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Role of large unstained cells in predicting successful stem cell collection in autologous stem cell transplantation

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ABSTRACT

Introduction: Sufficient stem cell collection is mandatory for Autologous stem cell transplantation (ASCT). Peripheral CD34+ stem CD34 + stem cell counting by flow cytometry is the gold standard method in both the predicting and timing of successful stem cell collection. Large unstained cells (LUC) are large peroxidase-negative cells that are displayed on certain automatic cell counters and present large lymphocytes, virocytes, blasts, abnormal cells and hematopoietic stem cells. In this study, we evaluated the role of LUC parameters in the timing and prediction of successful stem cell collection.

Methods: Patients with a diagnosis of multiple myeloma, lymphoma and testis tumor who proceed to ASCT were included in this study. Preapheresis LUC parameters were analyzed with Siemens ADVIA® 2120i system., Kruskal Wallis, Mann-Whitney U, Spearman Rho and receiver–operator curve (ROC) tests were used for analyses.

Results: Ninety patients were evaluated. Peripheral CD34 + cell count was positively correlated with both LUC count ($p = 0014$) and LUC percentage ($p = 0{,}01$). LUC percentage in peripheral blood was positively correlated with mobilized stem cell count in the yield ($p = 0.003$). We found a LUC count of $> 0.485 \times 10^9$/L as a cut-off value for detecting $> 20 \times 10^6$/L CD34 +cells in the peripheral blood with a sensitivity of 64.6% and specificity of 75%. We defined $> 2.15\%$ as a cut-off value for LUC percentage to collect $> 5 \times 10^6$/kg of stem cells with a sensitivity of 64% and specificity of 63%. Additionally, total nucleated cell (TNC) count was negatively correlated with LUC percentage ($p = 0.014$) and positively correlated with LUC count ($p = 0.001$).

Conclusion: LUC parameters are readily available, simple and cheap tools that can be useful in both timing of CD34 count by flow cytometry in peripheral blood and in the prediction of successful mobilization. LUCs can also be an indicator of graft composition.

1. Introduction

High-dose chemotherapy combined with autologous stem cell transplantation (ASCT) is the treatment of choice for multiple myeloma (MM), relapsed lymphomas and solid tumors [1,2]. Sufficient hematopoietic stem cell collection before high dose chemotherapy is mandatory for this treatment. Although stem cells can be collected from bone marrow by repeated aspiration of the pelvic crest, the most preferred method is collecting from peripheral blood by leukapheresis after mobilization of stem cells as it provides less stress and faster engraftment [3]. G-CSF alone, or in combination with chemotherapy, is commonly used for mobilization of stem cells from bone marrow to peripheral blood. Plerixafor, a CXCR4 chemokine receptor antagonist, can be added to these mobilization regimens to increase stem cell mobilization, particularly in poor mobilizers [4].

Although a minimum dose of 2×10^6/kg CD34 + peripheral stem cell collection is necessary for successful engraftment, the optimal amount is 4–5 $\times 10^6$/kg for prompt engraftment [5,6]. The single most predictive parameter for successful mobilization is the preapheresis peripheral CD34 + stem cell count by flow cytometry [7,8]. Levels for exhibiting at least 20×10^6/L CD34 +cells in the peripheral blood are sufficient to initiate peripheral stem cell collection. However, peripheral CD34 + stem cell counting by flow cytometry is still a complex, expensive and time-consuming procedure that requires a well-established laboratory and experienced stuff.

In addition to the given CD34 + cell dose, it has been reported that

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the composition of the yield can influence transplantation outcomes such as overall survival (OS), progression-free survival (PFS), hematologic recovery and transfusion reactions due to stem cell infusion in patients undergoing ASCT [9–11]. The prognostic effect of total nucleated cell (TNC) dose of bone marrow grafts is especially well established in patients underwent allogeneic stem cell transplantation [12,13]. Also, it has been shown that TNC dose could be a predictor of transplant outcomes in peripheral blood allogeneic stem cell transplantation [14]. But the data about the role of TNC dose for peripheral ASCT is limited.

Large unstained cells (LUCs) are large peroxidase-negative cells that are automatically displayed on specific automatic cell counters as absolute number and percentage. They generally refer to large lymphocytes and other atypical cells such as virocytes, blasts, and hematopoietic stem cells [15,16]. Their potential as a clinical parameter was evaluated in diagnosing viral infections, immune activation of HIV infection, diagnosis of acute leukemias and prediction of neutropenia phase of cancer patients [16–19]. But there is limited data concerning LUCs as a parameter in stem cell mobilization.

