MAJOR ARTICLE

Baseline Platelet Count and Creatinine Clearance Rate Predict the Outcome of Neutropenia-Related Invasive Aspergillosis

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Background. Invasive aspergillosis (IA) is a life-threatening infection for immunocompromised patients. Improvement in IA outcome has been hampered by lack of early prognostic factors, namely, those available before starting chemotherapy (baseline) or early in the course of IA (nonbaseline). We hypothesized that prognostic factors can be identified before chemotherapy, ≤7 days from the first positive serum *Aspergillus* galactomannan index (s-GMI).

Methods. We analyzed 98 patients with multiple myeloma who developed neutropenia-related IA and had a positive s-GMI. Three response criteria were used: kinetics of s-GMI, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) definitions, and 6-week survival. Baseline and nonbaseline variables were analyzed separately.

Results. Independent response predictors at baseline were a platelet count ≥65,000 platelets/mm^3 (odds ratio [OR], 1.009; 95% confidence interval [CI], 1.001–1.017; $P = .03$) by s-GMI kinetics, and a platelet count ≥65,000 platelets/mm^3 (OR, 1.009; 95% CI, 1.002–1.017; $P = .01$) and a creatinine clearance rate ≥53 mL/min (OR, 1.024; 95% CI, 1.006–1.042; $P = .009$) by EORTC/MSG criteria, with response rates of 83% and 28% when both variables were above or below these cutoffs, respectively ($P < .001$). Only baseline creatinine clearance rate ≥53 mL/min predicted 6-week survival ($P = .003$). Normalization of the s-GMI ≤7 days after the first positive s-GMI and neutrophil recovery were the nonbaseline factors associated with positive outcomes.

Conclusions. Two simple, inexpensive to measure, widely available, and routinely collected prechemotherapy values, platelet count and creatinine clearance rate, predict IA outcome and stratify patients into low-, intermediate-, and high-risk categories, while early evaluation of s-GMI allows timely treatment modification. These findings may improve patient outcomes by optimizing management strategies for this serious infection and may prove valuable in designing clinical trials of interventions to improve IA outcomes.

Invasive aspergillosis (IA) is the leading invasive mycosis in patients with hematological malignancies and remains associated with unfavorable outcomes [1]. Various prognostic factors have been identified, including extent of the infection, persistent neutropenia, and use of systemic corticosteroids [2–17]. However, most of these variables are available only after the diagnosis of IA and cannot be successfully applied toward early intervention or treatment modification [18].

Identification of prognostic factors that are available before starting chemotherapy or early during the disease course would improve our ability to individualize antifungal strategies [18] and to design clinical trials of IA, a challenging task when applying conventional criteria,

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particularly when *Aspergillus*-specific laboratory markers are not included in the primary study end point [18]. Indeed, a recently completed large randomized clinical trial enrolled 454 patients at 165 multinational sites over approximately 3 years but failed to meet the primary end point for superiority of combination therapy over monotherapy [19]. This likely occurred because the study's primary end point, 6-week all-cause mortality, was not *Aspergillus*-specific and mortality can be caused by several non-IA related factors, such as graft-versus-host disease and others [18].

Galactomannan is a cell wall component of *Aspergillus* species that is released by growing hyphae during active aspergillosis. The serum *Aspergillus* galactomannan index (s-GMI) is an excellent surrogate marker for the diagnosis of IA in patients with hematological cancers [18], and s-GMI positivity precedes the overt manifestations of IA [20]. Furthermore, we and others have shown that s-GMI serves as a valid surrogate end point for clinical outcome, with a strong correlation between normalization of s-GMI and treatment success and survival [21–25]. We therefore hypothesized that simple and objective early prognostic factors for IA can be identified before commencing the chemotherapy course that precedes IA development and can be detected early during the disease course by using s-GMI, an *Aspergillus*-specific marker.

PATIENTS AND METHODS

We conducted a retrospective study of all episodes of IA in patients with multiple myeloma cared for at the Myeloma Institute for Research and Therapy, University of Arkansas for Medical Sciences, between January 2003 and December 2009. The study was approved by the Institutional Review Board. Evaluation included a review of medical records and radiologic tests, including computerized axial tomography of sinuses and lungs.

One hundred and sixteen episodes of IA were diagnosed during the study period, as previously reported [26]. For this analysis, we focused on patients who developed IA during neutropenia. Ninety-eight episodes were evaluable after exclusion of 12 that developed in nonneutropenic settings, 4 that were recurrent, and 2 during which s-GMI was negative. Patients were managed according to predefined standards of care, as described elsewhere [26], including use of fluconazole prophylaxis and serial measurement of s-GMI (≥3 times/week) during periods at risk (ie, following myelosuppressive chemotherapy or receipt of a melphalan-based conditioning regimen for autologous hematopoietic stem cell transplantation [MEL-ASCT]). Mould-active agents (voriconazole or liposomal amphotericin B) were used at the first positive s-GMI and confirmation of IA on the basis of host, clinical, and radiologic criteria. Cases were classified as proven or probable, according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) definitions [27], or as probable, without prespecified radiologic findings [26].

