The Effect of Family-Centered Supportive Program on Chemotherapy-Induced Symptoms in Patients with Acute Lymphoblastic Leukemia (ALL)

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ABSTRACT

Background: Acute lymphoblastic leukemia is a disease of the hematopoietic system and chemotherapy is recommended as the primary treatment. As many chemotherapeutic agents have severe adverse effects, patients require to be supported by their family to deal with chemotherapy-related symptoms. This study attempted to investigate the effect of family-centered supportive programs on chemotherapy symptom control in patients with acute lymphoblastic leukemia.

Materials and Methods: Sixty-six patients with acute lymphoblastic leukemia undergoing chemotherapy along with their caregivers participated in this nonrandomized clinical trial. Patients in Shariati and Taleghani Hospital were assigned to intervention (n=33) and control group (n=33), respectively. A survey of family-centered supportive program was conducted via in-person and telephone up to 6 cycles of chemotherapy. The chemotherapy symptom assessment scale was administered to record the data during 6 cycles of chemotherapy treatment. The control group only received routine interventions. Data were analyzed using Chi-square and Mann–Whitney U tests.

Results: The results of the study indicated that there was a statistically significant difference in terms of the frequency of 9 chemotherapy-induced symptoms including nausea, shortness of breath, problems related to skin and nails, a sore/sensitive mouth or throat, anorexia, weight gain or loss, headache and sore/scratchy/dry eyes between the control and intervention group. There was also a statistically significant difference in the severity and level of discomfort of 19 chemotherapy-induced symptoms between the control and intervention group.

Conclusion: Family-centered supportive program can be considered as an approach to decrease the frequency, severity and discomfort level of chemotherapy-induced symptoms.

Keywords: Acute lymphoblastic leukemia; Chemotherapy; Family-centered supportive program; Support

INTRODUCTION

Leukemia, a malignant disease of the hematopoietic system, is the fifth most common cancer worldwide, especially in Iran. It is also important to note that the trend in overall incidence of leukaemia has generally been increasing1-2. Leukemia can be classified as acute and chronic types, and further sub classified as lymphoid and...
myeloid types. Acute lymphoblastic leukemia (ALL) is a malignant disease in which bone marrow dysfunction progresses very rapidly and is characterized by proliferation of immature lymphoid cells in bone marrow, peripheral blood and other organs. Although ALL is more common in children, it can also affect adults and elderly patients. Adult patients presenting with ALL have a poor prognosis, and therefore require more intensive therapy.

Chemotherapy remains the standard first-line treatment for ALL patients or those who are considered to be candidates for Hematopoietic Stem Cell Transplantation. The complications or symptoms of chemotherapy may include chest pain, anorexia, nausea, vomiting, diarrhea, skin redness and rash, hair loss, angioedema, depression and anxiety, pancytopenia, anemia, neutropenia, leukopenia, lymphopenia, thrombocytopenia, infection and sepsis, stomatitis, oral and anal mucositis, pain, weight loss, and elevated liver enzymes. These complications are usually temporary and can be minimized or prevented by careful management. Inappropriate control of side effects leads the patients to set aside the treatment or decrease the optimal treatment dose, poor quality of life, increased mortality and increased length of mental and social symptoms. Therefore diagnosis, prevention and control of side effects make it easier for patients to tolerate difficult, hard times and help them pass through tough situations.

Nurses are in the special position among the healthcare system professionals. It is the nurse’s responsibility to assess the patient prior to chemotherapy administration, monitor and administer chemotherapy, manage the side effects of chemotherapy, care and provide advice to the patient after chemotherapy. Nursing care as well as patient and family education play a vital role in reducing the side effects and improving the outcomes of chemotherapy. Some studies have shown that the interventions are effective in reducing chemotherapy-related symptoms. However, in each study, their efficacy is limited to treat one or two chemotherapy-induced side effects. At present, care approaches emphasize the use of complementary interventions and holistic care to improve the psychological acceptance of chemotherapy and physical side effects.

The studies show that health education, patient support, nutrition and dietary, self-management of symptoms and side effects at home are among the most important needs of patients under chemotherapy. The majority of patients receive chemotherapy in the outpatient clinic, which enables them to stay at home up the next chemotherapy session begins. Chemotherapy-related adverse events have negative impact on patient functioning and activities of self-care and family members frequently play a vital role in providing care. Therefore, Family-centered care programs can help alleviate the chemotherapy-related side effects. Various studies have pointed out the importance and the impact of family-centered care programs in providing optimal care to patients. For instance, family-focused care programs for patients with diabetes, Asthma and those undergoing cardiac surgery can improve patients' health outcomes. Family members can provide supportive care to patients, assist them in their self-care, and supervise their activities in their own home.

