

## ORIGINAL ARTICLE

# Six cases of permanent alopecia after various conditioning regimens commonly used in hematopoietic stem cell transplantation

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**Alopecia, a side effect of chemotherapy, is usually temporary and reversible. Irreversible alopecia has been reported after high-dose chemotherapy (HDC) and hematopoietic stem cell transplantation (HSCT) especially related to BuCy containing conditioning regimens; however, the overall incidence is not known. We conducted a retrospective study to identify patients with chemotherapy-induced permanent alopecia after HSCT. We describe six such patients, two males and four females, among 760 patients transplanted between 1997 and 2004. Median age was 45 years (range, 37–65). There were three Caucasians and three African-Americans. Median follow-up was 30 months. Conditioning regimens included BuCy, Bu/Cy and etoposide (VP16) (one of these patients received second autograft after Cy and TBI) and CyVP16 and TBI. Our data show that permanent alopecia is a significant long-term side effect of HSCT and can be seen across the spectrum of diseases and transplant types and with non-busulfan containing regimens. We have observed that patients usually accept permanent alopecia as the price for the cure and therefore true incidence of permanent alopecia may be underestimated. Our findings may also have medico legal and psychosocial implications that need to be taken into consideration when consenting patients for HSCT.**

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## Introduction

Alopecia is a common side effect of chemotherapy.<sup>1,2</sup> Emotionally it is one of the most distressing side effects especially in women.<sup>3</sup> Fortunately, in most cases it is

reversible with hair regrowth in 3–6 months.<sup>1</sup> Chemotherapy-induced alopecia (CIA) most commonly affect scalp hair since these are most rapidly growing but other body hair may be involved including axillary, pubic hair, eye brows and eye lashes. Majority of times this alopecia is reversible though regrowth time may vary between 3 and 6 months.<sup>1</sup> New hair may have different characteristics than original hair in form of texture, color or curls.

Alopecia, usually temporary, is universally seen in hematopoietic SCT (HSCT) setting after myeloablative chemotherapy. However, irreversible alopecia has been previously described in six different reports, but its real incidence has not been well studied.<sup>4–9</sup> Multiple causes have been described, although it has been mainly attributed to Bu-containing regimens. One report described permanent alopecia after Cy, thiotepea and carboplatin regimen.<sup>7</sup> Other potential causes for permanent alopecia include chronic GVHD (cGVHD) and cranial radiation.<sup>6</sup>

In this report, we describe six cases of permanent alopecia which, we had observed in our transplant center and compare our results to the already published reports in the medical literature.

## Patients and methods

This is a descriptive retrospective study, which was approved by the Institutional Board Review at the University of Florida under exempt status. A total of 760 transplants were performed at our institution during the period of 1997–2004. We identified six patients who experienced permanent Alopecia after high-dose chemotherapy (HDC) and hSCT. Permanent alopecia was defined as absence or incomplete hair re-growth at  $\geq 6$  months after transplant. These patients were identified from medical records and by questioning the faculty and nurse coordinators. Patients with chronic GVHD-related alopecia were excluded. We collected the following data: age, gender, ethnicity, hematologic diagnosis, disease status, time from transplant, conditioning regimen, type of alopecia, pretransplant chemotherapy or radiation, the presence of GVHD and its severity and any potentially related details from the social history such as previous employment and exposure to environmental chemicals. We also reviewed the previously published reports on permanent alopecia and compared it to our findings.

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## Results

Patient's characteristics are summarized in Table 1. There were two males and four females. Median age at transplant was 45 years (range, 37–65). Three patients were Caucasian and three were African-American. Diagnosis included multiple myeloma (MM) ( $n=3$ ), CML ( $n=1$ ), AML ( $n=1$ ) and Ewing's Sarcoma ( $n=1$ ). Four of these patients received autologous peripheral blood SCT (ASCT) and one of them with MM received tandem transplants. One patient underwent matched sibling transplant while one patient received unrelated umbilical cord blood (UCB) transplant. All these patients were evaluated and treated according to our Institution guidelines. Conditioning regimens included Bu and Cy in three patients that were administered as follows: Bu 0.75 mg/kg/dose orally every 6 h for 16 doses days -7 to -4 and Cy 60 mg/kg i.v. daily on days -3,-2; Bu, Cy and etoposide (BuCyVP16) in two patients and were administered as above in addition to VP-16 at 10 mg/kg i.v. daily on days -4 to -2. One of these patients received a second autograft after Cy 6000 mg/m<sup>2</sup> continuous infusion over 96 h and 600 cGy TBI in four fractions over 2 days. The sixth patient received CyVP16 and TBI as follows: Cy 1800 mg/m<sup>2</sup> i.v. daily and VP16 900 mg/m<sup>2</sup> i.v. daily both given on days -5 and -4 and TBI 1200 cGy in six fractions on days -3 to -1. Chemotherapy doses were calculated based on the lesser of ideal or actual body weight. Median follow-up of these patients was 30 months (range, 17–58 months). Current disease status of these patients include CR in three, very good partial remission (VGPR) in two and PR in one MM patients. The patient who received UCB transplant with GVHD prophylaxis using standard Tacrolimus and low-dose methotrexate (5 mg/m<sup>2</sup> days 1, 3, 6 and 11 after transplant) did not develop acute or cGVHD. All immunosuppression was stopped at 3 months. Another patient after sibling T-cell depleted allogeneic PBSCT with Cs developed limited cutaneous cGVHD that required minimal immunosuppressive therapy including 1 mg/kg prednisone with quick taper and substituting with Mycophenolate Mofetil (Cellcept) due to undesirable emotional side effects of the prednisone. The patient was off all immunosuppression within 6 months after transplant. All these patients developed alopecia soon after conditioning chemotherapy which turned out to be permanent.

