IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

Association between Perceived Stress and Neutropenia in Patients with Leukemia under Chemotherapy

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Received: 17, Feb, 2021
Accepted: 25, Apr, 2021

ABSTRACT

Background: The most prominent part of the cellular response of the immune system is driven by neutrophils. These cells tend to decline following chemotherapy in patients with leukemia. Neutropenia is an influential factor in the prognosis of cancer patients. Stress reduces white blood cells (WBCs) and neutrophils are linked to an increased risk of infectious diseases after chemotherapy. We investigated the association between neutropenia and perceived stress following chemotherapy.

Materials and Methods: We performed a cross-sectional study on 60 patients with leukemia in a university hospital. Participants completed self-report measures, including the demographic data and perceived stress scale (PSS) questionnaire. We compared rates of neutropenia, as a measure of chemotherapy prognosis, 10 days after chemotherapy in different stress levels. Moreover, the number of patients with polymorphonuclear (PMN) under 1000/microliter was compared at different stress levels.

Results: We found that neutropenia is directly correlated with negative stress perception and inversely correlated with positive stress perception. These effects appear more prominent in patients with PMN under 1000/microliter as the number of these patients was significantly more in groups with higher negative stress and less in groups with higher positive stress scores.

Conclusion: It can be concluded that stress is correlated with neutropenia, and stress management in patients with leukemia will be accompanied by better recovery outcomes and reduced risk of infectious disease.

Keywords: Neutropenia; Chemotherapy; Stress perception

INTRODUCTION

Leukemia is caused by abnormal changes in bone marrow cells along with an increase in the count of abnormal blood cells and a reduction in normal blood cells. This cancer falls into two subgroups of myeloid origin and lymphocytic origin, which both could either have a slow progression pattern called chronic leukemia or be rapidly progressing called acute leukemia[4, 5].

This medical illness is accompanied by a profound and inescapable psychological trauma. Traumatic stress symptoms might be so severe that they would match acute stress disorder criteria[6].

The main treatment of acute leukemia is chemotherapy. Suffering caused by chemotherapy and chemotoxicity adds to the inevitable threat of dying related to the disease itself and this will jeopardize patients' psychological state. Chemotherapy is accompanied by several complications including anorexia and weight loss, hair loss and mouth sores, cardiotoxicity, neurotoxicity, and most importantly, hematologic complications. Neutropenia is among the most prominent hematologic complications[7, 8].

Neutrophils are sensitive to chemotherapy medications and reach their nadir 7-10 days after chemotherapy, making chemotherapy a leading cause of neutropenia[9,6]. Neutropenia is the most important risk factor for life-threatening infections. Recurrent neutropenia is an important factor in adjusting the dose of chemotherapy[7].

For a long time, it's been known that an individual's psychological state affects disease manifestation and progression[10,11]. The hypothalamic–pituitary–adrenal axis (HPA axis) was the first axis found to have immunosuppressive function[12, 13]. Later on, the sympathetic system showed both anti-inflammatory and proinflammatory effects[14].

Moreover, growth hormone, thyroid hormones, and other hormones were observed to play anti-inflammatory roles[15]. Finally, the parasympathetic system was added to the theory of stress-derived immunomodulation[16].

It should be noted that there is a reciprocal connection between the immune system and the brain, thereby, the immune system can operate on the brain and initiate the four downstream pathways described[17]. These connections are described as immune-neuro-endocrine feedback circuits[18].

Kazumasa et al. have shown that chronic psychological stress decreases neutrophil functions in elderly men[20].

Donaldson et al. in a psychoneuroimmunological study examined the effects of visualization or mental imagery on immune system response, specifically on depressed white blood cell (WBC) count. They also showed that visualization is associated with an increase in WBC count in cancer, HIV, and other viral infections patients after 90 days [21].

It has known that the level of cancer acceptance is highly effective in the course of the disease [22]. It has been demonstrated that stress increases the risk of infectious disease in women with breast cancer under chemotherapy due to changes in immune function [22].

Thus, chronic psychological stress decreases immune function and can lead to an increased risk of cancer progression[22]. This immune-modulatory effect changes neutrophil counts[22].

While the nature of leukemia is predictable, close contact of the patient with the medical staff during chemotherapy periods provides an opportunity for preventive interventions to boost the immune system of patients[22].