Family and patient support could embrace physical, mental, spiritual, social and financial aspects. Although some studies have used financial and social support programs, supportive-educative nursing programs as well as mental supportive cares, due to its applicability for nurses, have been used with more frequency. Supportive educative nursing program play a central role in ameliorating problems presented by patients diagnosed with Diabetes Mellitus, Lymphedema after breast cancer and heart failure. Educational-supportive programs have been found effective in helping reduce the side effects in patients receiving chemotherapy. There are studies showing the positive impact of education and support programs on the process of treatment in cancer patients receiving chemotherapy, but they were designed based on the unique needs of patients treated in those countries. Furthermore, the participants in these studies were either cancer patients or patients diagnosed with malignant hematologic disorders such as Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, Lymphoma and Hodgkin Lymphoma. In addition,
chemotherapy-induced side effects were compared during only 2 cycles of chemotherapy so that researchers concluded that further studies are required to better control the side effects over multiple cycles of chemotherapy\textsuperscript{28-29}.

Due to the rising incidence of cancer and leukemia in Iran, developing an appropriate treatment plan that aims to solve the problems of cancer patients undergoing chemotherapy is essential\textsuperscript{30}. As chemotherapy is required for a large number of patients diagnosed with ALL, family support programs will help them manage and reduce the side effects of chemotherapy. Hence, this study was conducted to assess the effect of a family-centered supportive program on the frequency, severity and discomfort level of chemotherapy-induced symptoms in patients with ALL.

**MATERIALS AND METHODS**

This is a non-randomized clinical trial which was conducted between January 2019 and July 2019.

**Participants and setting**

The study included 66 patients diagnosed with ALL along with their families who met the following inclusion criteria: age more than 18 years, capable of reading, writing and speaking in Persian, able to provide informed consent, confirmed diagnosis of ALL, scheduled to receive first or second cycle of chemotherapy. Family members who were between 18 and 60 years old participated in the study. They were able to provide patient care at home and satisfied with participating in the study. Also, they were not one of the employees of the health system. Participants were excluded from the study if any of them refused to continue participating in the study, or patients refused to continue chemotherapy for any reason, or the patient dies. Moreover, if there were a history of chemotherapy in family members, they would not be included in the study. This did not happen in this study.

The research study was conducted in chemotherapy wards of Shariati and Taleghani Hospital. Chemotherapy protocols used in the treatment of ALL consisted of Vincristine, Etoposide, Cytarabine, Cytosar, Methotrexate, Cyclophosmaide, Endoxan and Daurubicin. Moreover, patients in two hospitals were routinely given information specific to their chemotherapy.

**Intervention**

Family-centered supportive program was considered as an intervention in this study. The program focused on making care decision, mutual interaction, sharing information, providing support and empowering families\textsuperscript{31-32}. Some ways to accomplish this program were: patient/family education, patient's diet and psychological support of patients over several stages: a) teaching materials were prepared in the forms of booklets and videos based on treatment protocols, patients' medical records, the views of nurses working in chemotherapy units and the more common problems encountered by patients and their families, b) in the first meeting with patients and their relative family members, educational videos were shown and booklets and videos were distributed to participants. Verbal information was also given regarding the content of booklets and videos, and the questions of patients were answered appropriately, C) the patients were asked to complete a questionnaire to identify learning needs, and then the care team consulted with a dietitian for a nutritionally balanced diet, d) in the next session of chemotherapy occurred 2 weeks later in the chemotherapy clinic, patients and their families were educated regarding the chemotherapy administration and symptom management and were provided dietary information, e) follow-up telephone calls were made by the end of each 6 cycles of chemotherapy to support patients /families and discuss new challenging issues encountered by patients. In addition, those patients/families who were found to have psychiatric problems in training sessions or during follow-up telephone calls were referred to a psychiatrist for psychiatric consultation.
Outcomes
Frequency, severity and discomfort level of 24 chemotherapy-induced symptoms were outcomes of the study. These symptoms were nausea and vomiting before treatment, nausea, vomiting, constipation, diarrhea, pain (patient specifies where), shortness of breath, signs of infection, bleeding or bruising, pins and needles/numbness of hands and feet, problems with skin and nails, hair loss, a sore/sensitive mouth or throat, change in appetite, weight gain or loss, sore/scratchy/dry eyes, feeling weak, feeling unusual fatigue, difficulty sleeping, headaches, feeling distressed/anxious, feeling pessimistic/unhappy, change in sexual life and irregular periods (female patients).

Data collection procedures
Demographic and clinical information of patients including age, sex, marital status, education, ALL stage, duration of disease and chemotherapy session were collected from medical records or by asking the patients. The questionnaire collected information on all members of a family including age, sex, marital status and education. The chemotherapy symptom assessment scale (C-SAS), a 24-item scale, designed for the assessment of frequency, severity and discomfort level of symptoms experienced by patients receiving chemotherapy. It consisted of 3 parts: in the first part, the patients were asked whether they had experienced any side effects of chemotherapy, to which they were given only a 'yes' or 'no' answer. In the second part, they were asked to delineate the severity of side effects they had experienced during chemotherapy as “mild,” “moderate,” and “severe”. Finally, in the third part, they were asked to report the level of discomfort caused by chemotherapy on a four-point Likert-scale: none, mild, moderate and severe. High scores reflected a greater severity and discomfort of chemotherapy-induced symptoms. Brown et al. (2001) confirmed the internal consistency of the C-SAS. In this study, Cronbach's Alpha was used to assess the reliability, and Cronbach's Alpha coefficient was 0.72.

