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Cervical Papanicolaou Smears in Hematopoietic Stem Cell Transplant Recipients: High Prevalence of Therapy-Related Atypia during the Acute Phase

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A B S T R A C T

Hematopoietic stem cell transplant (HSCT) recipients have a higher risk of cervical cancer. Papanicolaou (Pap) smear is the standard tool for screening cervical cancer, but there is limited research about the cervical cytology in HSCT recipients. Here, we retrospectively included adult female patients who underwent allogeneic or autologous HSCT at National Taiwan University Hospital during 2009 to 2015 and reviewed their Pap smears before and after HSCT. There were 248 allogeneic and 131 autologous HSCT recipients in our study. In allogeneic HSCT recipients, 38.7% (96 of 248) had pre-HSCT Pap smears and 17.1% (44 of 248) had post-HSCT Pap smears. In the autologous HSCT recipients, 35.1% (46 of 131) had pre-HSCT Pap smears and 13.7% (18 of 131) had post-HSCT Pap smears. Compared with allogeneic HSCT recipients without post-HSCT Pap smears, more recipients with post-HSCT Pap smears received bone marrow–derived stem cells (18.2% versus 4.9% respectively; $P = .0077$) and had longer overall survival (median overall survival, not reached versus 22.1 months; $P < .0001$). The abnormal rates of post-HSCT Pap smear were 13% (6 of 44) and 11% (2 of 18) in allogeneic and autologous recipients respectively, higher than in the general Taiwanese population (1.22%). Infections were rare in post-HSCT Pap smears. Of note, 11% (5 of 44) of post-HSCT Pap smears from allogeneic recipients showed therapy-related atypia, manifesting as enlarged hyperchromatic nuclei, vacuolated cytoplasm, and occasional tadpole-like cells. These atypical cytological features mimic precancerous lesions, but cervical biopsies and human papilloma virus tests were negative. The atypical cytological features resolved spontaneously in the subsequent follow-up Pap smears. On average, Pap smears with therapy-related atypia were sampled at day +77, significantly earlier than those without therapy-related atypia ($P = .016$). Therapy-related atypia was more frequent in post-HSCT Pap smears sampled within 100 days after HSCT (before day +100, 4 of 5, 80%, versus after day +100, 1 of 39, 2.56%; $P = .0002$). The strong temporal relationship suggests these atypical cytological changes resulted from conditioning regimen, most likely busulfan-containing chemotherapy. No therapy-related atypia were observed after total body irradiation or nonbusulfan-containing chemotherapy. In conclusion, therapy-related atypia was common in post-HSCT Pap smears sampled within 100 days after HSCT. Clinical information is critical for correct cytological diagnosis.

INTRODUCTION

Cervical cancer is a common gynecological cancer associated with human papilloma virus (HPV) infection. Squamous cell carcinoma is the most common histological type of cervical cancer. HPV infection results in cervical squamous cell carcinoma in a stepwise fashion, from low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), to squamous cell carcinoma [1]. Cervical Papanicolaou (Pap) smear is an effective tool to screen cancer and precancerous lesions [2-5]. Immunocompromised women, including hematopoietic stem cell transplant (HSCT) recipients, have a higher risk of cervical cancer [6,7]. Some authors recommend annual Pap smear for HSCT recipients [8,9], but the optimal ages to start and discontinue screening remain unclear [2].

There is limited research about the cervical cytology in the HSCT recipients [10,11]. Cytological examination of post-HSCT

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Pap smears is largely based on experience in general population and cancer patients. For instance, it is a well-known pitfall that radiotherapy and chemotherapy cause cytological atypia mimicking cancer [12-18]. HSCT recipients could have certain therapy-related atypia mimicking cancer and precancerous lesions, but the morphology, timing, prevalence, and associated therapeutic agent have not been clarified. Here, we report our institutional experience in Pap smears in allogeneic and autologous HSCT recipients.

MATERIALS AND METHODS

Patients

In this study, we retrospectively included the adult female patients undergoing HSCT during 2009 to 2015 at National Taiwan University Hospital (NTUH) in Taiwan. There were 248 allogeneic and 131 autologous HSCT recipients in our study. The detailed clinical features were listed in Tables 1 and 2. HSCT day 0 was defined as the first day of the stem cell infusion. This study has been approved by the research ethnic committee of NTUH (IRB NO. 201601037RIND).

Conditioning Regimens for Autologous HSCT Recipients

In total, 131 autologous HSCT recipients were included in our study. Twenty-four patients received BCNU 300 mg/m^2 body surface area (BSA) daily on day -6; etoposide 200 mg/m^2 BSA daily on days -5 to day -2; cytarabine 100 mg/m^2 BSA per dose, twice daily, on days -5 to day -2, total 8 doses; melphalan 140 mg/m^2 BSA daily on day -1 (BEAM), 25 patients received BEAM with rituximab 375 mg/m^2 BSA for 1 day (R-BEAM), 68 patients received high-dose melphalan (for the patient with normal renal function, melphalan dose was 100 mg/m^2 BSA daily for 2 days; for the patient with renal insufficiency, melphalan dose was 70 mg/m^2 BSA daily for 2 days), and 13 patients received other conditioning regimen (refer to the footnote of Table 2).