In this paper, from a cross-sectional perspective, we intend to study the relationship between perceived stress and neutropenia along with leukopenia in leukemic patients who underwent chemotherapy.

MATERIALS AND METHODS

Participants

This is a cross-sectional study in which, 60 in-patients diagnosed with acute myeloid, lymphocytic (non-M3 AML) were recruited between June 2019 and November 2019 from the Imam Khomeini hospital, the major university hospital in Tehran, Iran. The diagnosis of AML is based on the infiltration of bone marrow or peripheral blood by ≥20 percent blasts that manifest characteristic morphologic, cytochemical, immunophenotypic, and cytogenetic/molecular features. In some cases, even with <20 percent infiltration of bone marrow or peripheral blood, AML can be diagnosed by the presence of myeloid sarcoma or specific chromosomal and/or molecular abnormalities. The patients underwent standard 7+3 induction regimen of Cytarabine: 100 to 200 mg/m2 daily as a continuous infusion for 7 days; Daunorubicin: 60 to 90 mg/m2 intravenous push on each of the first 3 days of treatment followed by consolidation regimen with HiDAC (high-dose cytarabine) 3,000 mg/m2 over 1 hour every 12 hours for 6 days (total of 12 doses).

A convenient sampling method was performed on the patients that met the inclusion criteria, and the sample size was calculated by a statistical consultant based on previous studies. The inclusion criteria were 1) no other infectious disease involvement during the study, 2) no drug intake except for routine chemotherapy medication prescribed by the specialist, 3) complete consciousness through the study, 4) all with neutropenia after chemotherapy. Patients without the above criteria were excluded .The level of consciousness and cognition was assessed by an expert. Participants in the study completed written personal consents. This study was approved by the Tehran University of Medical Sciences Ethics Committee. ANC less than 1000/microliter was considered as neutropenia. Eligible participants were competent to provide personal consent and complete demographic and stress questionnaire. We should note that two of our patients passed away during the study.

Measures

Sociodemographic variables including age, sex, and education were obtained from demographics questionnaire, and disease characteristics stress symptoms were assessed by the perceived stress scale (PSS) questionnaire before undergoing chemotherapy. PSS is a widely used psychological measure to appraise situations in an individual's life as stressful. It was designed in 1983 by Cohn et al[23]. This scale has 24 items each with 5 alternatives (0 = Never, 1 = Almost Never, 2 = Sometimes, 3 = Fairly Often, 4 = Very Often). PSS assesses the negative and positive perception of the stress subscale, which is significantly correlated with life events, depressive symptoms, enjoyment of health services, social anxiety, and low life satisfaction. It is a scale to assess the general experience of stress in different age groups[8]. Overall, PSS is an applicable questioner with acceptable psychometric properties.

Initial complete blood count (CBC) information before chemotherapy was registered. After chemotherapy, CBC results were followed, and data were recorded on the 10th day, the day with maximum reduction in neutrophil count, and on the same day, patients were asked to fill out the demographic data form and the PSS questionnaire (The standard "forward-backward" translation procedure was used to translate the PSS from English into Persian)[24].

Statistical analysis

Demographic information and other categorical variables were summarized using descriptive statistics, reported by raw data and relative abundance. The statistical analyses adjusted for age, gender, and type of leukemia (non-M3AML). Quantitative variables in this study were reported by mean and standard deviation. Based on the positive perceived stress (PPS) and negative perceived stress scores (NPS), patients were divided into three groups. The PPS groups were as follows: 1- equal or less than 12, 2- between 13 to 17, and 3- equal or greater than 17, and the NPS groups were divided this way: 1- equal or less than 10, 2- between 11 to 15 and 3- equal or greater than 15. Mean polymorphonuclear neutrophils (PMN) of patients were compared with a one-way ANOVA statistical test between groups, and pairwise comparison was performed by the Tukey test. The abundance of participants with PMN> 1000/microliter in different groups was compared with Chi-square or Fisher's exact test (in all tests, the level of significance was considered less than 5%).

RESULTS

Participant characteristics

The demographic information of patients was as follows: Of 60 leukemia patients under chemotherapy, there were 37 men and 23 women with a mean age of 31 years (17-44 years).