In the first chemotherapy session, the researcher questioned the patients to complete the demographic and clinical questionnaires as well as C-SAS. Some clinical data were also collected from patients' medical records. In the second chemotherapy session, the questionnaire was completed in the in-person interview mode, and during the third to sixth chemotherapy session, the researcher questioned the participants over the telephone and filled in the responses. Length of time, frequency, and way of data collection are shown in Table1.

The researcher did not interfere with the routine interventions done for all patients. The way in which the questionnaire was completed and the amount of time allocated for questionnaire completion were similar in both control and intervention group.

Sample size
Cohen effect-size method was used to measure the sample size. The sample size was 33 in each group (EF=70). Type I error and power of the test were 0.05 and 90%, respectively.

Sampling
Patients and their families participated in the study with convenience sampling. Each group (control and intervention) consisted of 33 patients with their families. Regarding the limitations of number of patients with ALL and in order to avoid sample contamination, Shariati and Taleghani hospital were considered as intervention and control group, respectively.

Blinding
Patients, family members and researchers were not blinded to intervention, but the study statistician was blinded to the control and intervention group.
Statistical methods
SPSS was used to determine the frequency, percentage, median, mean and standard deviation of variables. Mann–Whitney U test was used to determine the difference between the two groups in terms of age and duration of disease. Mann–Whitney U test was used for severity and level of discomfort associated with chemotherapy symptoms. P=0.05 was considered statistically significant.

Table 1: Complete questionnaires based on chemotherapy session, week and intervention implementation

| Chemo session | First | Second | Third | Fourth | Fifth | Sixth |
|---------------|-------|--------|-------|--------|-------|-------|
| Week          |       |        |       |        |       |       |
| Intervention implementation | In-person | In-person | Telephone follow-up | Telephone follow-up | Telephone follow-up | Telephone follow-up |

RESULTS
Participant flow
As shown in Figure 1, 83 ALL patients were hospitalized in Shariati and Taleghani hospitals to receive chemotherapy between January 2019 and July 2019. Seventeen Patients were excluded from the study.
The two groups had similar distributions of variables, including age, sex, disease duration, chemotherapy course, and disease grade. There was a statistically significant difference between the two groups in marital status (p= 0.009) and education (p= 0.015) of patients. Marital status and educational level of family members involved in the patient’s care were similar between the two groups. There was a statistically significant difference between the two groups with regard to age (p<0.001) and sex of family members (p= 0.027) (Table 2).

| Variables                        | Intervention N(%) | Control N(%) | P  |
|----------------------------------|-------------------|--------------|----|
| **Patients**                     |                   |              |    |
| Age(year)*                       | 28.27(7.068)      | 26.91(8.357) | 0.477 |
| Sex                              |                   |              |    |
| Male                             | 14(42.4)          | 14(42.4)     | 1   |
| Female                           | 19(57.6)          | 19(57.6)     | 1   |
| Marital Status                   |                   |              |    |
| Single                           | 17(51.5)          | 27(81.8)     | 0.009 |
| Married                          | 16(48.5)          | 6(18.2)      | 0.009 |
| Education                        |                   |              |    |
| Elementary education and high-school certificate Diploma | 7(21.2)          | 12(36.4)     | 0.015 |
| University degree                | 13(39.4)          | 3(9.1)       | 1   |
| Duration of disease (Months)*    | 2.73(0.719)       | 2.67(0.54)   | 0.7  |
| Chemotherapy session             |                   |              |    |
| First                            | 15(45.5)          | 16(48.5)     | 0.805 |
| Second                           | 18(54.5)          | 17(51.5)     | 0.805 |
| Grade of disease                 |                   |              |    |
| Grade I                          | 33(100)           | 33(100)      |      |
| Family members                   |                   |              |    |
| Age(year)*                       | 38.48(12.66)      | 50.12(9.63)  | <0.001 |
| Sex                              |                   |              |    |
| Male                             | 5(15.2)           | 13(39.4)     | 0.207 |
| Female                           | 28(84.8)          | 20(60.6)     | 0.207 |
| Marital status                   |                   |              |    |
| Single                           | 4(12.1)           | 3(9.1)       | 0.689 |
| Married                          | 29(87.9)          | 30(90.9)     | 0.689 |
| Education                        |                   |              |    |
| Elementary education and high-school certificate Diploma | 16(48.5)          | 18(54.3)     | 0.319 |
| Diploma                          | 11(33.3)          | 13(39.4)     | 0.319 |
| University degree                | 6(18.2)           | 2(6.1)       | 0.319 |

*Mean (SD)

**Outcomes**

There was a statistically significant difference in terms of 9 chemotherapy-induced symptoms, including nausea after chemotherapy, vomiting after chemotherapy, shortness of breath, problems related to nails and skin, sore/sensitive mouth or throat, change in appetite, weight loss and headache between the control and intervention group. As shown in Table 3, there was also a statistically significant difference in terms of vomiting after...
chemotherapy, shortness of breath, problems related to nails and skin, a sore/sensitive mouth or throat, change in appetite, weight gain or loss, and sore/scratchy/dry eyes between the two groups in only one cycle of total six cycles of chemotherapy. Moreover, there was a statistically significant difference between the two study groups in terms of sore/scratchy/dry eyes as well as nausea after chemotherapy and headache in 2 and 3 cycles of chemotherapy, respectively (Table 3).