In this study, we investigated whether the LUCs could predict the initiation of the apheresis procedure correlating with the preapheresis CD34 + stem cell count, and whether LUCs could predict the collection success with the aim of targeting $\geq 5 \times 10^6$/kg collected CD34 + stem cells. We also evaluated the relationship between LUCs and composition of the yield.

2. Materials and methods

2.1. Patients

For this study, patients who were 18 years and above, and who underwent ASCT were retrospectively evaluated. Patients who had a diagnosis of multiple myeloma, relapsed lymphoma and refractory germ cell testicular tumor were included in this study. This study was approved by the ethical committee of our institute.

2.2. Study parameters

In addition to patients' characteristics, preapheresis peripheral white blood cell counts (WBC), LUC counts, and peripheral CD34 + cell counts were evaluated. Yield's TNC counts, mononuclear cell counts (MNC), leukocyte counts and CD34 + cell counts were also evaluated. Preapheresis complete blood counts (CBC), including number and percentage of LUCs, were analyzed with Siemens ADVIA® 2120i system. Preapheresis peripheral CD34 + stem cells, collected CD34 + stem cells, and TNC and MNC numbers were counted in the "Navios" Flow Cytometer instrument (3 Laser, 10 Color, Beckman Coulter, Miami USA) by using Stem Kit (Beckman Coulter, USA).

2.3. Statistical analyses

Spearman's Rho test was used to analyze the correlation of LUCs with peripheral and collected CD34 + stem cell count, TNC count and MNC count. Kruskal Wallis and Mann-Whitney U tests were used to compare parameters within underlying diseases and mobilization protocols. Receiver–operator curve (ROC) analysis and calculation of area under the curve (AUC) were used to analyze the discrimination ability of LUC parameters for both detecting $> 20 \times 10^6$/L CD34 +cells in the peripheral blood and collecting $> 5 \times 10^6$/kg stem cells. A p-value of < 0.05 was considered statistically significant with a 95% confidence interval.

3. Results

Ninety patients were evaluated in this study. Median age was 56 (20−77). Fifty-six (62.2%) patients were male and 34 (37.8%) were female. Sixty-eight patients (75.6%) had multiple myeloma, 19 patients (21.2%) had lymphoma and 3 (3.3%) patients had testis tumor. The stem cell mobilization protocol was G-CSF alone in 60 patients (66.7%), high-dose chemotherapy plus G-CSF in 23 patients (25.6%) and plerixafor plus G-CSF in 7 patients (7.8%). Patients' characteristics, LUC parameters, and peripheral blood and yield's CD34 + cell counts are shown in Table 1.

Median preapheresis peripheral CD34 + cell count was 48×10^6/L (range: 9–766 $\times 10^6$/L). LUC count was positively correlated with peripheral CD34 + cell count (p = 0014). There was also a positive correlation between LUC percentage and peripheral CD34 + cell count (p = 0,01). LUC count ROC area under curve for detect $> 20 \times 10^6$/L CD34 +cells in the peripheral blood was 0.72. The cut-off value of LUC count was $> 0.485 \times 10^9$/L to detect $> 20 \times 10^6$/L CD34 +cells in the peripheral blood with a sensitivity and specificity of 64.6% and 75%, respectively. LUC percentage ROC area under curve for detect $> 20 \times 10^6$/L CD34 +cells in the peripheral blood was 0.452. The cut-off value of LUC percentage was 2.05% to detect $> 20 \times 10^6$/L CD34 +cells in the peripheral blood with a sensitivity and specificity of 48.8% and 50%, respectively.

The median collected CD34 + cell count in the yield was $4{,}58 \times 10^6$/kg (range 0.51–32.76) and median CD34 + cell concentration in the yield was 809.5/μL (range 156– 12,261). There was no significant correlation between absolute LUC count and collected CD34 + cell count in the yield (p = 0.603), but LUC percentage was positively correlated with collected CD34 + cell count in the yield (p = 0001). Similarly, while the LUC count was not correlated with CD34 + cell concentration of the yield (p = 0.424), LUC percentage was positively correlated with CD34 + cell concentration of the yield (p = 0.001). LUC percentage ROC area under curve for collecting 5×10^6/kg of stem cells is 0.669 and the cut-off value of LUC percentage was > 2.15% to collect at least 5×10^6/kg of stem cells with a sensitivity of 64% and specificity of 63%.