Three response criteria were used to examine prognostic factors: response according to s-GMI kinetics, with survival, as previously defined [21]; the EORTC/MSG response definitions [28]; and 6-week survival regardless of cause of death. Response by s-GMI kinetics was defined as survival and repeatedly negative s-GMI for ≥2 weeks after the first negative s-GMI in the absence of new extrapulmonary lesions of IA, while failure was defined as persistently positive s-GMI. Death within the 14-day period of negative s-GMI was also considered failure, unless aspergillosis could not be documented at autopsy.

We examined potential predictors immediately prior to starting the chemotherapy regimen after which IA was diagnosed (baseline) and potential predictors after IA was diagnosed (nonbaseline). Baseline variables included sex, age, body surface area (BSA), body mass index (BMI; defined as the weight in kilograms divided by the square of the height in meters), myeloma status, treatment (chemotherapy or MEL-ASCT), number of prior ASCTs, cumulative corticosteroid doses (prednisone equivalent) and receipt of other immunosuppressants (60 days and 30 days before diagnosis of IA, respectively), white blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count, platelet count, absolute CD4 cell count, creatinine clearance rate, serum bilirubin level, cytomegalovirus (CMV) serologic status, and iron overload, defined as increased marrow iron stores [29].

Nonbaseline variables included ANC at diagnosis of IA; CMV reactivation, defined as ≥600 copies/mL by plasma quantitative polymerase chain reaction; site of IA (lung, sinuses, other); value of first positive s-GMI; normalization of s-GMI ≤7 days from the first positive s-GMI; duration of neutropenia (ANC, <500 neutrophils/mm^3); neutrophil recovery (ANC, ≥500 neutrophils/mm^3 on 3 consecutive days); and cumulative corticosteroid doses given ≤6 weeks after diagnosis.

Separate statistical analyses for baseline and nonbaseline variables were conducted. Univariate analysis was performed using the Fisher or χ^2 test (as appropriate) for categorical variables and the Wilcoxon test for continuous variables. Variables with a P value <.1 were entered in a multivariate logistic regression analysis. Receiver operating characteristic (ROC) curves were used to determine the best cutoff for the continuous variables that were significant by multivariate analysis. Kaplan-Meyer curves were constructed and compared using the log-rank test. All tests were 2-tailed, and P values <.05 were considered statistically significant.

RESULTS

The characteristics of 98 evaluable cases of IA are shown in Table 1. Antineoplastic treatments were myeloablative MEL-ASCT and myelosuppressive chemotherapy in 50 and 48 patients, respectively. Aspergillosis was classified as proven in 5 cases and probable in 93; 61 case were probable by EORTC/MSG definitions [27], and 32 were probable without prespecified radiologic findings [26].

Factors Associated With Response, as Defined by s-GMI Kinetics

Response defined on the basis of s-GMI kinetics was observed in 72 of 97 patients (74.2%) but could not be assessed in 1 patient (lost to follow-up). Baseline predictors of response by univariate analysis were higher BSA, BMI, and platelet count; lower serum bilirubin level; adequate or low marrow iron stores; and controlled myeloma (Table 2). Higher platelet count was the only significant prognostic variable by multivariate analysis (odds ratio [OR], 1.009; 95% confidence interval [CI], 1.001–1.017; $P = .03$). The best cutoff for platelet count was 65,000 platelets/mm^3, with a sensitivity of 62% and a specificity of 72%. A Kaplan-Meier curve (Figure 1) shows a 91% probability of response at 6 weeks for patients with a baseline platelet count ≥65,000 platelets/mm^3, compared with only 68% for patients with a lower count ($P = .01$).

Normalization of s-GMI within 7 days and neutrophil recovery were the only 2 nonbaseline variables that predicted good outcome by univariate analysis (Table 2) and by multivariate analyses (normalization of s-GMI: OR, 5.356 [95% CI, 1.316–21.901; $P = .02$]; neutrophil recovery: OR, 32.734 [95% CI, 3.630–295.164; $P = .002$]) (Table 3).