Table 3: Frequency of chemotherapy-induced symptoms over 6 courses of follow-up in the control and intervention group

| Course of chemotherapy | Group          | 1     | 2     | 3     | 4     | 5     | 6     |
|-----------------------|----------------|-------|-------|-------|-------|-------|-------|
| Nausea and vomiting before treatment | Intervention | 5(15.2) | 3(9.1) | 1(3.0) | 0     | 0     | 0     |
|                        | Control       | 4(12.1) | 3(9.1) | 1(3.0) | 1(3.0) | 0     | 0     |
|                        | P             | 0.5    | 0.66  | 0.75  | 0.5   | -     | -     |
| Nausea after chemotherapy | Intervention | 33(100) | 33(100) | 32(97) | 27(81.8) | 17(51.5) | 13(39.4) |
|                        | Control       | 33(100) | 33(100) | 33(100) | 33(100) | 31(93.3) | 32(97) |
|                        | P             | -      | 0.5   | 0.01  | 0.00  | 0.00  | 0.00  |
| Vomiting after chemotherapy | Intervention | 17(51.5) | 18(54.5) | 14(42.4) | 7(21.2) | 2(6.1) | 2(6.1) |
|                        | Control       | 26(78.8) | 25(75.8) | 20(60.6) | 9(27.3) | 5(15.2) | 4(12.1) |
|                        | P             | 0.02   | 0.07  | 0.13  | 0.56  | 0.21  | 0.33  |
| Constipation | Intervention | 32(97) | 33(100) | 33(100) | 33(100) | 33(100) | 31(93.9) |
|                        | Control       | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                        | P             | 0.5    | -     | -     | -     | -     | 0.24  |
| Diarrhea | Intervention | 3(9.1) | 1(3)  | 1(3)  | 1(3)  | 1(3)  | 0     |
|                        | Control       | 4(12.1) | 2(6.1) | 2(6.1) | 1(3)  | 2(6.1) | 0     |
|                        | P             | 0.5    | 0.5   | 0.75  | 0.48  | -     | -     |
| Pain (patient specifies where) | Intervention | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                        | Control       | 33(100) | 31(93.9) | 33(100) | 33(100) | 33(100) | 33(100) |
|                        | P             | -      | 0.24  | -     | -     | -     | -     |
| Shortness of breath | Intervention | 21(63.6) | 31(93.9) | 31(93.9) | 31(93.9) | 29(87.9) | 31(93.9) |
|                        | Control       | 33(100) | 32(97) | 33(100) | 32(97) | 32(97) | 33(100) |
|                        | P             | 0.00   | 0.5   | 0.24  | 0.5   | 0.17  | 0.24  |
| Signs of infection | Intervention | 32(97) | 31(93.9) | 27(81.8) | 29(87.9) | 26(78.8) | 30(90.9) |
|                        | Control       | 33(100) | 32(97) | 32(97) | 32(97) | 31(93.9) | 32(97) |
|                        | P             | 0.5    | 0.5   | 0.5   | 0.17  | 0.07  | 0.3   |
| Bleeding or bruising | Intervention | 33(100) | 32(97) | 33(100) | 31(93.9) | 33(100) | 32(97) |
|                        | Control       | 33(100) | 33(100) | 33(100) | 32(97) | 32(97) | 32(97) |
|                        | P             | -      | 0.5   | -     | -     | 0.5   | 0.75  |
| Pins and needles/.numbness of hands and feet | Intervention | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                        | Control       | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                        | P             | -      | -     | -     | -     | -     | -     |
| Problems with the skin and nails | Intervention | 21(63.6) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                        | Control       | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                        | P             | 0.00   | -     | -     | -     | -     | -     |
**Course of chemotherapy**