Table 1
Clinical Features of Allogeneic HSCT Recipients

Characteristic	All	Patients with Post-HSCT Smear	Patients without Post-HSCT Smear	*P* Value
n	248	44	204	
Age at HSCT day 0, median (range), yr	44 (19-73)	42 (26-62)	45 (19-73)	.4308
Age at Pap smear sampling, median (range), yr	–	44 (29-62)	–	
Indication for HSCT				
AML	130 (52.4%)	17 (38.6%)	113 (55.4%)	.0649
ALL	53 (21.4%)	9 (20.5%)	44 (21.6%)	
CML	6 (2.4%)	3 (6.8%)	3 (1.5%)	
NHL	13 (5.2%)	5 (11.4%)	8 (3.9%)	
HL	1 (.4%)	0	1 (.5%)	
MDS/MPD	29 (11.7%)	6 (13.6%)	23 (11.3%)	
Anemia	12 (4.8%)	2 (4.5%)	10 (4.9%)	
Others	4 (1.6%)	2 (4.5%)	2 (1.0%)	
Stem cell source				
BM	18 (7.3%)	8 (18.2%)	10 (4.9%)	.0077*
PBSC	205 (82.7%)	33 (75.0%)	172 (84.3%)	
BM and PBSC	25 (10.1%)	3 (6.8%)	22 (10.8%)	
Donor type				
HLA-matched sibling	111 (44.8%)	19 (43.2%)	92 (45.1%)	.1555
HLA-matched unrelated donor	46 (18.5%)	9 (20.5%)	37 (18.1%)	
HLA-matched parent	1 (.4%)	1 (2.3%)	0	
HLA–partially mismatched related donor	23 (9.3%)	3 (6.8%)	20 (9.8%)	
HLA-mismatched unrelated donor	56 (22.6%)	12 (27.3%)	44 (21.6%)	
Haplotype	11 (4.4%)	0	11 (5.4%)	
Conditioning regimen				.0909†
MAC	101 (40.9%)	23 (52.3%)	78 (38.4%)	.3719
BuCy	61 (24.6%)	14 (31.8%)	47 (23.0%)	
TBI-Cy	22 (8.9%)	6 (13.6%)	16 (7.8%)	
BuCy with fludarabine	3 (1.2%)	1 (2.3%)	2 (1.0%)	
BuCy with etoposide	1 (.4%)	0	1 (.5%)	
ATG-Cy for SAA	4 (1.6%)	2 (4.5%)	2 (1.0%)	
Other: MAC‡	10 (4.0%)	0	10 (4.9%)	
RIC	146 (59.1%)	21 (47.7%)	125 (61.6%)	.4495
FluBuCy	120 (48.4%)	17 (38.7%)	103 (50.5%)	
FluCy	5 (2.0%)	0	5 (2.5%)	
FluBu	4 (1.6%)	0	4 (2.0%)	
FluBuAraC	2 (.8%)	0	2 (1.0%)	
other: RIC§	15 (6.0%)	4 (9.1%)	11 (5.4%)	
Other regimens				
R-BEAM	1 (.4%)	0	1 (.5%)	
GVHD				
Hyperacute GVHD	35 (14.1%)	6 (13.6%)	29 (14.2%)	.9204
Acute GVHD	158 (63.7%)	27 (61.4%)	131 (64.2%)	.7218
Chronic GVHD	137 (55.2%)	30 (68.2%)	107 (52.5%)	.0575

Data presented are n (%) unless otherwise indicated.
AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; MDS/MPD, myelodysplastic syndrome/myeloproliferative neoplasm; SAA, severe aplastic anemia. PBSC, peripheral blood stem cells; AraC, cytarabine.
* *P* value is less than .05.
† The *P* value of chi-square test is the result of comparison between MAC and RIC regimens.
‡ Other MAC includes the following regimens: fludarabine/cyclophosphamide/TBI (n = 3), fludarabine/cytarabine/busulfan/cyclophosphamide (n = 3), fludarabine/cytarabine/cyclophosphamide/TBI (n = 1), fludarabine/cyclophosphamide/TBI (n = 1), and clofarabine/cyclophosphamide/TBI (n = 1).
§ Other RIC includes the following regimens: fludarabine/cytarabine/busulfan/cyclophosphamide (n = 5), fludarabine/melphalan/busulfan/cyclophosphamide (n = 1), fludarabine/TBI (n = 1), fludarabine/melphalan (n = 1), fludarabine/cytarabine/TBI (n = 1), fludarabine/cyclophosphamide/TBI (n = 1), busulfan/cyclophosphamide (n = 2), busulfan/cyclophosphamide/etoposide (n = 2), fludarabine/bendamustine/cyclophosphamide (n = 1).