Factors Associated With Response, as Defined by EORTC/MSG Criteria

Response was observed in 59 of 93 cases (63.4%). Assessment was not possible in 5 patients (lost to follow-up before the 6-week time point). Baseline variables associated with response by univariate analysis were higher BMI, platelet count, and creatinine clearance rate; lower serum bilirubin level; and controlled myeloma (Table 2). Higher baseline platelet count (OR, 1.009; 95% CI, 1.002–1.017; $P = .01$) and higher baseline creatinine clearance rate (OR, 1.024; 95% CI, 1.006–1.042; $P = .009$) were independent predictors by multivariate analysis (Table 3). The cutoffs for platelet count and creatinine clearance rate were 65,000 platelets/mm^3 (sensitivity 66%, specificity 71%) and 53 mL/min (sensitivity 76%, specificity 53%), respectively. The probability of response was 83% when both variables were above cutoffs, 69% when platelet levels were ≥65,000 platelets/mm^3 but the creatinine clearance rate was <53 mL/min, and 61% when the creatinine clearance rate was ≥53 mL/min but platelet levels were <65,000 platelets/mm^3. When both variables were below cutoffs, the probability of response was only 28% ($P < .001$) (Figure 2).

Higher ANC at diagnosis of IA, neutrophil recovery, and normalization of s-GMI within 7 days were the only nonbaseline variables significantly associated with response by univariate analysis (Table 2), while only normalization of s-GMI within 7 days (OR, 2.900; 95% CI, 1.009–8.333; $P = .048$) remained significant by multivariate analysis (Table 3).

Factors Associated With 6-Week Survival

Sixty-seven patients (68.4%) were alive at 6 weeks. Baseline predictors of survival by univariate analysis included higher BMI, WBC, platelet counts, and creatinine clearance rate; lower serum bilirubin level; lower number of prior ASCTs; nonreceipt of immunosuppressants other than corticosteroids; and controlled myeloma (Table 2). Only higher creatinine clearance rate (OR, 1.031; 95% CI, 1.010–1.052; $P = .003$) remained significant on multivariate analysis with a cutoff of 53 mL/min (sensitivity 78%, specificity 58%) (Table 3).

Higher ANC at diagnosis of IA, s-GMI normalization within 7 days, and neutrophil recovery were associated with 6-week survival by univariate analysis (Table 2) but not by multivariate analysis (Table 3). Figure 3 shows the Kaplan-Meier survival curves according to normalization of s-GMI ≤7 days after the first positive s-GMI and neutrophil recovery.

DISCUSSION

To our knowledge, our study is the first to examine the significance of baseline prechemotherapy prognostic factors for neutropenia-related aspergillosis and to do so using platelet count and renal function, 2 simple, inexpensive to measure, widely available, and routinely collected data. Two nonbaseline variables, normalization of s-GMI ≤7 days after the first positive s-GMI and neutrophil recovery, were also identified as independent prognostic factors for IA.

That platelet count independently predicted the outcome of IA should not be surprising. Indeed, platelet counts are good indicators of bone marrow reserve and hence the likelihood of timely neutrophil recovery; platelet counts independently predict the ability to mobilize autologous peripheral blood stem cells [30] and hematological recovery following high-dose chemotherapy and ASCT [31] and are used to plan dosage schedules for antineoplastic therapies [32, 33]. The protective effect of higher platelet counts may also result from the ability of platelets to interfere with the virulence of *Aspergillus* species [34] and to act synergistically with antifungal agents against these pathogens [35].

Several chemotherapeutic agents, including intravenous MEL used in MEL-ASCT, are renally excreted, and MEL-treated

Table 1. Characteristics of 98 Patients With Multiple Myeloma and Neutropenia-Related Invasive Aspergillosis Defined at Baseline and After the Diagnosis of Aspergillosis

Characteristic	Value
At baseline[a]	
Sex, male:female	53:45
Age, years	61 (38–81)
Body surface area, m^2	1.81 (1.30–2.55)
Bone mass index	25.60 (16.20–43.37)
Active myeloma	81 (83)
Antineoplastic treatment	
ASCT	50 (51)
Chemotherapy	48 (49)
Prior ASCT	1 (0–4)
Months from diagnosis of underlying disease to IA	24 (0–186)
Days from chemotherapy to diagnosis of IA	11 (0–32)
Receipt of corticosteroids	94 (96)
Cumulative prednisone equivalent dose in mg	1150 (0–7590)
Other immunosuppressive therapies[b]	17 (17)
WBC count, cells/mm^3	3365 (10–26,610)
ANC, neutrophils/mm^3	2178 (0–22,314)
ALC, lymphocytes/mm^3	375 (0–4554)
Platelet count, $\times 10^3$ platelets/mm^3	73 (7–345)
Serum level of uninvolved Ig, mg/dL	222 (10–985)
Absolute CD4 cell, count/mm^3	189 (19–1192)
Creatinine clearance rate, mL/min	60 (2–171)
Serum bilirubin level, mg/dL	0.6 (0.2–1.6)
Cytomegalovirus seropositive	65 (66)
At diagnosis of aspergillosis	
ANC, neutrophils/mm^3	14 (0–10,900)
Days with ANC <500 neutrophils/mm^3	10 (1–54)
Days with ANC <100 neutrophils/mm^3	7 (1–27)
s-GMI tests, No.	21 (4–64)
Cytomegalovirus reactivation[c]	14/65 (21)
Concomitant respiratory viral infection[d]	12 (12)
Classification of aspergillosis	
Proven	5 (5)
Probable	61 (652)
Probable without prespecified radiologic findings[e]	32 (33)
Antifungal treatment	
None	6 (6)
Voriconazole	55 (56)
Liposomal amphotericin B	25 (26)
Other[f]	12 (12)

Data are No. or proportion (%) of patients or median (range).