Median preapheresis WBC count was 31,475/μL (range 2780–107,600). LUC count was positively correlated with preapheresis peripheral WBC count (p = 0001), while LUC percentage was negatively correlated with preapheresis peripheral WBC count (p = 0001). There was no significant correlation between preapheresis peripheral WBC and peripheral CD34 + stem cell count (p = 0.745). But, preapheresis peripheral WBC count was negatively correlated with both collected CD34 + cell count in the yield (p = 0.035) and CD34 + cell concentration of the yield (p = 0.033). Preapheresis platelet count was not correlated with both peripheral CD34 + cell count and collected CD34 + cell count of the yield. Preapheresis platelet count negatively correlated with LUC percentage (p = 0.001) and positively correlated with LUC count (p = 0.001).

Median WBC count of the yield was 176,500/μL (range 56,300–431,300). We observed that yield's WBC count was not

Table 1
Patient characteristic.

		Parameters (n (%) or median with min–max)
Age		56 (20–77)
Gender	Male	56 (62.9%)
	Female	34 (37.1%)
Diagnosis	Multiple Myeloma	68 (75.3%)
	Non-Hodgkin's Lymphoma	14 (15.7%)
	Hodgkin's Lymphoma	5 (35.6%)
	Testis Tumor	3 (3.4%)
Mobilizing Regimen	G-CSF	60 (84.3%)
	Chemotherapy plus G-CSF	23 (15.7%)
	Plerixafor plus G-CSF	7
Preapheresis Peripheral CD34 + Cell Count		48 (9–766)
Yield's CD34 + Cell Count		4.58 (0.51–32.76)
LUC %		2 (0.6–13.4)
LUC count (x10^9/L)		0.55 (0.13–6.68)

correlated with collected CD34 + cell count in the yield (p = 0.825), CD34 + cell concentration of the yield (p = 0.526), peripheral CD34 + cell count (p = 0.176) and LUC percentage (p = 0.102). But LUC count was positively correlated with yield's WBC count (p = 0.001).

Median TNC and MNC counts of the yield were 9.12 × 10^8/kg (range 2.64–34.5 ×10^8/kg) and 4.01 × 10^8/kg (range 0.9–10.62 ×10^8/kg), respectively. We found that TNC count was negatively correlated with LUC percentage (p = 0.014) and positively correlated with LUC count (p = 0.001). Similarly, MNC count was negatively correlated with LUC percentage (p = 0.001) and positively correlated with LUC count (p = 0.001). TNC count was not correlated with both preapheresis CD34 + cell count (p = 0.792) and collected CD34 + cell count of the yield (p = 0.949), but there was a negative correlation between TNC count and CD34 + cell concentration of the yield (p = 0.022). As for TNC, MNC count was not correlated both preapheresis peripheral CD34 + cell count (p = 0.479) and collected CD34 + cell count of the yield (p = 0.718) but there was a negative correlation between MNC count and CD34 + cell concentration of the yield (p = 0.042).

We were unable to find a significant correlation between age and CD34 + stem cell counts of both peripheral blood and yield. Other comparisons between underlying diseases and mobilization protocols in terms of LUC percentage, LUC count, peripheral CD34 + cell count, collected CD34 + cell count, peripheral WBC count, TNC count and MNC count were given in Tables 2 and 3.

4. Discussion

Large unstained cell values are routinely reported as a part of differential count in hemogram results by automated hematology analyzers like Siemens ADVIA 2120 and the Technicon H6000. Flow cytometry and cytochemistry were used in these analyzers to differentiate leukocytes according to size, complexity, and peroxidase staining. LUCs are peroxidase-negative cells and are not categorized in the subgroup of leukocytes like neutrophils, monocytes, eosinophils, lymphocytes, and basophils. Virally activated lymphocytes, plasma cells, hairy cells, pediatric lymphocytes and peroxidase-negative blasts are usually displayed as LUC in the differential count [20]. Because the hematopoietic progenitor cells are not stained with peroxidase, or stained very little, they are generally displayed as LUC in the differential count [21].

