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Risk Factor for Rash in Patients Receiving Cytarabine and Idarubicin Induction Therapy for Acute Myeloid Leukemia

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Abstract. *Background/Aim: Rash is a common adverse event (AE) observed during cytarabine and idarubicin induction therapy in patients with acute myeloid leukemia (AML). Previous studies have highlighted the challenge in predicting the onset and duration of rash. This study aimed to determine the factors that affect the onset of rash in patients receiving induction therapy for AML. Patients and Methods: This retrospective study involved 97 patients with AML who received induction chemotherapy with cytarabine and idarubicin at the Department of Hematology, Kyushu University Hospital between January 2008 and June 2022. The factors associated with rash were identified through a multivariate stepwise logistic regression analysis. Subsequently, the patient's characteristics were compared between those with risk factors and those without risk factors using a matched pair analysis. Results: Pre-existing leukopenia [odds ratio (OR)=3.294; 95% confidence interval (CI)=1.272-8.531] and good performance status (PS=0) (OR=2.717; 95%CI=1.087-6.792) were significant risk factors for rash development. Conversely, the matched pair analysis indicated that patients with pre-existing leukopenia, excluding those with a PS score of 0, exhibited a significantly (p=0.015) higher incidence of rash than those without it. Conclusion: Both multivariate logistic regression analysis and matched pair analysis identified pre-existing leukopenia as a primary risk factor for rash development associated with cytarabine and idarubicin chemotherapy.*

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Key Words: Risk factors, rash, adverse events, acute myeloid leukemia, cytarabine and idarubicin induction therapy.

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults. Effective therapy for AML requires induction therapy followed by curative-intent post-induction therapy, including allogeneic hematopoietic stem cell transplantation (1). The standard induction therapy for AML is cytarabine administered continuously for seven days in combination with anthracycline for the first three days, commonly referred to as "7+3" (2-4).

Japanese patients undergoing induction therapy with cytarabine and an anthracycline have reported fatal adverse events (AEs), including sepsis, bleeding, febrile neutropenia, acute cardiac toxicity, and late-onset cardiac failure (4). Moreover, relatively frequent occurrences of rash, fever, and elevated liver enzymes have been reported (5).

Previous studies highlighted the incidence of various AEs during chemotherapy with cytarabine and idarubicin induction therapy in patients with acute AML. Interestingly, most AEs, excluding rash, manifest during the anticipated period as indicated by the medication instruction sheet (MIS), an original document devised in our laboratory for AE monitoring. The accuracy rate of the sheet for predicting the onset and duration of a variety of AEs was 68.2%, with the lowest rate (29.4%) observed for rash. In our data, the incidence rate of rash was 43.6%, with a median onset time of eight days and a recovery period of 15 days (6).

Rash can cause significant physical discomfort and psychological distress, profoundly affecting the health-related quality of life of patients (7-9). Additionally, worsening skin symptoms may impede the effective management of cancer chemotherapy (7, 8). Therefore, identifying the risk factors for rash associated with cytarabine and idarubicin induction therapy is crucial for implementing timely and appropriate measures to address this issue.

In the present retrospective study, the risk factors for rash were assessed using a multivariate logistic regression analysis. Subsequently, a matched pair analysis was conducted to compare the backgrounds of patients between those with identified risk factors and those without.

Patients and Methods

Study design, setting, and patient population. This study was conducted in accordance with the principles of the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research by the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour and Welfare of Japan. The study was approved by the Ethics Committee of Kyushu University Graduate School and Faculty of Medicine (approval no. 22151-01) and Doshisha Women's College of Liberal Arts (approval no. 2022-19). The requirement for obtaining informed consent was waived due to the retrospective nature of the study. Ninety-seven eligible patients who received cytarabine and idarubicin induction therapy at the Department of Hematology, Kyushu University Hospital during January 2008 and June 2022 were included in this study. Among them, 39 patients overlapped with our previous study, which evaluated the accuracy of MIS for predicting the onset and the duration of AEs (6).

Treatment schedules. The patients received 24-hour infusions of cytarabine (100 mg/m^2) for seven days starting on day 1 and 30-min infusions of idarubicin (12 mg/m^2) for three days starting on day 1. Adequate amounts of corticosteroids or antihistamines were administered in patients who developed rash.