| Symptom                          | Group          | 1  | 2  | 3  | 4  | 5  | 6  |
|----------------------------------|----------------|----|----|----|----|----|----|
| Hair loss                        | Intervention   | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                                  | Control        | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
| P                                |                | 0.001 | -   | -   | -   | -   | 0.5 |
| A sore/sensitive mouth or throat | Intervention   | 24(72.7) | 33(100) | 33(100) | 33(100) | 33(100) | 32(97) |
|                                  | Control        | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
| P                                |                | 0.001 | -   | -   | -   | 0.5 | 0.05 |
| A change in appetite             | Intervention   | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 29(87.9) |
|                                  | Control        | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
| P                                |                | 0.002 | 0.5 | 0.66 | 0.58 | 0.42 | 0.03 |
| Weight gain or loss              | Intervention   | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                                  | Control        | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
| P                                |                | 0.001 | -   | -   | -   | 0.05 | 0.21 |
| Sore/scratchy/dry eyes           | Intervention   | 16(48.5) | 29(87.9) | 30(90.9) | 23(69.7) | 21(63.6) | 18(54.5) |
|                                  | Control        | 28(84.8) | 28(84.8) | 30(90.9) | 25(75.8) | 24(72.7) | 26(78.8) |
| P                                |                | 0.002 | 0.5 | 0.66 | 0.58 | 0.42 | 0.03 |
| Feeling weak                     | Intervention   | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                                  | Control        | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
| P                                |                | 0.001 | 0.5 | 0.66 | 0.58 | 0.42 | 0.03 |
| Feeling unusual fatigue          | Intervention   | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                                  | Control        | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
| P                                |                | 0.001 | -   | -   | -   | 0.05 | 0.21 |
| Difficulty sleeping              | Intervention   | 33(100) | 33(100) | 33(100) | 33(100) | 32(97) | 31(93.9) |
|                                  | Control        | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
| P                                |                | 0.001 | -   | -   | -   | 0.05 | 0.24 |
| Headaches                        | Intervention   | 33(100) | 32(97) | 31(93.9) | 28(84.8) | 26(78.8) | 24(72.7) |
|                                  | Control        | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
| P                                |                | 0.002 | 0.5 | 0.24 | 0.02 | 0.00 | 0.00 |
| Feeling distressed/anxious       | Intervention   | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                                  | Control        | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
| P                                |                | 0.001 | -   | -   | -   | 0.05 | 0.21 |
| Feeling pessimistic/unhappy      | Intervention   | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                                  | Control        | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
| P                                |                | 0.001 | -   | -   | -   | 0.05 | 0.21 |
| Change in sexual life            | Intervention   | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
|                                  | Control        | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) | 33(100) |
| P                                |                | 0.001 | -   | -   | -   | 0.05 | 0.21 |
| Irregular periods (female patients) | Intervention | 19(57.6) | 19(57.6) | 19(57.6) | 19(57.6) | 19(57.6) | 19(57.6) |
|                                  | Control        | 19(57.6) | 19(57.6) | 19(57.6) | 19(57.6) | 19(57.6) | 19(57.6) |
| P                                |                | 0.001 | -   | -   | -   | 0.05 | 0.21 |

*Chi-squared or Fisher's exact test*
The severity of chemotherapy–induced symptoms are shown in Table 4. The severity of 19 adverse effects was different between the two groups. There was a statistically significant difference in vomiting after chemotherapy over a period of time, bleeding or bruising, feeling pessimistic/unhappy, and change in sexual life between the two study groups over 2 periods of time. Moreover, there was a statistically significant difference in the severity of nausea after treatment and signs of infection over 3 periods of time. There was also a statistically significant difference between the severity of constipation, pain, shortness of breath, pins and needles/numbness of hands and feet, and sore/scratchy/dry eyes over 4 periods of time; the severity of problems related to the skin and nails, sore/sensitive mouth or throat, change in appetite, weight gain or loss, feeling weak, feeling unusual fatigue, difficulty sleeping, headache, and feeling distressed/anxious over 5 periods of time between the control and intervention group.

Table 4: Severity of chemotherapy-induced symptoms over 6 courses follow-up in the control and intervention group

| Course of chemotherapy | Group | Symptom                          | Median | Median | Median | Median | Median | Median |
|------------------------|-------|----------------------------------|--------|--------|--------|--------|--------|--------|
| Control                | 0.01  | Nausea and vomiting before treatment | 0.26   | 0.34   | 0.15   | 0.00   |
| Intervention           | 0.002 | Nausea after chemotherapy        | 0.23   | 0.24   | 0.01   | 0.00   | -      | -      |
|                          | 0.01  | Vomiting after chemotherapy      | 2.5    | 2.5    | 2.5    | 2.5    | 2.5    | 2.5    |
|                          | 0.001 | Diarrhea                         | -      | -      | -      | -      |
|                          | 0.002 | Pain (patient specifies where)   | 0.00   | 0.00   | 0.00   | 0.00   | 0.00   |
|                          | 0.004 | Shortness of breath              | 0.00   | 0.00   | 0.00   | 0.00   | 0.00   |
|                          | 0.007 | Signs of infection               | 0.00   | 0.00   | 0.00   | 0.00   | 0.00   |
|                          | 0.002 | Bleeding or bruising             | 0.00   | 0.00   | 0.00   | 0.00   |
|                          | 0.01  | Pins and needles/numbness of hands and feet | -      | -      | -      |