Multivariable analysis

We compared neutropenia between different groups of PPS and NPS. Mean neutropenia was 0.84/microliter with an 8.04 standard deviation and 64.76 variances. The mean of positive stress perception was 13.77 with a 5.15 standard deviation and 26.6 variances, while the mean of negative stress perception was 12.03 with 5.8 standard deviation and 33.8 variances. One-way ANOVA results showed that the mean of neutropenia was significantly different between positively perceived stress groups (p=0.002). Pairwise comparison manifested that this difference was due to the difference of mean in <12

and >17 groups (p=0.01). However, 13-17-scores did not vary significantly from other groups (p > 0.1). Neutropenia was also not similar to negatively perceived stress groups. Difference was between <10 and >15 groups (P=0.08), and 11-15 and >15 groups (p=0.06), but there was no significant difference between <10 and 11-15-scores (p=0.08). These results were adjusted for gender and education.

Table 1: Statistical indices, variance, standard deviation, and mean of NPS, PPS, and neutropenia

	Variance	Standard deviation	Mean
Negatively perceived stress	33.8	5.8	12.03
Positive perceived stress	26.6	5.15	13.77
Neutropenia	64.76	8.04	0.84/microl

Table 2: Statistical results based on ranking of groups with positive perceived stress and negative perceived stress and neutropenia

Positive perceived stress	**N**	**Mean±SD**
≤12	16	69.6(16) *
13-17	7	38.9(7) *
>17	3	15.8(3) *
Negative perceived stress		
10≤	1	5.3(1) **
11-15	8	38.1(8) **
>15	17	85.01(18) **
1.25 ± 0.57**	21	11-15
0.88 ± 0.57**	20	>15

*p <0.01; **p-value<0.001

Table 3: Statistical results based on the ranking of groups with positive perceived stress and negatively perceived stress in patients with PMN< 1000/microl

Positive perceived stress	**N**	**Percentage (n)**
69.6(16) *	16	≤12
38.9(7) *	7	13-17
15.8(3) *	3	>17
		Negative perceived stress
5.3(1) **	1	10≤
38.1(8) **	8	11-15
85.01(18) **	17	>15

*p <0.01; **p-value<0.001

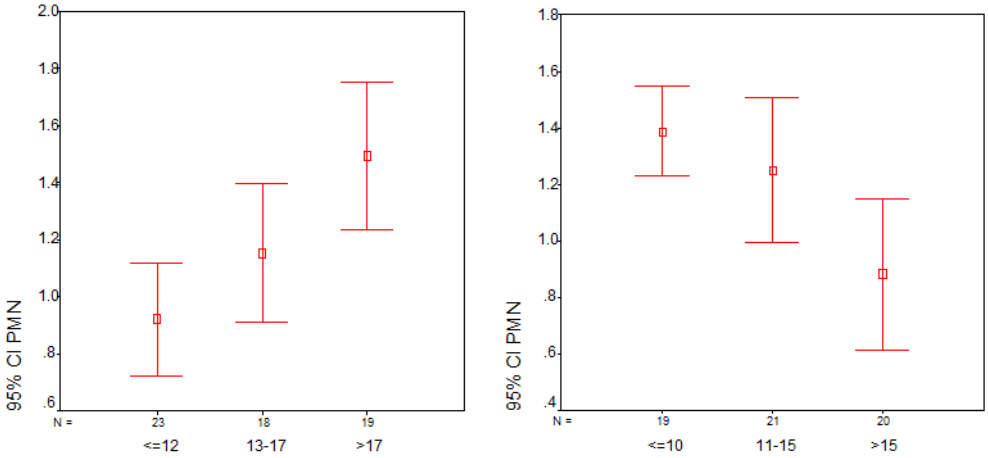

Figure 1. Mean and confidence interval of PMN count in three stress group

(Left Panel: pss, Right panel:nps)

DISCUSSION

Based on this cross-sectional study of newly diagnosed acute leukemic patients we can claim that perception of stress is correlated with neutropenia after chemotherapy. We showed that neutrophil count can be affected by both PPS and NPS. This will be more prominent when PMNs reach under 1000/microliter count.

Previously it was demonstrated that methotrexate-related neutropenia in rheumatoid arthritis (RA) patients is significantly related to lower scores in mini-mental state examination(as a scale of cognition) and higher scores on the Hospital Anxiety and Depression Scale. Moreover, a greater proportion of RA patients with neutropenia had probable dementia[28].

Considering the importance of chemotherapy in the treatment of acute leukemia, and the lack of alternative therapies, it would be essential to implement psychotherapy programs and psychological screening programs for these patients. To omit factors like unconsciousness that might disturb our interpretation of the results, we evaluated patients for their level of consciousness and cognition.

