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Occurrence of Granulocytic Sarcoma After Allogenic Hematopoietic Stem Cell Transplantation

Pamukcuoglu M[1*], Pepeler MS[1], Ulkuden B[1], Gocun PU[2], Akyurek N[2], Aki SZ[1] and Sucak GT[1]

[1]Department of Hematology, Faculty of Medicine, Gazi University, Ankara, Turkey.

[2]Department of Pathology, Faculty of Medicine, Gazi University, Ankara, Turkey.

[*]Correspondence:
Merve Pamukçuoğlu, Department of Hematology, Ankara Numune Education and Research Hospital, Ankara, Turkey, Ankara, Turkey
Tel: 00 90 (505) 2458374, E-mail: drmpamuk@yahoo.com.

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Stem cells, Myeloid sarcoma, Patients.

Introduction
Myeloid sarcoma (MS), chloroma and granulositic sarcoma (GS) are all used to describe tumours which proliferate as a result of blasts in the extramedullary parts of the body [1]. Chloroma took its'name from the colour of the tumour [1,2]. It is usually green [1] Granulositic sarcoma occurs in Myelodysplastic syndrome (MDS), Chronic Myelocyter Leukemia (CML) and in 2-8% of AML patients, at a younger age [3,4]. It usually seen at 1-81 years of age and the size of GS can be from 2 to 20 cm [1]. Compression symptoms of pain and bleeding were as a result of the mass effect of GS. We determined the localizing of mass by Positron emission tomography with fluoro-D-glucose integrated with computed tomography (FDG-PET CT) [1,5]. Mass is of containing immature granulocytic series cells and also pathological examination is very difficult [6]. There are three pathologic groups. Group-1 predominantly contains myeloblasts which are poorly differentiated. Group -2 contains moderately differentiated myeloblasts and promyelosites. Promyelosites are dominant. Group-3 contains an equal value of well matured promyelosites and myelosites [4]. Mitotic activity is very different in GS. Kİ-67/MIB1 score was always high (50%-95%) [1,7]. When we take a biopsy from a different part of the tumor mitotic activity can change [4]. Single body macrophage demonstrates faster tumor cell turnover [4], but GS does not always have uniform structure nor uniform chromosomal anomalies [4,7].

GS occuring after Allogenic Stem Cell Transplantation (ASCT) has been an important issue in recent years [1]. Some parts of our body can escape from the stem cell protective effect against tumor cells. Treatment of GS which occurs after stem cell trasplantation (SCT) is very difficult for clinicians [4]. We need further studies to understand the occuring mechanism of GS to find a better choice of treatment.

Materials and Methods
Patients
A total of 120 AML patients, who were treated with allogenic stem cell transplantation (ASCT), were enrolled in this study. We studied two diagnostic subgroups which included denova AML and secondary AML. Diagnosis of AML was made according to the World Health Organization (WHO) 2001 criteria and French-American-British (FAB) criteria. Risk stratification in AML was used to estimate sitogenetic findings, age, white blood cell count, minimal residual disease (MRD) and denova or secondary subtypes of AML. The risk assessment of patients was classified as low, intermediate and higher risk. We also used the European Bone Marrow Transplantation Risk Score (EBMT) and Hematopoetic Cell Transplantation-Comorbidity Index (HCT-CI/SORROR) risk stratification in pre-transplant AML patients. According to the Eastern Cooperative Oncology Group (ECOG), patients were divided into two groups. In the first group (group-1) patients had ECOG-0 and ECOG-1; in the second group (group-2) patients had ECOG-2, ECOG-3 and ECOG-4. There were 108 patients in group-1 (90%) and 12 (10%) patients in group-2. We tried to determine the extramedullary disease (Granulocytic Sarcoma) at the relapse. We try to examine the factors that affect the extramedullary relapse (EMR) and anti-leukemic effect of graft-versus-host disease (GVHD).

Statistical Analyses
SPSS 15 statistical program was used. Patients characteristics were calculated with descriptive statistics. We used chi-square test for categorical values while Mann Whitney U test was used for

non-categorical values. Cox-regression analysis was also used. P < 0,05 was considered to be of significant value.