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| Course of chemotherapy | Group  | Median | Median | Median | Median | Median | Median |
|------------------------|--------|--------|--------|--------|--------|--------|--------|
| Problems with the skin and nails | Intervention | 2      | 3      | 2      | 2      | 1      | 0      |
|                         | Control | 3      | 3      | 3      | 3      | 3      | 3      |
| Hair loss               | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | -      | -      | 0.5    | 0.24   | -      | 0.24   |
| A sore/sensitive mouth or throat | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | 0.003  | 0.31   | 0.00   | 0.00   | 0.00   | 0.00   |
| A change in appetite    | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | 0.018  | 0.01   | 0.00   | 0.00   | 0.00   | 0.00   |
| Weight gain or loss     | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | 0.56   | 0.023  | 0.02   | 0.00   | 0.00   | 0.00   |
| Sore/scratchy/dry eyes  | Intervention | 2      | 2      | 2      | 2      | 2      | 3      |
|                         | Control | 2.5    | 2      | 1.5    | 1      | 1      | 2      |
|                         P | 0.19   | 0.049  | 0.00   | 0.15   | 0.003  | 0.00   |
| Feeling weak            | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | 3      | 3      | 3      | 3      | 3      | 3      |
|                         P | 0.02   | 1      | 0.00   | 0.00   | 0.00   | 0.00   | 0.00   |
| Feeling unusual fatigue | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | 3      | 3      | 3      | 3      | 3      | 3      |
|                         P | 0.05   | 1      | 0.05   | 0.00   | 0.00   | 0.00   | 0.00   |
| Difficulty sleeping     | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | 3      | 3      | 3      | 3      | 3      | 3      |
|                         P | 0.005  | 0.14   | 0.00   | 0.00   | 0.00   | 0.00   | 0.00   |
| Headaches               | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | 3      | 3      | 3      | 3      | 3      | 3      |
|                         P | 0.02   | 1      | 0.00   | 0.00   | 0.00   | 0.00   | 0.00   |
| Feeling distressed/ anxious | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | 3      | 3      | 3      | 3      | 3      | 3      |
|                         P | 0.05   | 0.49   | 0.00   | 0.00   | 0.00   | 0.00   | 0.00   |
| Feeling pessimistic/unhappy | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | 3      | 3      | 3      | 3      | 3      | 3      |
|                         P | 0.005  | 1      | 0.24   | 0.005  | 0.17   | 0.11   | 0.24   |
| Change in sexual life   | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | 3      | 3      | 3      | 3      | 3      | 3      |
|                         P | 0.00   | 1      | 0.5    | 0.05   | 0.17   | 0.11   | 0.24   |
| Irregular periods (female patients) | Intervention | 3      | 3      | 3      | 3      | 3      | 3      |
|                         | Control | 3      | 3      | 3      | 3      | 3      | 3      |
|                         P | -      | 1      | -      | -      | 0.75   | 0.51   |

There was a statistically significant difference of level of discomfort between the control and intervention group in terms of the 19 symptoms. Both study groups had a statistically significant difference in terms of bleeding or bruising, feeling pessimistic/unhappy and change in sexual life over 2 periods of time. There was a statistically significant difference between the control and intervention group in terms of nausea after chemotherapy, signs of infection over 3 periods of time; constipation, pain, shortness of breath, pins and needles/numbness of hands and feet,
sore/scratchy/dry eyes over 4 periods of time, problems related to the skin and nails, a sore/sensitive mouth or throat, changes in appetite, weight gain or loss, feeling weak, feeling unusual fatigue, difficulty sleeping, headache, feeling distressed/anxious over 5 periods of time (Table 5).

Table 5: The level of discomforts caused by chemotherapy-induced symptoms over 6 courses follow-up in the control and intervention group

