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Original Article

The efficacy of *Allium ampeloprasum* L. in reducing neutrophil recovery time in childhood cancer with febrile neutropenia: a randomized, double-blind, placebo-controlled trial

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Abstract: Introduction: Febrile neutropenia is a serious complication of cancer chemotherapy that can result in delays in treatment. This study evaluates the efficacy of *A. ampeloprasum* L. at neutrophil recovery time in children with chemotherapy-associated febrile neutropenia. Methods: This single-center, parallel-group, double-blind, randomized clinical trial was conducted at an oncology hospital. Patients selected among childhood cancers with febrile neutropenia. Overall, 97 febrile neutropenic children were enrolled. The intervention group (n=49) was given *A. ampeloprasum* L. in capsules (500 mg twice daily) for seven days plus supportive care. The control group (n=48) was treated similarly with supportive care and placebo capsules. Total white blood cell (WBC) and absolute neutrophil counts (ANC) were checked daily and neutrophil recovery time in both groups was compared. Results: Patients in the intervention group experienced shorter neutrophil recovery compared to the control group (4.02 ± 2.32 days vs. 6.38 ± 2.80 days, respectively, P less than 0.001). The intervention group was discharged from the hospital earlier than the control group with a mean of two days, but it did not reach statistical significance (P=0.133). Mean WBC and ANC were not significantly different in the two groups. Herbal medicine was well tolerated, and no adverse effect was reported. Conclusions: A fresh, lyophilized extract from deciduous leaves of *A. ampeloprasum* L. can effectively shorten the ANC recovery time leading to an earlier release from the hospital. The trial was registered in the Iranian Registry of Clinical Trials with registration No. IRCT2015051615666N2 (http://www.irct.ir/).

Keywords: *A. ampeloprasum* L., cancer, children, febrile neutropenia, leek, Iranian traditional medicine, randomized controlled trial

Introduction

Neutropenia is considered one of the most severe side effects of cytotoxic and immunosuppressive chemotherapeutic agents, which puts patients at risk of opportunistic infections [1, 2]. Currently, the standard of care in patients with febrile neutropenia is broad-spectrum antibiotic therapy and supportive care. Granulocyte-colony stimulating factor (G-CSF) should not be routinely used in the management of fever and neutropenia unless in high-risk patients who are at risk for infection-associated complications [3]. Although the patients usually tolerate G-CSF, some minor side effects such as bone pain, headache, and malaise, may accompany it, and the most serious one is a rupture of the spleen [4]. In addition, the cost and availability of the product are other concerns that may cause major economic prob-

lems for cancer patients and their families who have to deal with other costs of their treatment courses [5-7].

Recently, the use of complementary and alternative medicine has become more prevalent in cancer treatment and its complications [8, 9].

The genus *Allium* from the family of Amaryllidaceae includes different species such as onion (*Allium cepa* L.), garlic (*Allium sativum* L.), and leek (*Allium ampeloprasum* L.) [10].

Allium Ampeloprasum L. - The family of *Amaryllidaceae* - is a traditional plant commonly used as a vegetable in the Iranian food basket. In addition to the nutritional value of this plant, many of its medicinal properties are described in traditional herbal medicine, including anticancer, anti-inflammatory, and immune-boosting properties [11, 12].

Patients widely use *A. ampeloprasum* L. due to their healing properties, defined by the abundant Sulphur compounds [13]. The two most important and well-known bioactive Sulphur compounds are allicin and ajoene. Allicin is beneficial for human health due to its anti-inflammatory, anti-thrombotic, antimicrobial, anti-cancer, and anti-atherosclerotic activities [13, 14]. Another large group of bioactive ingredients in *A. ampeloprasum L.* with great significance in human food includes Sulphur-free polyphenolic compounds such as anthocyanins, flavonols, tannins, flavonoids, phenolic acids, phytosterols, carotenoids, and saponins. Polyphenols are antioxidants that play an essential role in preventing oxidative injury to cellular constituents, which may help lessen the risk of chronic diseases [15, 16].