Results

General Charateristics

One hundred and twenty patients were included in this study. Seventhy (58.3%) of the total 120 patients were male and 50 (41.7%) were female. The median age of the patients was 38 years (min-max range:18-64 years). One hundred (83.3%) patients had denova AML, 17 (14.2%) had secondary AML, Five (4.2%) out of the total 120 patients were considered low risk, 25 (20.8%) patients had intermediate risk and 87 (72.5%) patients had higher risk. 3 (2.5%) patients' risk was unknown at the time of diagnosis. Ninethy (70%) of the patients were in remission following the first remission induction chemotherapy. Only 1 patient had allogenic stem cell transplantation (ASCT) under the progressive disease. According to the European Bone Marrow Transplantation (EBMT) Risk Score; 59 (49.2%) patients had >2 risk level, 61 (50.94%) patients had ≤ 2 risk level prior to ASCT. According to the Sorror risk score; 106 (88.3%) patients had ≤ 2 risk score, 14 (11.7%) patients had >2 risk score prior to ASCT.

One hundred and eight (90%) patients had a full-match related donor, three (2.5%) patients had a full-match relative donor, 7 (5.8%) patients had a full-match unrelated donor, 2 (1.7%) patients had non-full-match sibling donors. 111 (92.5%) patients had 10/10 HLA match donors, 6 (5%) patients had a 9/10 HLA match donor, 3 (2.5%) patients had a 8/10 HLA match donor. Peripheral stem cell was used in 118 (98.3%) patients and bone marrow stem cell was used in only 2 (1.7%) patients. The median count of CD34+ cells was $4x10^6$ (min-max: $1.26x10^6$-$8.20 x10^6$).

One hundred and four (86.7%) patients had myeloablative region, 16 (13.3%) patients had non-myeloablative region prior to ASCT and only 4 patients had total body irradation (TBI).

Following the ASCT 77 (64.2%) patients had Greft Versus Host Disease (GVHD) while 43 (35,8%) patients had no GVHD. Out of 77 patients 17 patients had acute GVHD, 47 patients had chronic GVHD and 7 patients had both acute and chronic GVHD, 1 patient had hyperacute GVHD, 7 patients had acute and chronic GVHD, 3 patients had hyperacute and acute GVHD, 2 patients had acute, hyperacute and chronic GVHD. For the prophylactic treatment of GVHD; methtraxate and cyclosporin were administered to 112 (93.3%) patients, the other 8 (6.7%) patients receiving cyclosporin and micofenalat mofelit (MMF).

Variables		Number (N)	Percentage (%)
		N 120	100 %
Gender	Male	70	58.3
	Female	50	41.7
Subtype of AML	Denova	103	85.9
	Secondary	17	14.2
Risk Score	Low	5	4.2
	Intermediate	25	20.8
	Higher	87	72.5
	Unknown	3	2.5
ECOG	Group-1	108	90
	Group-2	12	10
EBMT	≤ 2	61	50.94
	> 2	59	49.06
SORROR	≤ 2	106	88.3
	> 2	14	11.7
Donor	Full-match related	108	90
	Full-match relative	3	2.5
	Full-match-non- relative	7	5.8
	Non-full-match sublings	2	1.7
Stem cell origin	Peripheral	118	98.3
	Bone marrow	2	1.7
Treatment region	Myeloablative	104	86.7
	Non-myeloablative	16	13.3
GVHD	Positive	77	64.2
	Negative	43	35.8
GVHD prophylacsi	CSA and MTX	112	93.3
	CSA and MMF	8	6.7
Relaps Positive		40	33.3
Negative		80	66.7
Loss of Chimerism	Positive	16	13.6
	Negative	102	86.4
İmmunosuppressive Treatment	Positive	32	26.7
	Negative	86	71.7
DLI	Positive	22	18.3
	Negative	98	81.7

Table 1: General Characteristics of Patients.

N: Number of patients, %: Percentage of patients, GS: Granulositic Sarcom, ECOG: Eastern Cooperative Oncology Group, GS: Granulocytic Sarcoma, CNS: Central Nervous System, Group-1: ECOG-0 and ECOG-1; Group-2; ECOG-2, ECOG-3 and ECOG-4. EBMT: European Bone Marrow Transplantation Risk Score, DLI: Donor Lymphocyte Infiltration, GVHD: Graft Versus Host Disease.

