CHANGES IN NUTRITIONAL STATUS OF PEDIATRIC PATIENTS WITH OSTEOSARCOMA TREATED WITH THE MAP REGIMEN IN 2022-2024 AND ASSOCIATED FACTORS

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ABSTRACT

Objectives: To evaluate changes in nutritional status among pediatric osteosarcoma patients treated with the MAP regimen at K Hospital between 2022 and 2024, and to explore potential associations.

Methods: A retrospective descriptive study was conducted on 50 medical records of pediatric patients with osteosarcoma who received MAP regimen and were discharged between 2022 and 2024.

Results: At treatment initiation, 34% of patients had malnutrition by BMI (14% underweight and 20% overweight/obese), and 4% were stunted. During treatment, body weight decreased and showed a slow recovery after the 4th cycle. The prevalence of anemia increased progressively, reaching 90% by 6th cycle. The malnourished group had a significantly longer mean hospital stay than the overweight/obese group (117.5 vs. 76 days, $p < 0.05$). The rate of good response to neoadjuvant chemotherapy was 70%. Patients with normal BMI and those who were overweight had higher response rates than the malnourished group, although the difference was not statistically significant ($p > 0.05$).

Conclusions: Pediatric osteosarcoma patients treated with the MAP regimen are at risk of malnutrition (including weight loss, anemia, and leukopenia) during treatment. Appropriate nutritional care strategies are needed to improve nutritional status, quality of life, and treatment outcomes.

Keywords: Osteosarcoma; nutrition; MAP regimen.

I. INTRODUCTION

Osteosarcoma is a rare primary malignant bone tumor arising from mesenchymal osteogenic cells [1]. The disease most commonly affects children and young adults. Osteosarcoma accounts for approximately 56% of all bone cancers in individuals under 20 years old. In Vietnam, it represents about 5% of all pediatric malignancies.

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The MAP chemotherapy regimen, consisting of high-dose methotrexate combined with cisplatin and doxorubicin, is currently used in osteosarcoma treatment at the National Cancer Hospital (K Hospital) and is considered the standard regimen in Europe and the United States.

Patients treated with the MAP regimen may experience multiple chemotherapy-related adverse effects that significantly affect nutritional intake. Doxorubicin may cause nausea, vomiting, abdominal pain, and diarrhea. Cisplatin induces nausea and vomiting in up to 95% of cases within 1-4 hours after administration, and is also associated with gastrointestinal disturbances and anorexia. High-dose methotrexate can cause oral mucositis, nausea, vomiting, diarrhea, and loss of appetite. Therefore, the nutritional status of osteosarcoma patients tends to deteriorate during treatment.

A retrospective study by Karen Ringwald-Smith et al. in 48 pediatric osteosarcoma patients showed that the prevalence of underweight at diagnosis was 8%, overweight 15%, and obesity 8%. After treatment, the proportion of underweight patients increased to 17%, while overweight decreased to 8% and obesity to 2% [2].

Nutritional status significantly influences treatment outcomes. Osteosarcoma patients receiving MAP chemotherapy typically undergo surgery at week 12. Malnutrition is associated with delayed wound healing due to prolonged inflammation, reduced fibroblast proliferation, decreased collagen synthesis, and impaired angiogenesis. Several studies have also shown that poor nutritional status is associated with higher rates of surgical site infection and delayed wound healing [3]. In addition, malnutrition and muscle wasting negatively affect postoperative functional recovery, reducing muscle strength, limiting mobility, and increasing the risk of joint stiffness.

In Vietnam, particularly at the National Cancer Hospital, studies on nutritional status in osteosarcoma patients, as well as factors influencing it and its relationship with treatment and surgical outcomes, remain limited. Therefore, this study was conducted to evaluate changes in nutritional status among pediatric osteosarcoma patients treated with the MAP regimen from 2022 to 2024 and to analyze associated factors.

2. SUBJECTS AND METHODS

2.1. Study population

The study included medical records of pediatric patients with osteosarcoma treated at the Pediatric Department, National Cancer Hospital (K Hospital), Vietnam. Patients received the MAP chemotherapy regimen (methotrexate, doxorubicin, and cisplatin) as neoadjuvant treatment, followed by surgery, and continued with at least ≥4 cycles of adjuvant chemotherapy after surgery. All patients were discharged between 01 January 2022 and 31 December 2024.

Inclusion criteria:

- Age from 5 to under 18 years.

- Histopathological diagnosis of osteosarcoma.

- Tumor located in long bones.