There is not much research on the phytochemical constituents of *A. ampeloprasum* L. A study by Garcia-Herrera showed that it is a good source of fiber, zinc, ascorbic acid, and other organic acids such as oxalic acid, malic acid, glutamic acid, and citric acid. Besides, more than twenty individual fatty acids have been identified in wild leek, including saturated fatty acids like palmitic acid, as well as a high percentage of polyunsaturated fatty acids like linoleic acid [17]. Moreover, pentanol (18%), 2,5-methyl furyan (7%), ocodecane (9%), di-propyl sulfide (5.6%), methyl aluminum sulfide (4.3%), tetrahydro-2-5 dimethyl tiofan (4/4%) and camphor (3.2%) are some of the identified constituents [11].

Experimental animal studies have suggested the potential benefits of *A. ampeloprasum* L. in boosting the immune system and helping the body control infections, but limited studies in humans have been done [18, 19].

Allium species (bulb or leaf) have a beneficial effect on increasing the immune system [12]. *Allium* species demonstrated in vitro ability to induce proliferation of human immune cells, especially CD16+ natural killer cells [20]. The total phenolic content of *Allium* species has immunomodulatory effects, which are carried out by modulating innate (such as neutrophils and natural killer cells) and acquired (cytokines, B cells, and Th1/Th2 balance) immune components [21]. In addition, animal studies showed the potential effect of *Allium* species on increasing white blood cells [22].

Also, some people in Iran believe that *A. ampeloprasum L.* helped their children to improve their neutropenia faster after chemotherapy administration [23], though robust and validated studies did not support this belief. Traditionally, many people eat *A. ampeloprasum* L. [23] as part of [19] their regular diet to boost their immune system [10].

Accordingly, we decided to do a clinical trial on the effect of *Allium* on neutrophil recovery post-chemotherapy administration in childhood leukemia.

The aim of this study, as the first randomized clinical trial in children with lymphoblastic leukemia, was to clarify whether *A. ampeloprasum* L. (**Figure 1**) can shorten neutrophil recovery time after chemotherapy in patients hospitalized for febrile neutropenia.

Materials and methods

Study design

This single-center, parallel-group, double-blind, randomized clinical trial was conducted at Amir Oncology Hospital, a tertiary-care teaching hospital in Southern Iran. Patients were consecutively selected among children with cancer in the age range of 2-18 years who were admitted due to febrile neutropenia from October 2015

Figure 1. Schematic representation of *A. ampeloprasum* L. plant.

to February 2017. The research followed the guidelines of the Declaration of Helsinki and Tokyo for humans, and written informed consent was taken from the patient and their parents. The Ethics Committee of Shiraz University of Medical Sciences approved the study with the ethics code CT-P-9371-7331. The trial was registered in the Iranian Registry of Clinical Trials with registration No. IRCT20150516-15666N2 (http://www.irct.ir/).

During the study period, 107 patients met the inclusion criteria. Nine patients did not give consent to participate. One patient died due to septic shock one day after admission. The rest of the patients (n=97) were randomly divided into two equal groups. To randomly assign individuals to two equal groups to receive the intervention, the Permuted Block Randomization method with a block size of 6 has been used. The consort guideline is shown in **Figure 2**. Group 1 (control group; n=48) was treated with conventional supportive care, including broad-spectrum antibiotics and G-CSF with a dose of 5 mcg/kg injected subcutaneously. Group 2 (intervention group; n=49) consisted of patients who were additionally treated with *A. ampeloprasum* L. fresh leaf freeze-dried juice. Given that it was a double-blind study, group 1 received a placebo along with the treatment protocol. The patients and investigators were blind to randomization. The concealment of allocation was performed by the pharmacist who prepared the medications.

White blood cell (WBC) count and absolute neutrophil count (ANC) were checked daily. The ANC recovery time was recorded (the time to ANC ≥ 500/mm^3) in each patient. The primary outcome was to compare neutrophil recovery time between the two groups. The secondary outcome was to compare the duration of hospitalization and treatment complications between the intervention and control groups. The effectiveness of treatment for the primary outcome was defined if ANC recovery took place less than seven days after starting the medication. For the secondary outcome, it was defined if the hospital stay was seven days or less.