Clinical parameter, data collection, and assessment. The following data were obtained from the electronic medical records in Kyushu University Hospital and analyzed retrospectively: patients' demographic characteristics, such as sex; age; Eastern Cooperative Oncology Group performance status (PS) score; laboratory results, including serum creatinine level, aspartate aminotransferase level, alanine aminotransferase level, C-reactive protein level, leukocyte count, hemoglobin level, and platelet count; and AEs that appeared before the initiation of chemotherapy. The frequency of laboratory tests was determined based on the physician's discretion. AEs were monitored before and after chemotherapy, and the severity was classified according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistical analyses. Chi-square test or Wilcoxon rank-sum test was used to compare categorical variables, while *t*-test was used to compare continuous variables. To identify the risk factors associated with rash, a multivariate stepwise logistic regression analysis was performed, and age, sex, PS score, and myelosuppression observed before chemotherapy were included as independent variables. Data were analyzed using JMP Pro® 16.2 (SAS Institute, Cary, NC, USA). To compare the characteristics between patients with risk factors, such as pre-existing leukopenia and a PS score of 0 and those without risk factors, a matched pair analysis (matching 1:1 for age and risk factors) was carried out to minimize the selection bias and confounders. The matched pair analysis was performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). In addition, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics (10, 11). A p-value of <0.05 was considered significant.

Results

Patient baseline clinical characteristics. The patients' baseline demographics are shown in Table I. Of the 97 patients, 55 (56.7%) were men. The median age was 50.0 years (quartiles: 16-67). The majority of patients obtained an ECOG PS score of 0 (n=41, 42.3%) or 1 (n=46, 47.4%). Notably, fever (n=35, 36.1%) and myelosuppression, such as leukopenia (n=38, 39.2%), hemoglobin decrease (n=90, 92.8%), and thrombocytopenia (n=85, 87.6%) occurred before the initiation of chemotherapy.

Comparison of demographics between patients with skin rash and those without. A total of 57 patients (58.8%) developed skin rash during cytarabine and idarubicin therapy (Table II), of whom 23 (40.4%), 31 (54.4%), and three patients (5.3%) developed grade 1, 2, and 3 symptoms, respectively (data not shown). Forty-one of them (71.9%) required treatment with corticosteroids or antihistamines for symptom relief.

Significant differences were observed in the prevalence of a PS score of 0 (52.6% *vs*. 30.0%, p=0.045) and pre-existing leukopenia (49.1% *vs*. 25.0%, p=0.029) between patients with rash and those without such symptom. Other variables were not significantly different between the two groups.

Results of the multivariate logistic regression analysis indicated that pre-existing leukopenia [odds ratio (OR)=3.050; 95% confidence interval (CI)=1.230-8.039; p=0.016] and a PS score of 0 (OR=2.559; 95%CI=1.056-6.476; p=0.037) were significant risks for the development of rash associated with cytarabine and idarubicin induction therapy (Table III).

Table I. *Baseline characteristics of patients at the beginning of cytarabine and idarubicin induction therapy.*

Number of patients	97
Sex	
Male (N, %)	55 (56.7%)
Female (N, %)	42 (43.3%)
Age (median years, range)	50.0 (16-67)
ECOG-PS score (N, %)	
0	41 (42.3%)
1	46 (47.4%)
2	6 (6.2%)
3	4 (4.1%)
Diagnosis (N, %)	
Acute myeloid leukemia	97 (100%)
Subjective symptoms prior to the initiation of induction therapy (N, %)	
Fever	35 (36.1%)
Anorexia	
Stomatitis	
Bone marrow function (any grade)	
Leukopenia	38 (39.2%)
Hemoglobin decrease	90 (92.8%)
Thrombocytopenia	85 (87.6%)
Clinical laboratory data (mean±SD)	
Serum creatinine (mg/dl)	0.75±0.23
Aspartate aminotransferase (IU/l)	27.1±21.8
Alanin aminotransferase (IU/l)	29.6±33.5
C-reactive protein (mg/dl)	3.2±5.8

ECOG-PS: Eastern Cooperative Oncology Group performance status.

Matched pair analysis. As shown in Table IV, 97 patients were divided into two groups: those with pre-existing leukopenia (n=38) and those without pre-existing leukopenia (n=59). The characteristics were compared between the two groups before and after 1:1 matching for age and a PS score of 0. Before data matching, the incidence of rash was significantly higher in the pre-existing leukopenia group (73.7% *vs*. 49.2%, p=0.029). Similarly, the rash was more common in the pre-existing leukopenia group (80.0% *vs*. 46.7%, p=0.015) as determined by the matched pair analysis (n=60).

Table V presents a comparison of patients' characteristics between patients with a PS score of 0 (n=42) and those with a PS score of ≥1 (n=55) before and after 1:1 matching for age and pre-existing leukopenia. The incidence of rash was significantly higher in patients with a PS score of 0 than in those with a PS score of ≥1 (p=0.045) before data matching. However, such a difference in the occurrence of rash was no longer significant after pair matching for age and pre-existing leukopenia (73.3% *vs*. 50.0%, p=0.110, n=60).