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; ASCT, autologous stem cell transplantation; IA, invasive aspergillosis; Ig, immunoglobulin; RSV, respiratory syncytial virus; s-GMI, serum *Aspergillus* galactomannan index; WBC, white blood cell.

[a] Baseline refers to variables measured immediately prior to starting the antineoplastic regimen after which IA was diagnosed.

[b] Other immunosuppressive therapies included sirolimus (in 12 patients) and alemtuzumab, rituximab, fludarabine, etanercept, and sirolimus + rituximab (in 1 each).

[c] Defined as >600 copies per mL of plasma by quantitative polymerase chain reaction.

[d] Concomitant viral infections included RSV (in 5 patients), influenza B virus (in 2), and RSV + influenza B virus, parainfluenza virus type 3, influenza A virus, metapneumovirus, and RSV + parainfluenza type 3 (in 1 each).

[e] As defined in [26].

[f] Other treatments included voriconazole + liposomal amphotericin B (in 4 patients), voriconazole + micafungin (in 2), micafungin (in 3), anidulafungin (in 2), and voriconazole + anidulafungin or voriconazole + placebo (in 1).

Table 2. Univariate Analysis of Predictive Outcome Variables in 98 Patients With Multiple Myeloma Who Developed Neutropenia-Related Aspergillosis

Variable	Outcome[a]		*P*
	Favorable	Unfavorable	
Response based on s-GMI kinetics[b]	n = 72	n = 25	
At baseline			
Body surface area, m^2	1.89 (1.30–2.35)	1.72 (1.40–2.55)	.03
Body mass index	26.15 (16.37–43.37)	23.20 (16.20–42.48)	.04
Active myeloma	56 (77.8)	24 (96.0)	.04
Platelet count, $\times 10^3$ platelets/mm^3	95.5 (13–345)	39 (7–258)	.005
Serum bilirubin level, mg/dL	0.6 (0.3–1.6)	0.8 (0.3–2.2)	.01
Iron overload	32/68 (47.1)	16 (72.7)	.04
After diagnosis of aspergillosis			
Normalization of s-GMI[c]	34 (47.2)	3 (12.0)	.002
Neutrophil recovery[d]	71 (98.6)	16 (64.0)	<.001
Response based on the EORTC/MSG definitions[e]	n = 59	n = 34	
At baseline			
Body mass index	26.24 (16.37–43.37)	23.25 (16.20–42.48)	.03
Active myeloma	44 (76.4)	33 (97.1)	.006
Platelet count, $\times 10^3$ platelets/mm^3	102 (13–345)	44,5 (7–258)	.003
Serum bilirubin level, mg/dL	0.6 (0.3–1.0)	0.7 (0.3–2.2)	.007
Creatinine clearance rate, mL/min	62 (2–171)	51 (7–86)	.004
After diagnosis of aspergillosis			
ANC, neutrophils/mm^3[f]	50 (0–10,900)	10 (0–5000)	.01
Normalization of s-GMI[c]	29 (49.2)	7 (20.6)	.006
Neutrophil recovery[d]	59 (100)	24 (70.6)	<.001
Response based on 6-week survival	n = 67	n = 31	
At baseline			
Body mass index	26.05 (16.37–43.37)	23.20 (16.20–42.48)	.04
Active myeloma	50 (74.6)	31 (100)	.002
Previous ASCTs, No.	1 (0–3)	2 (0–4)	.02
Receipt of other immunosuppressive agents	7 (10.4)	10 (32.3)	.008
WBC count, cells/mm^3	3840 (20–26,610)	2510 (10–18,100)	.03
Platelet count, $\times 10^3$ platelets/mm^3	102 (13–345)	42 (7–258)	.001
Serum bilirubin level, mg/dL	0.6 (0.3–2.2)	0.7 (0.3–1.6)	.02
Creatinine clearance rate, mL/min	62 (2–171)	50 (7–85)	.001
After diagnosis of aspergillosis			
ANC, neutrophils/mm^3[f]	80 (0–10,900)	10 (0–5000)	.01
Normalization of s-GMI[c]	30 (45.5)	7 (22.6)	.03
Neutrophil recovery[d]	67 (100)	21 (67.7)	<.001

Data are No. or proportion (%) of patients or median (range). Outcomes were examined according to the kinetics of serum *Aspergillus* galactomannan, the EORTC/MSG response definitions, and 6-week survival. Variables were defined at baseline and after the diagnosis of aspergillosis.