Inclusion and exclusion criteria

The following inclusion criteria were used: children who have lymphoblastic leukemia, age 2-18 years who were admitted due to febrile neutropenia.

Those who refused to take part in the study, infants younger than two years, and patients with a history of hypersensitivity reaction to *A. ampeloprasum* L. were excluded.

Plant material

Three samples of fresh *A. ampeloprasum* L. were purchased from medicinal plant markets in Shiraz, Fars province, south of Iran. A botanist confirmed the samples from the traditional pharmaceutical group, of the School of Pharmacy, Shiraz University of Medical Sciences. Among the samples, a bunch of longer and thicker leaves with a more juice amount (yield of direct extraction) was selected for later stages. The selected sample was kept at the Herbarium Center of the School of Pharmacy, Shiraz University of Medical Sciences, with a specified voucher (PM 778).

Preparation of drug

The selected sample of *A. ampeloprasum* L. was directly extracted by a juicer (Kenwood, Germany) to extract fresh juices. Regarding the ethnopharmacological aspects associated with the use of fresh *A. ampeloprasum* L. juice (100-120 ml/day), fresh juices of the same volume were filtered to remove fibers and hard components. The liquid was then pasteurized for 30 minutes at 63°C (145°F) in a Bain Marie. Afterward, it was concentrated and freeze-dried under a vacuum condition at a temperature of -50°C for 96 hours (Christ-alpha-1-2, Germany). Approximately 800 mg of dried

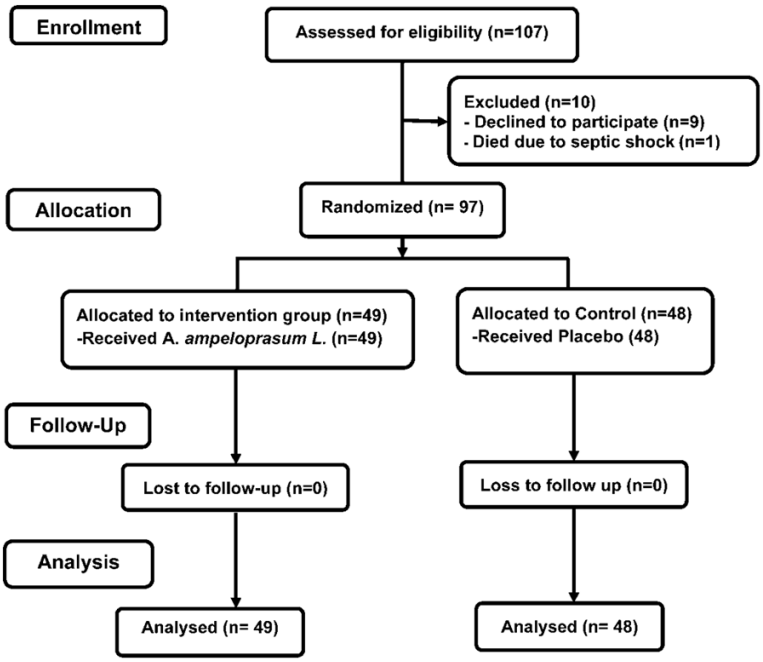

Figure 2. The study consort chart.

extract (adjusted from 100-120 ml of fresh juice) was obtained through the methods mentioned above. This process continued weekly to get the required amount of dry extract for the study participants. The powder from the freezer drying process was re-grinded and sieved into a fine powder (mesh ≈ 50). Finally, it was filled with a sufficient amount of sodium starch glycolate as a filler in two-colored capsules weighing 500 ± 25 mg. For optimization of the drug, all analysis for drug preparation was made within ten days [24]. Additionally, based on a study by Bernaert and co-workers [25], the maximum time of refrigerated storage in household practices was thirteen days.

Preparation of placebo

Parallel to the drug, similar capsules in shape and color were prepared and filled with 10% (W/W) of *A. ampeloprasum* L. leaf powder mixed with 90% (W/W) of sodium starch glycolate as a placebo. For the optimization of a placebo, a similar action such as the drug preparation was taken.