Discussion

In our previous report on the monitoring of AEs in patients with AML receiving cytarabine and idarubicin induction therapy, myelosuppression, such as reduction in hemoglobin content (94.9%), thrombocytopenia (87.2%), and leukopenia (35.9%), developed before chemotherapy initiation. Consistently, reduced hemoglobin levels (92.8%), thrombocytopenia (87.6%), and leukopenia (39.2%) occurred before the start of chemotherapy. Such myelosuppression is likely attributed to disease progression, wherein the excessive proliferation of leukemia cells hinders the synthesis of normal leukocytes and platelets in the bone marrow. Previous studies have demonstrated that most patients with AML experience pancytopenia, weakness, fatigue, infections, and other hemorrhagic manifestations. These symptoms arise due to the reduced capacity of cells to differentiate into mature cells, a consequence of the clonal proliferation of leukemia cells (2, 12).

The incidence rate of rash was 58.8% (23.7% for grade 1, 32.0% for grade 2, and 3.1% for grade 3) in the present study. This value was similar to that (61%) reported by Woelich *et al*. (13) in patients with AML receiving induction therapy with cytarabine, idarubicin, and cladribine. However, this rate was higher than that (43.6%) reported in our previous study (6) or that (38%) reported by Garcia-Manero *et al*. (14) in patients with AML treated with cytarabine and idarubicin in combination with vorinostat.

In the present study, we evaluated the risk factors for rash in patients with AML receiving cytarabine and idarubicin induction therapy by conducting a multivariate stepwise logistic regression analysis and a matched pair analysis. The logistic regression analysis indicated that pre-existing leukopenia (OR=3.294, 95%CI=1.272-8.531, p=0.033) and a PS score of 0 (OR=1.717, 95%CI=1.087-6.792, p=0.033) were significant risk factors for rash development. The higher incidence of rash in patients with good PS than in those with poor PS may initially appear counterintuitive, given that myelosuppression is typically more prevalent in patients with poor PS.

On the contrary, the matched pair analysis showed that the incidence of rash was significantly higher in patients who had pre-existing leukopenia than those who did not (80% *vs*. 46.7%, p=0.015) after pair matching for age and a PS score of 0; meanwhile, the incidence of rash was not significantly different between patients with a PS score of 0 and those with a PS score of ≥1 (73.3% for PS=0 *vs*. 50% for PS ≥1, p=0.110) after pair matching for age and pre-existing leukopenia. The disappearance of the significant difference in the incidence of rash between the good PS and poor PS groups in the matched pair analysis may be due to the lack of influence of pre-existing leukopenia. Consequently, pre-existing leukopenia emerges as the sole significant risk factor for rash associated with cytarabine and idarubicin induction therapy in patients with AML.

Patients with hematopoietic malignancies are prone to developing rash, primarily associated with immunosuppression (15). Yemisen *et al*. (15) reported a high incidence of severe rash in patients with febrile neutropenia exhibiting

Table II. *Comparison of characteristics between patients with skin rash and those without after receiving cytarabine and idarubicin therapy.*

	Presence of skin rash (N=57)	Absence of skin rash (N=40)	*p*-Value
Age (median, quartiles)	49 (31-59)	50 (35-60)	0.692
Sex (male/female)	32 / 25	23 / 170.940	
Performance status=0 (N, %)	30 (52.6%)	12 (30.0%)	0.045
Pre-existing leukopenia (N, %)	28 (49.1%)	10 (25.0%)	0.029
Pre-existing hemoglobin decrease (N, %)	52 (91.2%)	38 (95.0%)	0.758
Pre-existing thrombocytopenia (N, %)	51 (89.5%)	34 (85.0%)	0.730
Laboratory data	Mean±SD	Mean±SD	
Albumin (g/dl)	3.97±067	3.81±0.75	0.270
Blood urea nitrogen (mg/dl)	12.4±3.9	13.8±6.4	0.255
Serum creatinine (mg/dl)	0.73±0.24	0.78±0.22	0.374
Uric acid (mg/dl)	4.74±1.75	5.10±2.82	0.471
Total bilirubin (mg/dl)	0.72±0.35	0.71±0.35	0.894
Aspartate aminotransferase (IU/l)	27.5±23.6	26.6±19.3	0.840
Alanine aminotransferase (IU/l)	32.9±40.3	25.0±19.8	0.203
Lactate dehydrogenase (U/l)	627±1024	586±559	0.800
C-reactive protein (mg/dl)	3.11±5.4	3.33±6.34	0.851
Na^+ (mEq/l)	140.1±2.1	140.4±2.7	0.550
K^+ (mEq/l)	3.91±0.59	3.86±0.48	0.661
Cl^- (mEq/l)	104.4±2.9	104.2±4.2	0.887
Ca^{2+} (mEq/l)	9.1±0.7	8.93±0.57	0.204

Data were statistically compared using a chi-square test with Yates's correction for non-parametric analysis or *t*-test for parametric analysis.