Abbreviations: ANC, absolute neutrophil count; ASCT, autologous stem cell transplantation; EORTC/MSG, European Organization for Research and Treatment of Cancer/Mycosis Study Group; IA, invasive aspergillosis; s-GMI, serum *Aspergillus* galactomannan index; WBC, white blood cell.

[a] Favorable and unfavorable response outcomes are success and failure, respectively, for s-GMI kinetics and EORTC/MSG definitions; favorable and unfavorable outcomes are survived and died, respectively, for 6-week survival.

[b] Response by s-GMI kinetics was not assessed in 1 patient, who was lost to follow-up.

[c] Within 7 days after the first positive s-GMI.

[d] Defined as an ANC of ≥500 neutrophils/mm^3 on 3 consecutive days.

[e] Response by EORTC/MSG was not assessed in 5 patients, who were not available for response assessment at 6 weeks.

[f] At diagnosis of IA.

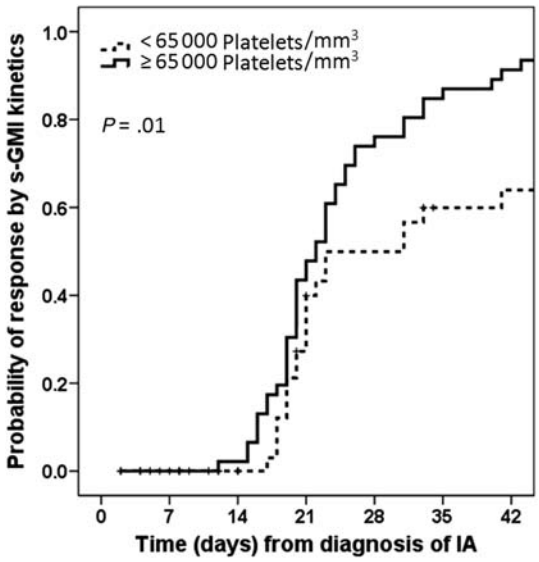

Figure 1. Probability of aspergillosis response by the kinetics of serum *Aspergillus* galactomannan in patients with multiple myeloma according to their baseline platelet counts. Abbreviations: IA, invasive aspergillosis; s-GMI, serum *Aspergillus* galactomannan index.

patients with renal failure have higher risk for severe oral mucositis as a result of higher drug exposure [36]. Higher MEL exposure is also known to result in more severe and prolonged myelosuppression and immunosuppression [37]. Our finding that patients with renal dysfunction experienced worse outcomes is in keeping with these reports [36, 37] and with our prior analysis identifying elevated serum creatinine level as an independent risk factor for severe oral mucositis following MEL-ASCT [38]. The importance of creatinine clearance rate as a prognostic factor for IA in settings other than multiple myeloma deserves further investigation.

Fifteen studies examined the prognostic factors for IA among patients with hematologic cancers (Table 4). Unfortunately, most variables evaluated were not obtained at baseline and hence cannot be applied towards early intervention, therapy modification, or stratification in clinical trials [18].

To better appreciate the reported prognostic factors for IA, we classified them as baseline (prechemotherapy) and nonbaseline factors, the latter further classified as nonbaseline, pre-IA (ie, after chemotherapy but before IA diagnosis) and nonbaseline, post-IA (after IA diagnosis).

Two studies of patients with acute leukemia treated with nonmyeloablative chemotherapy identified nonremission status as the only predictor of poor outcome [2, 14], while 3 of 5 studies of allogeneic SCT [3, 6, 7, 12, 17] identified pulmonary dysfunction, HLA-mismatched transplantation and nonmyeloablative conditioning [7], conditioning without antithymocyte globulin [17], and, surprisingly, younger age [6]. Five of 8 studies that evaluated patients with different underlying diseases and

Table 3. Multivariate Analysis of Outcome Predictors in 98 Patients With Multiple Myeloma Who Developed Neutropenia-Related Aspergillosis

Variable	Odds Ratio	95% Confidence Interval	*P*
Response based on s-GMI kinetics			
Baseline			
Platelet count (per 1000 platelets/mm^3)	1.009	1.001–1.017	.03
After diagnosis of aspergillosis			
Neutrophil recovery[a]	32.734	3.630–295.164	.002
s-GMI normalization ≤7 days from diagnosis of IA	5.356	1.316–21.901	.02
Response based on the EORTC/MSG definitions			
Baseline			
Platelet count (per 1000 platelets/mm^3)	1.009	1.002–1.017	.01
Creatinine clearance rate (per mL/min)	1.024	1.006–1.042	.009
After diagnosis of aspergillosis			
s-GMI normalization ≤7 days from diagnosis of IA	2.900	1.009–8.333	.048
Response based on 6-week survival			
Baseline			
Creatinine clearance rate (per mL/min)	1.031	1.010–1.052	.003
After diagnosis of aspergillosis			NS

Outcomes were examined according to the kinetics of serum *Aspergillus* galactomannan, the EORTC/MSG response definitions, and 6-week survival. Variables were defined at baseline and after the diagnosis of aspergillosis.