Microbial limit test

The microbial limit test including the total microbial count and screening for microorganisms such as *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Pseudomonas aeruginosa,* and *Candida albicans* was performed to ensure the safety of the drug and placebo. These evaluations were carried out according to the British Pharmacopoeia and International Guidelines [26, 27].

Study protocol

An oral capsule containing 500 mg of *A. ampeloprasum* L. extract powder was taken twice a day until the ANC reached 500/mm^3 or maximally for seven days (whatever comes sooner). For children who were unable to swallow capsules, the contents of the capsule were dissolved in yogurt and were taken. For those who were in the control group, the mentioned placebo capsules were administered.

Statistical analysis

Data were analyzed using SPSS software version 17 (SPSS Inc., Chicago, IL, USA). Descriptive data were presented as mean ± standard deviation, median and interquartile range (IQR), percentages, and appropriate charts. The student's t-test was used to compare the quantitative variables between the two groups. The chi-square test was used to compare qualitative variables between the two groups. The Kaplan-Meier survival curve and the Log Rank test were used to compare the difference in ANC recovery time and duration of hospitalization between the two groups. Variables with a *P* value less than 0.2 were entered in multivariable analysis. The Cox regression analysis was used to determine independent factors affecting drug effectiveness. A *P*-value of less than 0.05 was considered statistically significant.

Results

Ninety-seven patients completed the study. No attrition or early drug withdrawal occurred during the study period. Participants' mean age was 7.90 ± 4.57 years (range 2-18 years), and 52 (53.6%) of them were male. Demographics

Table 1. Demographic features of the studied patients based on gender, age, and type of illness

Parameter	Distribution of Patients	Control Group N (%)	Intervention Group N (%)	*P* Value
Sex	Female	23 (47.9%)	29 (59.2%)	0.312
	Male	25 (52.1%)	20 (40.8%)	
Age (y/o)	2-8	32 (66.7%)	26 (53.1%)	0.320
	9-14	12 (25%)	15 (30.6%)	
	15-18	4 (8.3%)	8 (16.3%)	
Type of Disease (Initial Diagnosis)	Leukemia	27 (56.3%)	25 (51%)	0.72
	Solid tumor	15 (31.3%)	19 (38.8%)	
	Lymphoma	6 (12.5%)	5 (10.2%)	

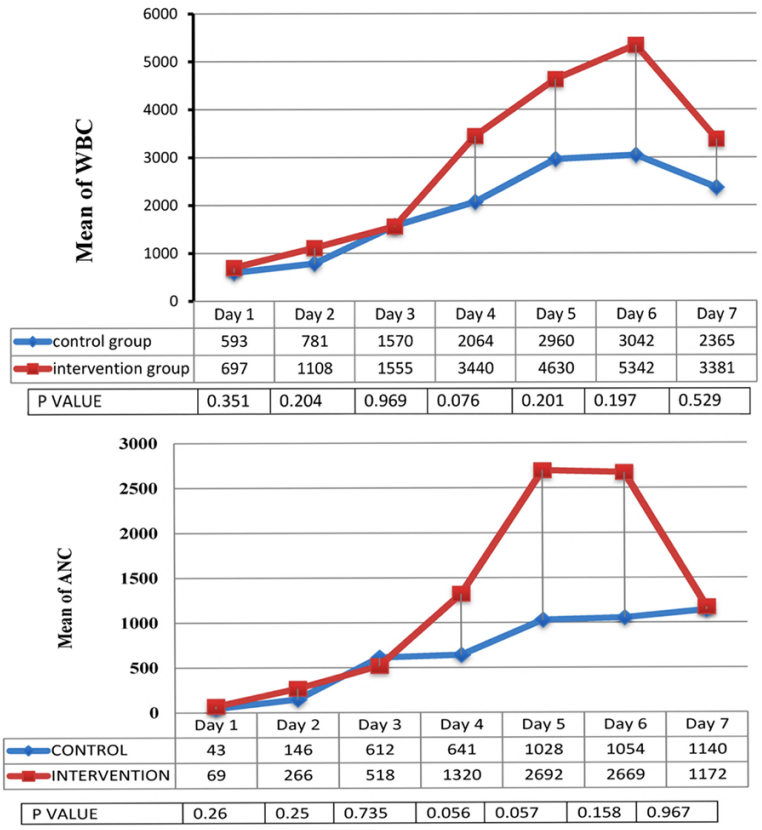

Figure 3. The trend of changes in mean ANC and WBC counts on different days of hospitalization in both treatment arms.

and some clinical characteristics of the studied patients were summarized in **Table 1**. The mean of WBC count and ANC from day one to seven are shown in **Figure 3**.

