability of BI in our study. Moreover, no collinearity was statistically demonstrated between the schedule and any other assessed potential risk factor for BIs. Furthermore, baseline prognostic factors possibly accounting for a selection bias of patients did not differ significantly between the two treatment groups. Egerer *et al.* reported a very low infection prevalence during VAD delivery by CII in the outpatient setting.[7] The lower infection prevalence (5.6% of cycles) detected in Egerer's outpatients as compared to among our hospitalized patients (13.9% of cycles) would suggest that the striking discrepancy in the risk of early BI displayed by our populations might depend on different exposures to nosocomial pathogens. Indeed, a relevant frequency of nosocomial BIs was observed in the group of hospitalized patients receiving VAD by CII. Moreover, as previously suggested[8] the higher dexamethasone doses used in the CII schedule than in the RII schedule might account, at least in part, for the higher risk of early BI associated with the former scheme. These observations and the detected similar effectiveness of the two schedules strongly suggest that, whenever feasible, RII administration to outpatients should be preferred. However, since the schedule was not detected to predict BI development significantly in each treatment cycle, patient hospitalization and/or the doses of dexamethasone administered are likely to represent additional risk factors for the development of infection only in the initial period of delivering the chemotherapy.

In agreement with others[2,3] we found that age, clinical stage at the start of chemotherapy and initial ANC did not influence the probability of infection following the initiation of chemotherapy. In contrast, male sex was confirmed as an important co-factor for the early risk of BI, correlating with smoking habits.[2] Since pneumonia accounted for a great proportion of infections in our study, this finding seems relevant, and suggests that accurate history taking could play a role in the screening of patients at higher risk of infection.

No generally accepted guidelines exist on the use of antibacterial prophylaxis in patients treated with VAD schemes. The increasing emergence of resistance to broad-spectrum antibiotics among Gram-negative bacteria[1,4] and the possible enhancement of systemic mycoses as a result of the combination of high treatment-related doses of corticosteroids and oral antibacterial agents[14] would suggest caution against the routine use of the latter during VAD therapy. Our study demonstrates that patients with profound hypogammaglobulinemia receiving VAD as first-line treatment have a high risk of BI up to the completion of the fourth month of therapy: in this setting hospitalization should be avoided, since nosocomial exposure to pathogens increases the risk of infections; according to previous suggestions,[15] however, antibacterial prophylaxis with i.v. immunoglobulins could be appropriate and effective in those patients requiring admission.

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Pre-publication Report & Outcomes of Peer Review

Contributions

CC: conception and writing of the paper, collection and analysis of data; AMN: conception and critical revision of the paper; CK: analysis of data; SM, VR, PF, MV: collection of data; LB, EM: critical revision of the paper. All authors were involved in the interpretation of data, drafting and final approval of the paper. Primary responsibility for the paper: EM; primary responsibility for Tables 1-2: CC; primary responsibility for Tables 3-4: CC, CK.

Disclosures

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Manuscript processing

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In the following paragraphs, Professor Cazzola summarizes the peer-review process and its outcomes.

What is already known on this topic

Patients with multiple myeloma are at risk of developing bacterial infections due to several factors but, excluding patients with advanced disease, specific risk groups have not yet been defined.

What this study adds

The findings of this study indicate that patients with multiple myeloma and profound hypogammaglobulinemia who received VAD chemotherapy as first-line treatment are at a particularly high risk of developing bacterial infections.