Until now, no study has targeted this aspect of chemotherapy-related neutropenia. The results of this study clearly show that patients with a higher negative stress perception background and more likely to developing neutropenia following chemotherapy. Accordingly, physicians should be cautious about severe infections when treating these patients.

One of our results was that patients with higher negative stress perception scores are more prone to having a PMN count under 1000/microliter. PMN's function in controlling bacterial and viral infection have been recognized for a long time. Solberg et al found that patients with the least number of PMN appear with staphylococcal, pneumococcal, and salmonella infections[30].

More recent studies have confirmed that PMN plays major role in HIV-1, lactobacillus, and many other infections[31, 32, 33]. Ali et al. showed that blood cultures of leukemia patients after treatment with decitabine regimen appeared positive with gram-positive bacteria, gram-negative bacteria, mixed and viruses in reducing order[34], which highlights our findings.

In a conclusion, patients' psychological status should be assessed, and additional therapy should be performed if needed for a better leukemia treatment outcome.

Studies on the role of stress and psychological status on the immune system have started to stand out. Chronic neutropenia can be developed by various pathophysiologies and a large variety of factors related to neutropenia that makes the classification almost impossible[35].

Previous studies found that chemotherapy-induced neutropenia did not show changes in the quality of life questionnaire (QOL) score at baseline and two weeks after chemotherapy[36]. Here, we observed that perception of stress is related to chemotherapy-induced neutropenia, thus it seems that the baseline psychological condition is affecting the changes in the immune system. In this study, we aimed to determine the importance of pathophysiology in the prognosis of chemotherapy, and the pathophysiology of this phenomenon was not examined among the leukemia patient population. Hence, future studies are required to investigate the underlying mechanisms of this phenomenon.

As mentioned earlier, two patients passed away in the course of our study. One was a 24-year-old girl with a high total stress score equal to 40 and NPS score equal to 28 (with a significant difference from average) and severe neutropenia equal to 0.3 who faced major health complications and died 20 days after chemotherapy. An interesting point is that the patient was not aware of her illness but her stress scores were very high. It could be interpreted that even the lack of knowledge of one's disease will not be effective in managing stress. However, this is merely a hypothesis that requires to be investigated. The other patient was a 19-year-old girl who also had higher total stress and NPS scores than the average.

The main limitation is the *cross-sectional design* of this *research, which does not allow researchers to establish causality*. The cognitive status of the

patients was assessed by expert opinion, mainly to clarify the competency of participants to fill out the questionnaires. However, it would be recommended to apply standard cognitive tests and examine how cognitive status might interfere with the results. Failure to assess the baseline anxiety/stress and no history of a psychiatric illness are among other shortcomings. Another limitation was the absence of the initial WBC count to compare the reduction in counts and assess the effect of chemotherapy and perceived stress on WBC reduction, which should be addressed in future studies.

The last limitation was the loss of two patients, which seems inevitable, but reducing the duration of the study will decrease this longitudinal effect.

Clinical implications

Stressful situations can deteriorate one's biological constitution. In our study, groups with lower PPS and higher NPS experiencing neutropenic event were at greater risk of suffering from worse treatment outcomes when treated with the same doses of chemotherapy medicine. It seems rational to suggest that these doses should be adjusted with patients' physical and psychological states.

Furthermore, the psychologic status of patients should be assessed, and additional therapy should be performed if needed for a better leukemia treatment outcome.

CONCLUSION

In contrast to positive stress perception, which can boost neutrophil recovery, negative perception of stress, due to neutropenia occurrence after chemotherapy, causes vital problems in leukemic patients. In general, besides the usual assessments, anxiety, depression, and dementia in patients undergoing chemotherapy should be evaluated. It should be noted that due to the type of study, we could not make a causal inference. A final suggestion is that patients could get help from a psychiatrist in the course of the disease and the treatment. Due to the vital role of PMNs to control serious infections, finding stress perception as a possible factor for their reduction is of great importance. Managing stress might prevent PMN count to fall to a high degree.

CONFLICT OF INTEREST

The authors declare no conflict of interest**.**

Ethical approval

This project was approved by the Ethics Committee of Imam Khomeini Hospital Complex of Tehran University of Medical Sciences. Moreover, the study was conducted according to the Helsinki declaration and no additional cost was imposed.

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