The mean ANC recovery time in the total population was 5.16 ± 2.77 days (range 2-11). The mean ANC recovery time in the intervention and control groups was 4.02 ± 2.23 and 6.38 ± 2.80 days, respectively (P less than 0.001). The median time to ANC recovery (ANC ≥ 500/mm^3) was three days (95% confidence interval (CI) 2.65-3.34) in the intervention group compared to six days (95% CI 5.07-6.92) in the control group (P less than 0.001) (**Figure 4**).

The median duration of hospitalization in all patients was six days (IQR 4-10). The median duration of hospitalization was five days (IQR 4-9.5) and eight days (IQR 5-11) in the intervention and control groups, respectively.

Concerning drug effectiveness, 41 patients (83.6%) in the intervention group and 26 individuals (54.2%) in the control group showed neutrophil recovery in the seven days of treatment (P less than 0.001) (**Figure 5A**). Moreover, 34 patients (69.4%) in the intervention group and 14 patients (29.2%) in the control group recovered their neutropenia five days after starting the medication (P less than 0.001) (**Figure 5B**). Early discharge from the hospital (≤ 7 days) happened in 33 (67.3%) patients in the *Allium* arm compared to 23 (48%) patients in the placebo arm (P=0.028) (**Figure 6**).

In univariate analysis, treatment with *A. ampeloprasum* L. (P=0.003), higher initial ANC and WBC counts (P less than 0.001), and higher initial platelet counts (P=0.008) were associated with faster ANC recovery. Similarly, higher

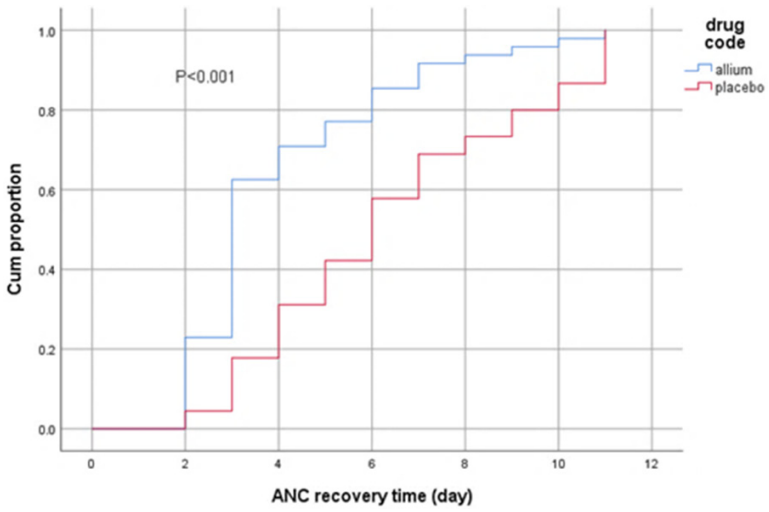

Figure 4. Kaplan-Meier survival curve of ANC recovery time in the two treatment arms.