Abbreviations: IA, invasive aspergillosis; EORTC/MSG, European Organization for Research and Treatment of Cancer/Mycosis Study Group; NS, not significant; s-GMI, serum *Aspergillus* galactomannan index.

[a] Defined as an ANC of ≥500 neutrophils/mm^3 on 3 consecutive days.

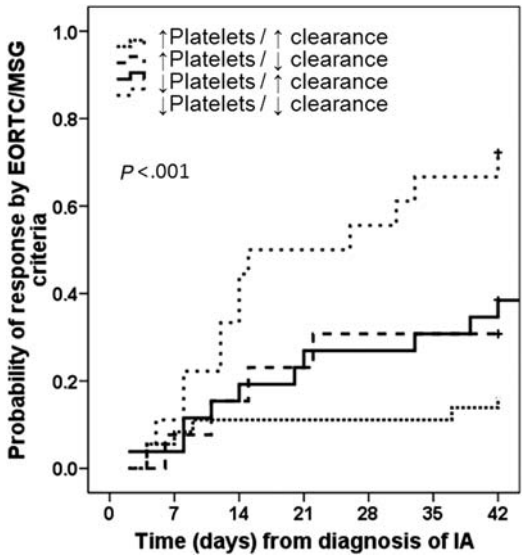

Figure 2. Probability of aspergillosis response by the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORCT-MSG) criteria in patients with multiple myeloma according to their baseline platelet count and baseline creatinine clearance rate. Abbreviations: IA, invasive aspergillosis; ↑ platelet, baseline platelet count ≥65,000 platelets/mm^3; ↓ platelet, baseline platelet count <65,000 platelets/mm^3; ↑ clearance, baseline creatinine clearance rate ≥53 mL/min; ↓ clearance, baseline creatinine clearance rate <53 mL/min.

therapies, including SCT [4, 5, 8–11, 16], did not identify baseline prognostic factors, while 3 suggested that relapsed malignancy [4], prior noninfectious respiratory disease [9], and receipt of 0.3 mg/kg/day of prednisone for >3 weeks ≤90 days before IA [22] negatively affected outcome. The large variation in early outcome predictors among these studies is likely the result of large heterogeneity in underlying diseases, therapeutic modalities, diagnostic methods, and antifungal strategies [2–17].

Nonbaseline pre-IA prognostic factors were identified in 4 of 15 studies, including neutropenia ≤30 or ≤60 days before IA [8, 12], serum bilirubin level of >6.5 mg/dL and serum creatinine level of >2.5 mg/dL [7], and prednisone dose of ≥7 mg/kg ≤1 week before IA diagnosis [3]. However, the common occurrence of these events and their timing in relation to IA limit their clinical usefulness.

Several post-IA factors were associated with poor outcomes, including extensive pulmonary or disseminated IA [4, 6, 7, 9–11], corticosteroids [6, 7, 9, 10, 12, 17], neutropenia (at diagnosis of IA or duration of persistent neutropenia) [5, 7, 11, 16], thrombocytopenia [17], renal [9, 12, 17] and other organ dysfunction [10, 12, 16], and relapsed malignancy [4, 9]. Severe graft-versus-host disease negatively impacted outcome in one study [3]. Unfortunately, these post-IA variables have limited clinical application because they are considered "too little, too late" [18].

Only 3 studies evaluated the prognostic significance of s-GMI. Positive s-GMI at diagnosis did not impact outcome in one study [8] but was associated with lower 12-week survival by univariate but not multivariate analysis in another [9], while higher s-GMI at diagnosis of IA independently predicted poor 6- and 12-week survival in a third, in which the rate of s-GMI decay ≤7 days after the first positive s-GMI was significantly associated with outcome [22]. Although we could not