The meaning of LUC values are not well-known by the physicians [15]. LUCs were studied in various conditions as a predictive or a diagnostic tool, with significant results being reported in some of these studies. Most of these studies, however, were published nearly a decade ago. In one of these studies, Shin et al. evaluated LUC percentage in the differential diagnosis of varicella, Kaposi's varicelliform eruption (KVE), and disseminated herpes zoster (HZ). They reported that the mean percentage of LUC in varicella patients was significantly higher than the upper limit of normal reference range and it was increased compared to %LUC of both KVE and disseminated HZ patients. They found a cut-off value of 3.55% for LUC percentage to favor diagnosis of varicella with 71.01% sensitivity and 84.44% specificity. They also found that LUC percentage was significantly decreased with the clinical improvement [17]. Another instructive feature of LUCs was reported by Rabizadeh et al. They demonstrated that LUC percentage of > 5% helps detection of leukemias in childhood [22].

Another predictive feature of LUCs was reported by Vanker et al. They observed that LUC percentage was increased in untreated and asymptomatic HIV infected patients. Additionally, LUC percentage was correlated with markers of immune activation and CD4 counts. They hypothesized that LUC percentage may prove valuable in identifying HIV-infected patients at risk of accelerated disease progression [16].

Bononi et al. evaluated LUCs in the prediction of the nadir phase of chemotherapy. They assessed 22 patients and demonstrated that LUC percentage reaches higher values at the nadir phase of chemotherapy. The number of LUCs increases during the pre- and post-nadir phase. They also found that LUCs are correlated with blasts and CD34 cells in the pre-nadir and post-nadir phases, with CD31/CD41 + cells in the pre-nadir phase, and with CD2/CD56 + cells in the post-nadir phase. They observed a negative correlation between neutrophil counts and LUCs. They argued that LUCs may be a valuable tool in the prediction of the nadir phase in patients receiving chemotherapy [18]. Some findings in this study were concordant with ours. Negative correlation was observed between neutrophil counts and LUCs in this study, similar to our finding that was observed between preapheresis white blood cell counts and LUC percentage. They also reported positive correlations between peripheral CD34 + cells and both LUC count and percentage, like our study.

Tanaka et al. evaluated the correlation between peripheral CD34 + cell count and hematopoietic progenitor cell (HPC) count provided by immature myeloid information channel of automatic cell analyzers in 118 stem cell apheresis from 72 healthy donors and patients. They found a significant correlation between HPC count and CD34 + cell count. They also defined a HPC count of > 21/μL as a cut-off value to collect > 2.0 × 10^6/kg of CD34 + cells. Although they did not use the nomenclature LUC to define HPC, those cells could still be assumed as LUCs. The HPC count in this study is a parameter similar to the LUC count in our study, and their findings are likewise similar to ours [23].

We could find only one study that evaluated LUCs in the stem cell mobilization setting. Teipel et al. retrospectively reviewed data from 7216 unrelated healthy donors that were mobilized with G-CSF. They

Table 2
Comparison of parameters according to underlying disease.

	Diagnosis		p
	Multiple Myelom (median, min-max)	Lymphoma and Testis Tumor (median, min-max)	
Preapheresis Peripheral WBC Count (x10^3/μL)	37.105 (8.02–107.6)	17.535(2.78–67.01)	0.001
LUC Count (x10^3/μL)	0.59 (0.15–4.18)	0.475 (0.13–6.68)	0.074
LUC Percentage (%)	1.9 (0.6–9.9)	2.75 (0.8–13.4)	0.068
Peripheral Blood CD34 + Cell Count (x10^6/L)	50 (11–307)	41.5 (9–766)	0.825
Yield's CD34 + Cell Count (x10^6/kg)	4.305 (0.51–21.44)	7.11 (0.91–32.76)	0.143
MNC Count (x10^8/kg)	4.09 (0.9–10.62)	3.26 (1.02–10.35)	0.89
TNC Count (x10^8/kg)	9.33 (3.25–33.19)	6.45 (2.64–34.5)	0.138

Table 3
Comparison of parameters according to mobilization regimen.