Table III. *Multivariate logistic regression analysis of the risk factors of skin rash in patients with acute myeloid leukemia receiving cytarabine and idarubicin.*

	OR	95% Confidence interval	*p*-Value
Age ≥60	1.084	(0.380-3.194)	0.881
Sex (male)	1.090	(0.436-2.734)	0.853
Performance status=0	2.559	(1.056-6.476)	0.037
Pre-existing leukopenia	3.050	(1.230-8.039)	0.016
Pre-existing reduction in hemoglobin levels	0.414	(0.052-2.380)	0.330
Pre-existing thrombocytopenia	1.490	(0.397-5.611)	0.548

hematological malignancy, including AML. They identified infections with opportunistic fungus or herpes labialis, anticancer drugs, and antimicrobial agents as major causes of rash. Thus, patients with reduced leukocyte counts are more susceptible to immunosuppression and subsequent infections, leading to the development of rash.

Cutaneous involvement substantially impacts the quality of life of hematologic patients and compromises the prognosis in different patients (16). Cytarabine and idarubicin induction therapy is followed by consolidation therapy and allogeneic hematopoietic stem cell transplantation. Therefore, it is important to maintain patient's quality of life.

Study limitations. The small number of patients, its single institutional nature, and the retrospective nature of the analyses. A large scale, multi-institutional study is warranted to elucidate the risk factors of rash associated with cytarabine and idarubicin induction therapy.

Conclusion

The presence of leukopenia before the start of chemotherapy was a significant risk factor for rash associated with cytarabine and idarubicin therapy, as determined by a multivariate logistic regression analysis and a matched pair analysis.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Table IV. *Comparison of the incidence of skin rash and characteristics between patients with reduced leukocyte count before chemotherapy (pre-existing leukemia) and those with normal leukocyte count, assessed before and after a matched paired analysis.*

Before data matching	Presence of pre-existing leukopenia (N=38)		Absence of pre-existing leukopenia (N=59)		p-Value
	N	%	N	%	
Presence of skin rash	28	73.7	29	49.2	0.029
Sex					
Male	24	63.2	31	52.5	0.412
Female	14	36.8	28	47.5	
PS=0	18	47.4	24	40.7	0.661
Age (mean years, quartiles)	52.0	(44.3-59.0)	47.0	(30.5-59.5)	0.252
After pair matching for age and PS=0	Presence of pre-existing leukopenia (N=30)		Absence of pre-existing leukopenia (N=30)		
	N	%	N	%	
Presence of skin rash	24	80.0	14	46.7	0.015
Sex					
Male	17	56.7	18	60.0	1.000
Female	13	43.3	12	40.0	
PS=0	12	40.0	12	40.0	1.000
Age (median years, quartiles)	52.5	(44.5-59.0)	53.0	(44.8-60.0)	0.969

Data were statistically compared using a Mann–Whitney *U*-test for age or a chi-square test with Yates's correction for other parameters. PS: Performance status.

Table V. *Comparison of the incidence of skin rash and characteristics between patients with a performance status (PS) score of 0 and those with a PS score of ≥1, as assessed before and after matched paired analysis.*

Before data matching	PS=0 (N=42)		PS ≥1 (N=55)		*p*-Values
	N	%	N	%	
Presence of skin rash	30	78.9	27	49.1	0.045
Sex					
Male	19	50.0	36	65.5	0.074
Female	23	60.5	19	34.5	
Pre-existing leukopenia	18	42.9	20	36.4	0.661
Age (mean years, quartiles)	46.0	(29.3-57.0)	50	(41.5-60.0)	0.093
After pair matching for age and pre-existing leukopenia	PS=0 (N=30)		PS ≥1 (N=30)		
	N	%	N	%	
Presence of skin rash	22	73.3	15	50.0	0.110
Sex					
Male	13	43.3	18	60.0	0.301
Female	17	56.7	12	40.0	
Pre-existing leukopenia	12	40.0	12	40.0	1.000
Age (median years, quartiles)	50.0	(30.8-59.0)	50.5	(31.5-59.0)	0.916

Data were statistically compared using a Mann–Whitney *U*-test for age or a chi-square test with Yates's correction for other parameters.

Authors' Contributions

Mayako Uchida: Conceptualization, methodology, data collection, formal analysis, and writing – original draft preparation. Shigeru Ishida, Erika Mochizuki, Nana Ozawa, Hiroko Yonemitsu, Hideki Ochiai, and Hanae Nakamura: Data collection. Takehiro Kawashiri, Hiroyuki Watanabe, Toshikazu Tsuji, Kimitaka Suetsugu, Koji Kato, and Nobuaki Egashira: Writing – review and editing. Koichi Akashi and Ichiro Ieiri: Writing – review and editing, supervision.

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