Extramedullary Relaps

Post-transplant relapse was seen in 39 (33.3%) patients; 31 (25.8%) of these 39 patients had bone marrow relapse, 6 (5%) had extramedullary relapse and 2 (1.7%) had both extramedullary and bone marrow relapse. Eightysix (71.7%) out of 120 patients had immunosuppressive treatment and 16 (13.3%) patients had lost their chimerism at the time of relapse. Of the 6 extramedullary relapse patients two had periorbital soft tissue relapse, 1 had breast soft tissue relapse, 2 had paragingival soft tissue relapse, 1 had lumbosacral and sternal soft tissue relapse, 1 had submandibular relapse.

The median age of this 8 patients were 26 years-old (min-max: 20-44). One of the 8 patients risk had low risk, 6 of them had

high and one of them had unknown at the initial. Three of the 8 patients were AML M1, 2 of the 8 patients was AML-M0, 3 of the 8 patients were AML-M2.

EMR relaps duration after the ASCT was median 685 days (min-max: 30-6935 days). Leukemia relaps duration of 31 patients after ASCT was median 1070 days (min-max: 29-1400 days). Four of the eight patients had immunesupresive treatment when EMR was occured. All of the EMR patients treated with a myeloablative treatment. 5 of the 8 patients treated with a peroral busulfan treatment, 2 of them treated with intravenouse busulfan treatment and 1 of them was not treated with busulfan.

Donor lymphocyte infusion (DLI) treatment was given to 22 (18.3%) patients after relaps. All of the eight patients had donor lymphosit infusion (DLI) treatment after the relaps and also discontinue of the immunesupresive treatment. Six (75%) patients treated with 1 bagage of DLI, 2 (25%) patients treated with 2 bagage of DLI. Five (62.5%) patients had remission, 3 (37.5%) patients had not remisssion after the DLI treatment. Four (50%) of the 8 patients had GVHD after the DLI treatment. Six (75%) of the 8 patients had complete remission, the other 2 patients treated with chemoterapy again, none of the patients had second stem cell transplantation.

Age	Median age: 26 (min-max: 20-44)
Risk	Low: 1 patient High: 6 patients Unknown: 1 patient
Subtype of AML	AML M0: 2 patient AML M1: 3 patients AML M2: 3 patients
Duration of Relaps	685 days (min-max:30-6935)
EMR patients	Only EMR: 6 patients EMR and BMR: 2 patients
Occuring places of EMR	Periobital soft tissuea:3 patients Breast soft tissuea: 1 patient Paragingival soft tissuea: 2 patients Lumbasacral and sternal soft tissuea: 1 patient Submandibular soft tissuea: 1 patient
Immunsupresive Treatment	4/8 patients
Busulfan Treatment	7/8 patients
DLI	8/8 patients
GVHD after DLI	4/8 patients
Responce of Treatment	CR: 6/8 patients Non-CR: 2/8 patients

Table 2: General Characteristics of EMR Patients.

AML: Acute Myeloid Leukemia, GS: Granulocytic Sarcom, EMR: Extramedullary Relaps, BMR: Bone Marrow Relaps, DLI: Donor Lymphosit Infusion, GVHD: Graft Versus Host Disesea, CR: Complete Remission.

The gender, AML subtype (denova or secondary), risk of disesea at the time of diagnosis, ECOG, the number of induction chemotherapy treatments, CD34+ infusion cell counts, TBI treatment, the EBMT and Sorror risk scores and GVHD did not affect extramedullary relapse ($p>0.05$). However loss of chimerisms did have an effect on extramedullary relapse ($p<0.05$).