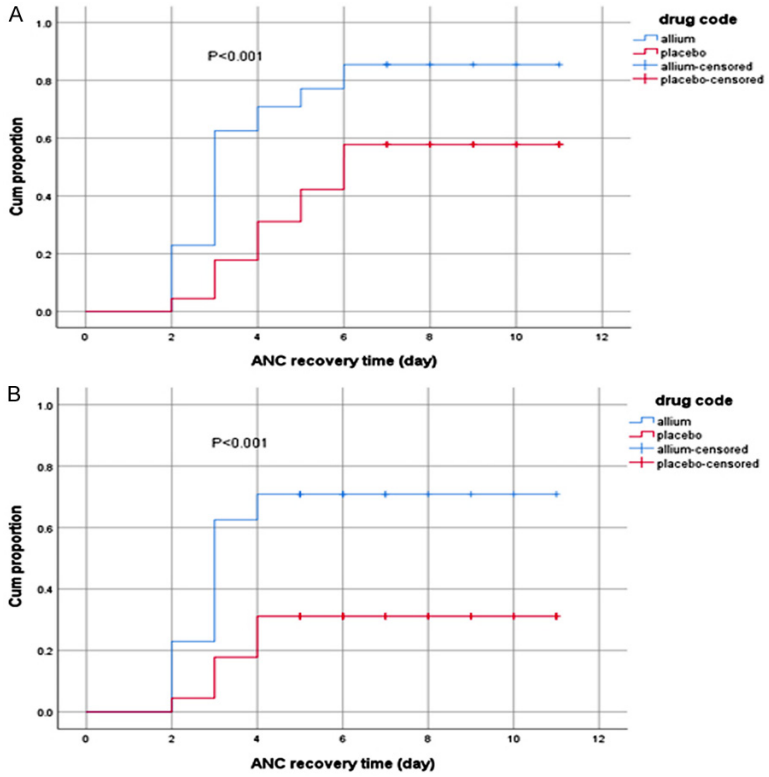

Figure 5. The cumulative proportion of patients with ANC recovery on day ≤ 7 (A) and day ≤ 5 (B) in both treatment arms.

initial ANC and platelet counts (P less than 0.001) and male sex (P=0.014) contributed to a shorter hospital stay. In Cox regression analysis, treatment with *A. ampeloprasum* L. (Odds ratio (OR) 2.61, 95% CI 1.55-4.39, P less than 0.001), higher initial ANC (OR 1.005, 95% CI 1.003-1.007, P less than 0.001), and younger age (OR 0.94, 95% CI 0.88-0.99, P=0.038) were independently associated with faster ANC recovery. Moreover, treatment with *A. ampeloprasum* L. (OR 1.92, 95% CI 1.09-3.39, P=0.23), higher initial WBC counts (OR 1.006, 95% CI 1.003-1.008, P less than 0.001), and younger age (OR 0.93, 95% CI 0.87-0.99, P= 0.32) were independent factors resulting in early discharge from hospital.

According to the outcome of microbial limit tests, no growth of respective pathogens was observed. Moreover, the total colony counts for either drug or placebo capsules were determined less than ten colonies on media. No adverse effect was reported with using *Allium* capsules, and the drug was well tolerated.

Discussion

The *Allium* species are well known for antibacterial, anti-inflammatory, anti-cancer, and immunomodulatory properties [10].

Despite plenty of animal studies, this current study was the first randomized, placebo-control, double-blind, clinical trial in pediatric cancer patients admitted due to neutropenic fever. Treatment with *A. ampeloprasum* L. resulted in faster bone marrow recovery compared to the control group. The median time to ANC recovery was three days earlier in the intervention arm compared to the placebo (P less than 0.001) (**Figure 4**). The patients in the *A. ampeloprasum* L. (Intervention group) arm experienced higher mean WBC and ANC than the placebo arm, though the difference was not

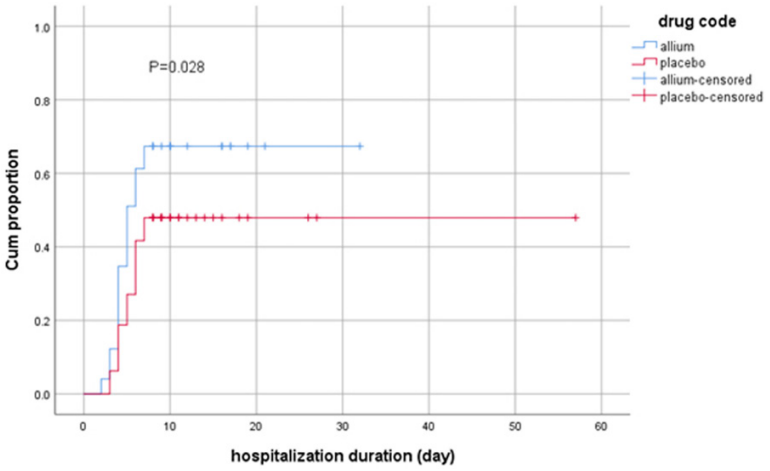

Figure 6. The cumulative proportion of patients with hospital length of stay ≤ 7 days in the two treatment arms.