Three of these patients had complete scalp alopecia (alopecia totalis) and one of these patients was a male and had no facial hair growth as well. Two female patients had

alopecia areata (patchy alopecia). One other female patient had incomplete scalp alopecia. None of these patients had any previous problem with alopecia or history of chemicals use. Using other acceptable ways to measure alopecia such as the National Cancer Institute Common Toxicity Criteria Version 2 (grades 0–2), we determined that one of these patients had grade 1 alopecia while the other five had grade 2. Assessment of hair loss in these patients was also retrospectively assessed using the World Health Organization (WHO) criteria for alopecia.<sup>10,11</sup> These criteria are as follows: grade 0, no significant hair loss; grade 1, minor hair loss not requiring a wig; grade 2, moderate hair loss but not requiring a wig; grade 3, severe hair loss requiring a wig; grade 4, total alopecia. We used description of the alopecia as documented in the medical records. We determined that one patient had grade 2, 4 patients had grade 3, and one male patient with grade 4.

The endocrine status of these patients was determined to our best ability by reviewing existing laboratory tests and notes. All young female patients became menopausal after transplant, and patient A5 had untreated hypothyroidism (as evidenced by elevated thyroid stimulating hormone (TSH) at 54.5 mIU/l) due to radioactive iodine given to her 15 years ago for hyperthyroidism. On the contrary the two males had sexual problems after autografts such as lack of desire and weak erection, but testosterone levels, both free and total, were normal. Thyroid tests were available on four other patients before or after the transplant and were normal.

The results of reviewing the published literature are summarized in Table 2 and discussed below.

## Discussion

Alopecia is a well-described toxicity of HDC and is universally seen after HDC but usually it is reversible. Still it is associated with considerable emotional and psychological trauma. Psychological effects of alopecia are understudied but it is one of the prime concerns among patients receiving chemotherapy especially women.<sup>12,13</sup> In one study, 8% women were found to be at risk of avoiding treatment secondary to fear of baldness.<sup>14</sup>

Irreversible/permanent alopecia has been described but its exact incidence remains unknown<sup>4–9</sup> and its mechanism is not well studied. It is mostly reported after high-dose Bu-containing regimens. Ljungman *et al.*<sup>8</sup> reported the largest series of patients with permanent alopecia where they

**Table 1** Characteristics of our patients experiencing permanent alopecia

Patient	Age	Sex	Race	Primary diagnosis	Conditioning regimen	Transplant type	Previous therapy	GVHD
A1	37	F	W	Ewing's sarcoma	CyVP16, TBI	ASCT	VP16, CY	No
A2 <sup>a</sup>	39	F	W	AML M4	BuCy	Allogeneic stem cell	Idarubicin, Ara-c	Yes
A3	51	M	AA	Multiple myeloma	BuCyVP16	ASCT	VAD	No
A4	55	M	W	Multiple myeloma	BuCyVP16; Cy TBI	Tandem ASCT	VAD	No
A5	65	F	AA	Multiple myeloma	BuCyVP16	ASCT	VAD	No
A6 <sup>a</sup>	40	F	AA	CML	BuCy	Umbilical cord stem cell	Gleevec, Idarubicin, Ara-c	No

Abbreviations: AA = African-American; Ara-c = cytarabine; ASCT = autologous stem cell transplant; VAD = vincristine, adriamycin and dexamethasone; VP16 = etoposide; W = white.

<sup>a</sup>Patients had irreversible alopecia areata.

**Table 2** Characteristics of patients experiencing permanent alopecia associated with HSCT in six previously reported studies

Study, first author	No. of patients	Age (median)	Conditioning regimen	Transplant type	GVHD association
Ljungman P	19	36	BuCy	Allo, ASCT	No
Vowels M	9	11	BuCy, CyTBI, BuCYMel	Allo(8), ASCT(1)	Yes
de Jonge ME	8	43	CTC	ASCT	No
Baker BW	6	NA	BuCy	Allo(2), ASCT(4)	No
Tosti A	2	26	BuCy, BuMel	ASCT	No
Tran D	1	23	BuCy	Allo	Yes
Current study	6	45	BuCy, BuCyVP16, CyTBI, CyVP16TBI	Allo, UCB, ASCT	No

Abbreviations: Allo = allogeneic stem cell transplant; ASCT = autologous stem cell transplant; CTC = cyclophosphamide thiotepa and carboplatin; Mel, melphalan; UBC = umbilical cord blood transplant; VP16 = etoposide.