| Course of chemotherapy | Group   | 1  | 2  | 3  | 4  | 5  | 6  |
|-------------------------|---------|----|----|----|----|----|----|
| Nausea and vomiting before treatment | Intervention | 3  | 2  | 1  | -  | -  | -  |
| Control                 | 2       | 2  | 3  | 1  | -  | -  | -  |
| P                      | -       | -  | 0.5| -  | -  | -  | -  |
| Nausea after chemotherapy | Intervention | 2  | 2  | 2  | 1  | 1  | 1  |
| Control                 | 3       | 3  | 2  | 2  | 2  | 2  | 2  |
| P                      | 0.11    | 0.32| 0.01| 0.000| 0.000| -  | -  |
| Vomiting after chemotherapy | Intervention | 3  | 2/6| 2  | 1  | 1  | 1  |
| Control                 | 2/5     | 2  | 1  | 1  | 1  | 1  | 1  |
| P                      | 0.85    | 0.06| -  | 0.23| 0.71| 0.66| -  |
| Constipation            | Intervention | 3  | 3  | 3  | 3  | 3  | 3  |
| Control                 | 3       | 3  | 3  | 3  | 3  | 3  | 3  |
| P                      | 0.29    | 0.07| 0.00| 0.00| 0.00| 0.00| -  |
| Diarrhea                | Intervention | 3  | 3  | 3  | 2  | 2  | 2  |
| Control                 | 3       | 3  | 3  | 3  | 3  | 3  | 3  |
| P                      | 0.002   | -  | 0.69| 0.001| 0.00| 0.00| -  |
| Shortness of breath     | Intervention | 2  | 3  | 2  | 2  | 1  | 1  |
| Control                 | 3       | 3  | 2  | 2  | 2  | 2  | 2  |
| P                      | 0.16    | 0.54| 0.001| 0.004| 0.00| 0.00| -  |
| Signs of infection      | Intervention | 2  | 3  | 2  | 2  | 1.5| 1  |
| Control                 | 3       | 3  | 2  | 2  | 2  | 2  | 2  |
| P                      | 0.27    | 0.26| 0.08| 0.007| 0.00| 0.00| -  |
| Bleeding or bruising    | Intervention | 3  | 3  | 2  | 2  | 2  | 2  |
| Control                 | 3       | 3  | 2  | 2  | 2  | 2  | 2  |
| P                      | 0.002   | 0.59| 0.15| 0.34| 0.26| 0.01| -  |
| Pins and needles numbness of hands and feet | Intervention | 3  | 3  | 3  | 3  | 2  | 2  |
| Control                 | 3       | 3  | 3  | 3  | 3  | 3  | 3  |
| P                      | 0.004   | 1  | 0.04| 1  | 0.00| 0.00| 0.001|
| Problems with the skin and nails | Intervention | 2  | 3  | 2  | 2  | 2  | 2  |
| Control                 | 3       | 3  | 3  | 3  | 3  | 3  | 3  |
| P                      | 0.00    | 0.16| 0.00| 0.00| 0.00| 0.00| 0.00|
| Hair loss               | Intervention | 3  | 3  | 3  | 3  | 3  | 3  |
| Control                 | 3       | 3  | 3  | 3  | 3  | 3  | 3  |
| P                      | -       | -  | 0.5| 0.24| -  | 0.24| -  |
| A sore/sensitive mouth or throat | Intervention | 2  | 3  | 2  | 2  | 2  | 2  |
| Control                 | 3       | 3  | 3  | 3  | 3  | 3  | 3  |
| P                      | 0.003   | -  | 0.00| 0.00| 0.00| 0.00| 0.00|
| Course of chemotherapy | 1 | 2 | 3 | 4 | 5 | 6 |
|------------------------|---|---|---|---|---|---|
| **Symptom**            | Group | Median | Median | Median | Median | Median |
| A change in appetite   | Intervention | 3 | 3 | 2 | 2 | 1 | 1 |
|                        | Control | 3 | 3 | 2 | 2 | 2 | 2 |
|                        | P | 0.58 | 0.01 | 0.01 | 0.00 | 0.00 | 0.00 |
| Weight gain or loss    | Intervention | 3 | 3 | 2 | 2 | 1 | 1 |
|                        | Control | 3 | 3 | 3 | 3 | 2 | 2 |
|                        | P | 0.56 | 0.02 | 0.02 | 0.00 | 0.00 | 0.00 |
| Sore/.scratchy./dry eyes | Intervention | 2 | 2 | 1/5 | 1 | 1 | 2 |
|                        | Control | 2 | 2 | 2 | 2 | 2 | 3 |
|                        | P | 0.19 | 0.40 | 0.15 | 0.00 | 0.00 | 0.00 |
| Feeling weak           | Intervention | 3 | 3 | 2 | 2 | 2 | 2 |
|                        | Control | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | P | 0.02 | 0.50 | 0.002 | 0.00 | 0.00 | 0.00 |
| Feeling unusual fatigue| Intervention | 3 | 3 | 2 | 2 | 2 | 2 |
|                        | Control | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | P | 0.05 | 0.50 | 0.05 | 0.00 | 0.00 | 0.00 |
| Difficulty sleeping    | Intervention | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | Control | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | P | 0.005 | 0.07 | 0.00 | 0.00 | 0.00 | 0.00 |
| Headaches              | Intervention | 3 | 3 | 2 | 2 | 2 | 2 |
|                        | Control | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | P | 0.02 | 0.08 | 0.00 | 0.00 | 0.00 | 0.00 |
| Feeling distressed/.anxious | Intervention | 3 | 3 | 2 | 2 | 2 | 2 |
|                        | Control | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | P | 0.05 | 0.24 | 0.00 | 0.00 | 0.00 | 0.00 |
| Feeling pessimistic/.unhappy | Intervention | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | Control | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | P | 0.005 | 0.50 | 0.24 | 0.005 | 0.17 | 0.11 |
| Change in sexual life  | Intervention | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | Control | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | P | 0.00 | 0.69 | 0.50 | 0.05 | 0.17 | 0.24 |
| Irregular periods (female patients) | Intervention | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | Control | 3 | 3 | 3 | 3 | 3 | 3 |
|                        | P | 0.00 | 0.50 | - | - | 0.75 | 0.51 |

**DISCUSSION**

The results of the study showed that the family-centered supportive program reduced the frequency of 9 chemotherapy-induced symptoms, including nausea after chemotherapy, vomiting after chemotherapy, shortness of breath, problems related to the skin and nails, sore/sensitive mouth or throat, change in appetite, weight loss, sore/scratchy/dry eyes and headache during 6 courses of chemotherapy and 12 weeks of follow-up. Moreover, family-centered supportive programs, during the same period, was found to positively influence the severity and discomfort level of following chemotherapy-induced symptoms: signs of infection, bleeding or bruising, feeling pessimistic/unhappy, change in sexual life, nausea after chemotherapy, sore/scratchy/dry eyes , pain, constipation, shortness of breath, pins and needles/numbness of hands and feet, change in appetite, weight loss, problems related to the skin.
and nails, sore/sensitive mouth or throat, weakness, unusual fatigue, difficulty sleeping, headache and anxiety or distress.

Strengths
The present study conducted at two university teaching hospitals. Moreover, this study has evaluated the effect of intervention on chemotherapy-induced symptoms during six cycles of chemotherapy.

Limitations
In the present study, the effect size was large. The findings revealed that some of the demographic information were not homogenized between the two study groups, thus homogenization could lead to more reliable results.