Discussion

Donor lymphocyte infusion (DLI) after SCT has a protective effect on bone marrow relapse but unfortunately has a less protective effect on EMR [8,9]. T cells may not reach EM sites and the immunological and repaired effect of T cells does not occur [8]. There is a lot of immunological escape mechanism in the extramedullary site of the body; for example there is down regulation of the FAS antigen and induction of FAS ligand expression [8]. Some parts of our body can escape the anti-leukemic effect of DLI or stem cell [8]. In addition, EMR may be caused as a result of the SCT partial loss of chromosome 6p [10]. One way in which EMR occurs is the traffic of T cells and NK cells. NK cells and T cells were higher in BM than in extramedullary tissue. Inflammations of extramedullary tissue and CD56 antigens had an important effect on the relapse. The GVL effect occurs in BM. This caused an inflammation of BM and changed the traffic of T cells. This protected BM rather than EM tissue . CD56 antigens were seen on NK cells. Some of the tissue had far more NK cells than other parts, such as neural tissuea, gut, pancreas, thyroid gland, adrenal gland, testes, ovary, visceral smooth muscle and cardiac muscle. As a result of these CD56 cells, tumour cells were homing this tissue and EMR occurred [5].

Isolated GS was very rarely seen [11]. The skin, lymph node, dura, soft palate, nasopharynx, orbit, testes, brain, salivary gland, anterior mediastinum, vagina, breast and skin, gynecological tract, pleura, chest wall, retroperitoneum and small intestine, pancreas were the areas of the body where it was seen to occur [4,6,12-15]. Granulositic sarcoma sometimes occurred only in a diffuse infiltration of skin without mass and bone marrow leukemia [2]. The most common sites of the body where this occurred were the periosteum, soft tissue, bone, lymph node and skin [6].

In recent years, extramedullary relapse (EMR) has been a very common topic of discussion after transplantation [1]. ASCT has been used in both acute lymphobastic lymphoma (ALL) and AML treatment [8]. We know that the anti-leukemic effect of GVHD protects patients from disease relapse especially as far as bone marrow is concerned [8]. The anti-leukemic effect of GVHD on the extramedullary site was less [1,8]. As in literature, we did not find any significant relationship between GVHD and non-GVHD patients with EMR.

After the ASCT, the duration of the relapse was longer in EMR than in cases of bone marrow relapse, especially 4-50 months after transplantation [1,5] and also EMR were more frequently seen after ASCT than following chemotherapy treatment and authologeous stem cell transplantation [5,8,9]. In this study we had 8 patients in whom GS came about after SCT and the relapse duration ranges of these patients varied from 1 to 24 months.

EMR was seen more commonly if a patient had AML M4-M5, advanced disease (higher risk) or had unfavorable cytogenetics

[5]. In our study, those patients who relapsed with EMR after SCT were all of a younger age (20-44 years old). 3 of them had higher risk at the time of diagnosis just as in other literature. In contrast, extra medullary relapsed patients were usually diagnosed AML-1 and AML-2.

Only one EMR patient was treated with total body irrigation (TBI) pretransplant regimen. In our study, the remaining patients were treated with busulfan pretransplant regimen in contrast to other literature. We know that EMR was seen less in busulfan based condition than in TBI [5]. Especially acute or chronic GVHD has been observed with EMR patients just as in our own study [8].

GS has no standard treatment and usually worsens as a result of treatment [1,4,7,11,16,17]. Early diagnosis and treatment of the disease is very important [3]. The best means of treatment is still chemo-radiotherapy [18]. We treated all GS with cytarabine based chemotherapy in the same way as AML [5,12] and local radiotherapy [1]. Stem cell transplantation was a standard treatment for isolated granulocytic sarcoma patients but there was no such kind of therapy for relapsed GS after stem cell transplantation [19,20].

Relapsed GS after SCT can depend on the host or donor source [13]. This can be understood from the chimerism of patients. If there was no loss of chimerism, it was shown that GS came from the donor stem cell [13]. However if there was loss of chimerism, it was shown that GS came from host source. There were also variable escape mechanism of the anti-leukemic effect of the stem cell. The main result taken from this limited number of patients is loss of chimerism have affect on occuring GS (host or donor source GS) after stem cell transplantation. We need to save patient's chimerism after stem cell transplantation protecting from EMR. There are a lot of factors and immunological mechanisms which may affect the occurrence of GS after SCT. If we can determine these factors and immunological mechanisms then we will be able to easily prevent the occurrence of GS by providing effective treatment against such mechanisms.

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