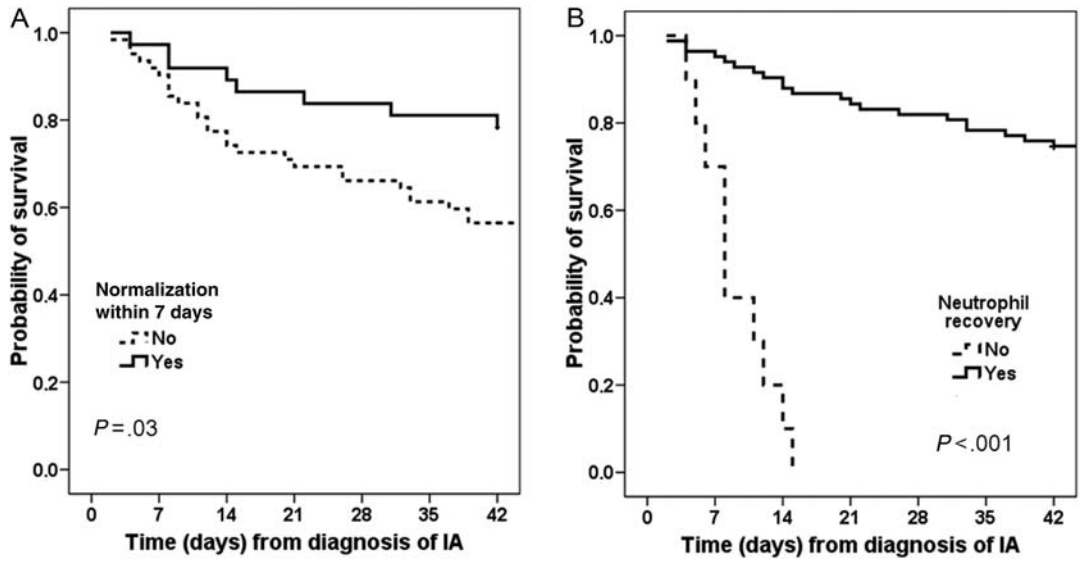

Figure 3. Probability of 6-week survival according to (A) normalization of serum *Aspergillus* galactomannan index ≤7 days after the first positive serum *Aspergillus* galactomannan index or (B) neutrophil recovery. Abbreviations: IA, invasive aspergillosis.

Table 4. Prognostic Factors for Invasive Aspergillosis Among Patients With Hematologic Cancers: Findings of Our Current Study in the Context of Prior Reports

Author, Year	Episodes of IA, No.	Setting	Treatment	Factors Associated With Poor Outcome		
				At Baseline	Nonbaseline, Before IA	Nonbaseline, After IA
Present study	98	Multiple myeloma with neutropenia	Chemotherapy[a] and ASCT	Platelet count <65,000 platelets/mm^3, creatinine clearance rate <53 mL/min	None	Positive s-GMI after 7 days from first positive s-GMI, persistent neutropenia
Acute leukemia receiving conventional chemotherapy						
Ribrag, 1993 [2]	21	Acute leukemia	Chemotherapy[a]	Leukemia not in remission	None	None
Pagano, 2010 [14]	140	AML	Chemotherapy[a]	Leukemia not in remission	None	Persistent neutropenia
Allo-SCT						
Ribaud, 1999 [3]	27	Hem Ca	Allo-SCT	None	Cumulative prednisone dose ≥7 mg/kg 1 week before IA	GVHD acute (grade ≥2) or extensive chronic
Cordonnier, 2006 [6]	51	Hem Ca	Allo-SCT (41), ASCT (10)	Age 12–35 years (vs <12, 36–47, and >47 years)	None	Diffuse (vs localized) lung infiltrates, pleural effusion, receipt of ≥2 mg/kg of corticosteroids at IA
Upton, 2007 [7]	405	Hem Ca	Allo-SCT (391), ASCT (24)	Pulmonary dysfunction, HLA-mismatch, NMA regimen	Total bilirubin level >6.5 mg/dL and creatinine level >2.5 mg/dL ≤7 days before IA diagnosis; 75% of patients had late IA	Late IA (>40 days after SCT), neutropenia at diagnosis of IA, receipt of ≥2 mg/kg of prednisone 1 week after IA diagnosis, disseminated IA
Mikulska, 2009 [17]	45	Hem Ca	Allo-SCT	Conditioning without ATG	None	Receipt of corticosteroids, low platelet count, low serum IgA level or creatinine level >1.5 mg/dL
Baddley, 2010 [12]	642	Various diseases	Allo-SCT (337), ASCT (78), SOT (227)	None	Neutropenia ≤30 days before IA diagnosis	Renal insufficiency, liver insufficiency or receipt of corticosteroids, late IA (>30 days after SCT), proven IA
Allo-SCT and conventional chemotherapy						
Yeghen, 2000 [4]	87	Hem Ca	Allo-SCT (32), ASCT (4), chemotherapy[a] (51)	Relapsed malignancy	None	Diffuse (vs localized) lung infiltrates