statistically significant. The difference started on the third day of *A. ampeloprasum* L. treatment and reached a peak on the fifth or sixth day of treatment (**Figure 3**). In previous studies, the beneficial properties of different *Allium* species on the immune system have been proven in animal models. Mirabeau and coworkers [18] examined the effects of single and combined oral intake of Onion liquid extract and garlic on the immunity of white rats and concluded that the use of both extracts separately increased the WBC counts and CD4 cells. Similarly, Hanieh and coworkers [19] examined the effect of garlic and onion on white Leghorn chickens' immune system and stated that a diet containing the mentioned *Allium* species had the potential to increase the immune system of the white Leghorn chickens. *A. cepa* agglutinin, an immunomodulatory protein, was reported to alleviate cyclophosphamide-induced immunosuppression in Wistar rats [28]. Moreover, it was shown that garlic and other plants of the Amaryllidaceae family provide protective activity in chemo-radiation damage in the mice species [29].

The effect of G-CSF on faster neutrophil recovery, shorter hospital length of stay, and shorter duration of antibiotic use in chemotherapy-induced febrile neutropenia was shown in a Cochrane systematic review [30]. According to the results, it seems that the combination of *A. ampeloprasum* L. and G-CSF is effective in shortening bone marrow recovery time and duration of hospitalization in chemotherapy-induced febrile neutropenia in children with lymphoblastic leukemia.

Regarding drug efficacy, more than 85% of patients in the intervention group got to benefit from the drug given that they achieved bone marrow recovery less than a week after they took *A. ampeloprasum* L. This was significantly higher than G-CSF-only treated patients who experienced bone marrow recovery in about 58% of the individuals (P=0.005). Moreover, a higher proportion of patients who were treated with *A. ampeloprasum* L compared to the placebo arm could be discharged from the hospital before day 7 of admission (67% vs. 48%, P=0.028).

Multivariable analysis confirmed that treatment with *A. ampeloprasum* L, higher initial ANC, and younger age were independently associated with faster ANC recovery and earlier discharge from hospital in febrile neutropenic children with cancer. Initial ANC on the day of admission was directly associated with ANC recovery time and hospital stay. For every 100 units increase in initial ANC, the chance of ANC recovery and early hospital discharge before day 7 of admission increased by 50% and 60%, respectively. Age had an inverse relation with BM recovery, so that increase in age may correlate with delayed neutrophil recovery and hospital discharge.

Finally, patients treated with *A. ampeloprasum* L plus G-CSF showed ANC recovery before day seven more than 2.5 times faster than G-CSF-only treated groups. Besides, the chance of early discharge from the hospital was almost doubled. It seems that *A. ampeloprasum* L. can successfully shorten neutrophil maturation time leading to earlier discharge from the hospital and lesser antibiotic use. Hence, it has a positive impact on reducing treatment costs. Moreover, in the era of increasing antibiotic resistance, earlier hospital discharge and less antibiotic consumption are a great success in controlling multidrug-resistant bacteremia in antimicrobial stewardship programs [31, 32].

Conclusion

A. ampeloprasum L. may effectively reduce ANC recovery time in combination with GCSF, leading to earlier discharge from the hospital, thus shortening hospitalization and reducing treatment costs. Besides, it may reduce antibiotic therapy duration, which has a significant role in preventing antibacterial resistance. The drug was well tolerated without any serious adverse effects. More extensive multicenter studies are required to confirm its efficacy and safety.

Limitation of study

However, in this study, it was better to check the level of *A. ampeloprasum* L, in patients after using this herb with a high-performance liquid chromatography method. We could not do this due to a lack of facilities.

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Disclosure of conflict of interest

None.

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