Numbers in brackets indicate the number of the specific transplant types included in the series.

described 19 patients who developed permanent alopecia among 65 total patients studied who were transplanted after Bu-containing regimen and survived more than 6 months. They prospectively studied Bu concentration in correlation to permanent alopecia in these patients. They reported higher Bu concentration to be significantly associated with permanent alopecia; however, there was no clear threshold for Bu above which all patients will develop permanent alopecia. de Jonge *et al.*<sup>7</sup> reported a cohort of eight patients who developed permanent alopecia after Cy, thiotepa and carboplatin chemotherapy for conditioning before autologous transplant in patients with breast, ovarian or germ cell tumors. They reported increasing exposure to carboplatin and thiotepa was associated with an increasing degree of permanent hair loss. No such association was found for the exposure to Cy. Baker *et al.*<sup>5</sup> described six patients who received BuCy conditioning for BMT and experienced incomplete scalp hair re-growth 7–27 months following BMT. Pharmacokinetic variability as a result of bioavailability of oral Bu<sup>15</sup> may be contributing to this association of the drug with permanent alopecia. It will be interesting to see if the use of currently available intravenous Bu will still be associated with any permanent alopecia.

Our data show that permanent alopecia is a significant long-term side effect of HSCT and can be seen across the spectrum of diseases and transplant types. Although most of the previous reports described Bu to be the main drug associated with permanent alopecia, others<sup>7</sup> and our data suggest that permanent alopecia can be seen in non-Bu-containing regimens as well. Other factors which have been studied include presence of chronic GVHD, older age and previous cranial radiation therapy,<sup>6</sup> but in our cohort, patients with alopecia related to cGVHD were excluded. Other potential contributing factor to permanent alopecia after HDC may be endocrine dysfunction such hypothyroidism or hypogonadism. Existing hypothyroidism may have contributed to the alopecia in patient A5 in our series. However, endocrine dysfunction have been reported at higher incidence after SCT than permanent alopecia,<sup>16,17</sup> and therefore, unlikely to be the cause of significant alopecia similar to that described in our cases. Furthermore, alopecia as one of the late effects in children after HSCT is more likely to be blamed on Bu exposure than the frequent hormonal deficiencies in such patient population.<sup>18</sup>

It is our observation that many patients usually accept permanent alopecia as the price for cure and find ways to hide it unless they are questioned about it during follow-up clinic visits. This may be responsible for under estimation of the true incidence of permanent alopecia after HDC. It is also rarely discussed as one of the late effects of HSCT. The incidence in our institution would be 0.9% (6 out of 760 total patients) if we believe that we have identified all the patients with permanent alopecia. Our study should bring awareness to the problem so that more diligent examination of hair re-growth and documentation would help provide us with a more accurate incidence of this phenomenon.

CIA is one of the most emotionally charged side effects that cancer patients, especially women and children, have to endure. Multiple improvements in the treatment of the other side effects of chemotherapy have been developed and introduced successfully, while the development of CIA treatments has been lagging behind with no available effective therapy.<sup>19</sup> Wang *et al.*<sup>19</sup> nicely reviewed the different aspects of this problem. There are no approved preventative treatments for CIA in humans although several experimental and pharmacological approaches are under evaluation. Treatments to prevent or minimize alopecia include physical means such as scalp tourniquets (no longer used due to patient discomfort)<sup>20</sup> and scalp hypothermia,<sup>11,21</sup> and pharmacologic means that include topical vitamin D<sub>3</sub> analogue,<sup>22</sup> ASI01,<sup>23</sup> Minoxidil<sup>24–26</sup> or Cs<sup>27,28</sup> and other experimental drugs.<sup>19</sup> Most of these treatments have either limited or very selective activity or have not been tested in humans yet.

Our findings presented here have medico legal and psychosocial implications that need to be taken into consideration when consenting patients for HSCT. We have observed that informed consents from our studies or studies from cooperative groups conducted in our institution uniformly mention alopecia or reversible alopecia as one of the potential side effects, but none mentions permanent alopecia as one of the potential long-term complications. We have also noticed that this is the first report from a Medical Institution in North America that describes the problem while all previous six reports were from other continents. Although, it may seem reasonable to any physician or patient that the risk of permanent alopecia is outweighed by the potential benefit of HSCT, the ultimate decision is still by the patient. Some patients

who fear permanent alopecia may select alternate regimen with less favorable outcomes.<sup>29</sup> Providing them with the most comprehensive array of complications and toxicities to expect from therapy is our ethical and legal responsibility. We hope that our report may also encourage more research into the issue that will lead to treatments aiming at preventing such complication and dealing with its consequences. Patients should be counseled on how to deal with such image problem psychologically and seek the help of available support groups.

In summary, we believe that our study brings renewed awareness to a significant patient issue of permanent alopecia after HDC, and that further studies are needed to assess actual incidence of permanent alopecia after HSCT, to identify compounding factors associated with higher risk, and to design treatments to alleviate the physical and psychological long-term effects of such complication.

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