Comparison to existing literature
Various approaches have been applied to reduce the frequency, sever and discomfort level of chemotherapy –induced symptoms. For instance, the results of one study showed the impact of symptom management education on frequencies of chemotherapy-induced symptoms, including nausea, vomiting, feeling distressed/anxious, pessimism/unhappiness, unusual fatigue, and difficulty sleeping. Moreover, severity of nausea and vomiting, distressed/anxious feelings, pessimistic and unhappy feelings decreased. By implementation of symptom management education, discomfort level of nausea and vomiting, feeling weak, feeling unusual fatigue, difficulty sleeping, feeling distressed/anxious, and feeling pessimistic/unhappy decreased 28. In another study conducted on patients receiving chemotherapy and their families were given structured information, the results showed statistically significant decrease in the frequencies of nausea, vomiting, constipation, pain, infectious signs, problems related to the mouth or throat, the skin and nails, appetite change, weight loss or weight gain, feeling distressed/anxious, feeling pessimistic/unhappy, unusual fatigue, difficulty sleeping. Moreover, severity of nausea and vomiting, constipation, dyspnea, appetite change, pain, sleep difficulty, headaches, weakness, unusual fatigue, feeling distressed/anxious and changes in menstrual cycle (in women) were statistically decreased in the intervention group compared to the control group. Furthermore, the level of discomfort of some side effects, including nausea, vomiting, constipation, pain, weight loss and weight gain, weakness, unusual fatigue, headaches, and changes in menstrual cycle (in women) significantly decreased in the intervention group 28. These two studies, same as the present study examined the total side effects of chemotherapy using C-SAS. It is important to note that both studies were conducted on patients diagnosed with different types of cancer. Hence, the origin and nature of disease as well as the type of the treatment protocol used in cancer patients may be different.

The effect of education and supportive interventions on frequency, severity and discomfort of chemotherapy-induced symptoms has been evaluated in other studies. The frequency and severity of nausea or vomiting 36-35, fatigue, anxiety and sleep disorders 37 were decreased in patients receiving chemotherapy following educational interventions. Other studies revealed that mindfulness-based psychological care 18, relaxation with guided imagery 38, psychological and behavioral interventions 39 decreased the pain, depression, anxiety and sleep problem in patients undergoing chemotherapy. However, another study conducted in Australia has shown no statistically significant difference in reducing severity of nausea, infection, hair loss, mouth or throat problems and fatigue among patients receiving educational interventions before chemotherapy 40. Family-centered supportive programs have had positive effects on diabetes 41, multiple myeloma 42, heart failure 43, postoperative pain relief 44, and coronary artery bypass graft surgery 22.

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The present study also failed to show any significant changes in severity and discomfort of nausea and vomiting before treatment, vomiting after treatment, diarrhea, hair loss and irregular periods (female patients) between the intervention and control group during six chemotherapy cycles. A few other studies have shown that educational and supportive programs have no effect on severity and discomfort of nausea and vomiting before treatment, diarrhea, hair loss and irregular periods in female patients. Also, in the current study, a significant change was observed in vomiting after treatment for one cycle between the two groups during six cycles of chemotherapy, which could be attributed to multiple factors. For instance, in the present study, patients in both groups after having been educated regarding the side effects of Ketril in detail received this medication to reduce the severity and discomfort of nausea and vomiting. This is one reason for suggesting that educational interventions may cause a reduction in the severity and distress of nausea and vomiting following chemotherapy. They also received injection of Vincristine leading to constipation, so patients rarely experienced diarrhea during the study. Another important feature of the present study was to assess the symptoms during 6 cycles of chemotherapy compared to other studies in which the symptoms were assessed before and after or during 3 cycles of chemotherapy.

Although no statistically significant difference was observed in terms of frequency, severity and discomfort level of 24 chemotherapy-induced side effects between the intervention and control group during 6 courses of chemotherapy, the efficacy of a family-centered support program was observed in one, two, three, four, or five cycles of chemotherapy. Therefore, family-centered supportive programs have the ability to reduce the frequency, severity and discomfort of chemotherapy-induced side effects in patients with ALL, compared to routine programs.

CONCLUSION
Although a family-based support program failed to reduce all chemotherapy-induced side effects, this approach showed a positive impact on the reduction of severity and distress of many chemotherapy-related side effects in patients diagnosed with ALL. Therefore, developing a chemotherapy guideline focusing on the family-based support program might help reduce or control chemotherapy-related adverse effects.

Preparing and implementing guidelines for engaging patients' families in caring for patients undergoing chemotherapy, as well as educating and supporting families, is one of the issues that should be considered. Nursing education in chemotherapy wards should focus on the side effects of chemotherapy and ways to reduce it.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest related to this article.
Ethics
This study was approved by Institutional Ethics Committee, School of Nursing and Midwifery and Rehabilitation, Tehran University of Medical Sciences (IR.TUMS.FNM.REC.1397.181). Participants signed an informed consent after the goals and the nature of the study was explained in detail.

IRCTID
This study was registered in the Iranian Registry of Clinical Trials on 2019.03.01 (Registration No: IRCT20170803035479N3).

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