Mobilization Regimen	G-CSF (median, min-max)	Chemotherapy plus G-CSF (median, min-max)	G-CSF plus Plerixafor (median, min-max)	p
Preapheresis Peripheral WBC Count (x10^3/μL)	38.58 (2.78–107.6)	13.87 (3.13–38.51)	37.41 (9.42–76.05)	< 0.001
LUC Count (x10^3/μL)	0.665 (0.21–6.68)	0.33 (0.13–1.29)	0.45 (0.14–1.08)	< 0.001
LUC Percentage (%)	1.85 (0.6–13.4)	3 (0.8–9.2)	1.4 (0.7–5.3)	0.003
Peripheral Blood CD34 + Cell Count (x10^6/L)	48 (11–246)	72 (13–766)	28 (9–100)	0.569
Yield's CD34 + Cell Count (x10^6/kg)	4.17 (0.51–21.44)	7.67 (1.16–32.76)	2.5 (0.91–8.27)	0.018
MNC Count (x10^8/kg)	4.445 (1.73–10.62)	2 (0.9–6.79)	4.56 (1.08–7.14)	< 0.001
TNC Count (x10^8/kg)	9.52 (2.79–34.5)	5.41 (4.03–19.19)	9.84 (2.64–12.01)	0.002

found a negative correlation between baseline LUC percentage in the beginning of mobilization regimen and peripheral CD34 + cell count after G-CSF mobilization [24]. In our study, we found a positive correlation between LUC percentage and peripheral CD34 + cell count after mobilization. We did not evaluate baseline LUC parameters. The fact that the negative correlation observed before mobilization in the study of Teipel et al. was observed as positive after mobilization in our study may be an indication that LUCs represent more mobilized stem cells.

While the absolute LUC count was positively correlated with peripheral CD34 + stem cell counts, there was not a significant correlation between absolute LUC count and collected CD34 + stem cell count in our study. This could be due to duration of apheresis. Because of patients' compliance and harvest goals, apheresis procedure could be terminated early, causing less to be collected than can actually be obtained, and this may affect the statistical analyses.

We found that both TNC and MNC counts of the yield were negatively correlated with LUC percentage and positively correlated with LUC count. Although the roles of TNC and MNC counts in allogeneic bone marrow stem cell transplantation are well known, there are very few studies on their effects in peripheral allogeneic stem cell transplantation, and almost no studies in ASCT. In one of these studies, Martin et al. evaluated the outcomes of 705 patients with hematologic malignancies who underwent reduced-intensity peripheral blood stem cell transplantation. They found that higher TNC dose was associated with improved overall survival and progression-free survival. Additionally, higher TNC dose was associated with a decreased relapse rate and an increased incidence of chronic graft-versus-host disease [14]. Upon reviewing the literature, we could not find a study that specifically evaluated the effect of TNC dose in ASCT, but there are some studies showing that graft composition may affect the outcome of transplantation [9,10].

One of the limitations of our study is that we were unable to identify exactly which cell group the LUCs were due to the retrospective nature of our study. Another limitation of our study is that we could not evaluate the effects of LUCs on engraftment because of insufficient data and relatively small sample size.

Peripheral CD34 + stem cell count by flow cytometry is the gold standard method for the timing of stem cell collection. But this method is time consuming and expensive, causes labor loss and requires experienced staff. It also takes at least two hours to get results. An average cost of stem cell counting by flow cytometry is about $130 per procedure, and repeated counts are needed primarily when chemotherapy was used for the mobilization [25]. Despite this, an average cost of hemogram is about $10 and it is already performed routinely during the mobilization period. Furthermore, the results could be obtained within minutes. So, LUC parameters might be helpful and assistive tools in the timing of peripheral CD34 + stem cell count by flow cytometry and they can reduce the number of unnecessary stem cell counts.

Here we showed that LUC parameters are positively correlated with peripheral and yield's CD34 + cell counts during peripheral stem cell mobilization. We additionally could define cut-off values for successful mobilization. Because LUC percentages and LUC counts are already existing parameters in hemogram analyses and do not require any additional cost, they can be a swift, functional, and simple tool in both the timing of peripheral CD34 + cell count and the prediction of successful mobilization.

Ethics approval and consent to participate

This study was approved by ethical committee of Firat University.

CRediT authorship contribution statement

Mustafa Merter: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Ugur Sahin**: Conceptualization. **Serhat Uysal**: Formal analysis. **Klara Dalva**: Conceptualization. **Meltem Kurt Yüksel**: Conceptualization, Investigation, Supervision.

Conflict of Interest

The authors declare no conflict of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon request.

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