Subira, 2002 [5]	41	Hem Ca	Allo-SCT (12), ASCT (3), chemotherapy[a] (24)	Allo-SCT		Persistent neutropenia
Gallien, 2008 [8]	34	Hem Ca (26), HIV infection (7), diabetes mellitus (1)	Allo-SCT (18), ASCT (2), chemotherapy[a] (5), others (9)	None	Neutropenia for ≥10 days ≤60 days before IA diagnosis	None
Nivoix, 2008 [9]	289	Mixed (192 Hem Ca), nonmalignant conditions (21), others	Allo-SCT (41), SOT (10), others	Allo-SCT, prior noninfectious respiratory disease	None	Progression of underlying cancer, ≥0.2 mg/kg of corticosteroids on day of IA diagnosis, disseminated IA, diffuse lung involvement, proven or probable IA (vs possible), creatinine clearance rate <60 mL/min, neutropenia (<500 neutrophils/mm^3) ≤4 days after start of IA treatment
Parody, 2009 [10]	130	Hem Ca	Allo-SCT (49), chemotherapy[a] (81)	Alternative donor for allo-SCT group	None	Disseminated IA, organ impairment, severe cytopenias, and receipt of ≥2 mg/kg/day of corticosteroids at IA diagnosis
Reuter, 2009 [11]	212	Hem Ca	Allo- and ASCT (49), chemotherapy[a] (163)	None	None	Extrapulmonary disease, duration of neutropenia
Koo, 2010 [22]	93	Mixed population (58 Hem Ca), solid tumor (6), others	Allo-SCT (34), SOT (11), others	Receipt of 0.3 mg/kg/day prednisone for >3 weeks ≤90 days before IA	None	High s-GMI at IA diagnosis, low s-GMI decay[b]
Ramos, 2011 [16]	44	Hem Ca	Allo-SCT (140), ASCT (32), chemotherapy[a] (277)	None	None	Persistent neutropenia, ICU admission, therapy with agents other than antimold azoles

Variables were defined at baseline (before chemotherapy); nonbaseline, before IA (ie, after the start of chemotherapy but before IA diagnosis); and nonbaseline, after IA (ie, after IA diagnosis).

Abbreviations: Allo-SCT, allogeneic SCT; AML, acute myelogenous leukemia; ASCT, autologous SCT; ATG, antithymocyte globulins; CNS, central nervous system; GVHD, graft-versus-host disease; Hem Ca, hematologic cancer; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IA, invasive aspergillosis; ICU, intensive care unit; IgA, immunoglobulin A; NMA, nonmyeloablative; SCT, stem cell transplantation; s-GMI, serum *Aspergillus* galactomannan index; SOT, solid organ transplantation.

[a] Myelosuppressive but not myeloablative.

[b] Decay calculated by dividing the difference between baseline s-GMI and s-GMI obtained around 1 week after the first positive s-GMI.

confirm a prognostic significance of a high s-GMI at diagnosis, the superior outcomes we observed among our patients whose s-GMI normalized ≤7 days are in agreement with this report [22] and with others showing strong correlation between declining s-GMI values and positive outcomes [21–25].

Our results have important clinical and research implications. Stratification of patients into low-, intermediate-, or high-risk categories according to baseline platelet count and creatinine clearance rate may allow risk-adapted strategies to IA [18] with low risk are patients best managed with diagnostic-driven, preemptive s-GMI-guided therapy while mould-active prophylaxis is reserved for patients at high risk of failure to pre-emptive therapy. Managing patients at intermediate risk can be individualized depending on the rapid availability of s-GMI results and other local considerations.

We previously reported that response based on s-GMI kinetics correlated well with the EORTC/MSG response criteria but were more objective and allowed earlier response classification (3 weeks) than the EORTC/MSG 6-week time point [21]. We now show that clinicians can use s-GMI to assess response at an even earlier time point, ≤7 days after the first positive s-GMI.

Because most patients with myeloma receive high doses of corticosteroids, usually in fixed predefined doses, and because of the narrow age distribution of this population [39], we could have missed a potential association between outcomes and older age or cumulative corticosteroid doses [3, 7, 12, 22]. Our focus on a homogeneous population (same underlying disease, care at a single institution with standardized antineoplastic therapies, and infectious disease management) represents an important strength because it eliminates the confounding variables associated with heterogeneous populations with different diseases and therapies. Nonetheless, the role of baseline platelet count and creatinine clearance rate as prognostic factors should be confirmed in other patient populations.

We conclude that platelet count and renal function, 2 simple, inexpensive to measure, widely available, and routinely collected laboratory data, can predict the outcome of neutropenia-related IA, even before the start of chemotherapy, and that the evaluation of s-GMI ≤7 days after the first positive s-GMI provides clinicians with the opportunity to modify therapy early during the course of IA.

Notes

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