Exclusion criteria:

- Incomplete medical records with missing key study data.

- Patients who discontinued treatment for any reasons.

- Patients with other concomitant malignancies or prior chemotherapy treatment.

- Presence of significant comorbid diseases.

- Patients with congenital malnutrition and/or growth retardation.

2.2. Study design and methods

- Study design: Retrospective descriptive study.

- Sample size: All eligible cases during the study period were included due to the rarity of the disease.

- Sampling method: Convenience sampling.

In total, 50 eligible medical records meeting the collected criteria were included in the analysis.

* Study setting and duration.

- Study period: March 2025 to December 2025.

- Study site: Pediatric Oncology Department, K Hospital.

* Study variables and indicators

- General characteristics: age, sex, ethnicity, place of residence, tumor location, surgical site, surgical method, treatment duration, disease stage, response to neoadjuvant chemotherapy (Huvos grading system), and postoperative complications.

- Nutritional status assessment: Body weight (at the start of 1st, 2nd, 4th, 5th, and 6th chemotherapy Cycle), Height, BMI, Weight-for-age index, Height-for-age index, Percentage of weight loss, Nutrition-related laboratory parameters: Creatinin, AST, ALT, Hemoglobin, Lymphocyte count, Total white blood cell count, Neutrophil count (before beginning of 1st, 2nd, 4th, 5th and 6th chemotherapy Cycle).

* Standard assessment

- Nutritional status was classification by WHO Growth Reference Data for 5-19 years (2007).

- Classification of anemia was based on the WHO criteria for anemia by haemoglobin (2011).

- Tumor response to neoadjuvant chemotherapy was assessed histologically using the Huvos grading system, with a good response defined as ≥90% tumor necrosis and a poor response as <90%.

2.3. Data analysis

- After data collection, the data will be cleaned and entered into a computer using Epidata 3.1 software. Statistical analyses will be performed using STATA version 12.0. Descriptive and inferential statistical analyses will be conducted, with a significance level of $\alpha = 0.05$ used for inferential statistics.

- The Chi-square (χ^2) test or Fisher's exact test will be used to compare differences between categorical variables.

2.4. Ethical considerations

- This retrospective study was conducted after approval by the Ethics Committee of the National Cancer Hospital (K Hospital), under approval number 1400/BVK-HĐĐĐ dated April 28, 2025.

- All information collected from study subjects was used exclusively for research purposes, was kept strictly confidential, and was not used for any other purposes.

3. RESULTS

50 medical records were included in the analysis, with ages ranging from 6 to 18 years. The most frequently observed ages were 14 and 15 years. The mean age was 13.2 years.

Table 1. General characteristics of study subjects (n=50)

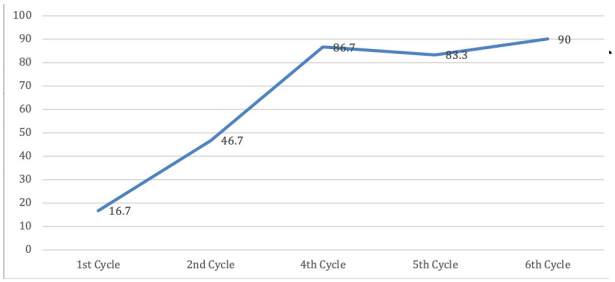
Characteristics		n	%
Gender	Male	31	62
	Female	19	38
Ethnicity	Kinh	47	94
	Others	3	6
Place of residence	Rural	29	58
	Urban/town/city	15	30
	Mountainous area	6	12
Tumor location	Humerus/forearm bones	6	12
	Femur/lower leg bones	44	88

Characteristics		n	%
Disease stage	Stage II	49	98
	Stage III	1	2
Surgical method	Limb-sparing surgery	43	86
	Amputation	7	14

Comment: Among the 50 patients included in the study, males accounted for the majority (62%), with a male-to-female ratio of 1.6:1. Most patients were of Kinh ethnicity (94%). A higher proportion of patients lived in rural areas (58%). The predominant tumor location was in the lower extremities, accounting for 88% of cases. Nearly all patients were diagnosed at stage II (98%). Limb-sparing surgery was performed in 86% of patients.

Table 2. Nutritional status of study subjects (n=50)

Indicators		n	%
Height-for-age	Stunted	2	4
	Normal	48	96
BMI-for-age	Underweight	7	14
	Normal	33	66
	Overweight/Obesity	10	20



Picture 1. Anemia status at the beginning of chemotherapy cycles (n=50)

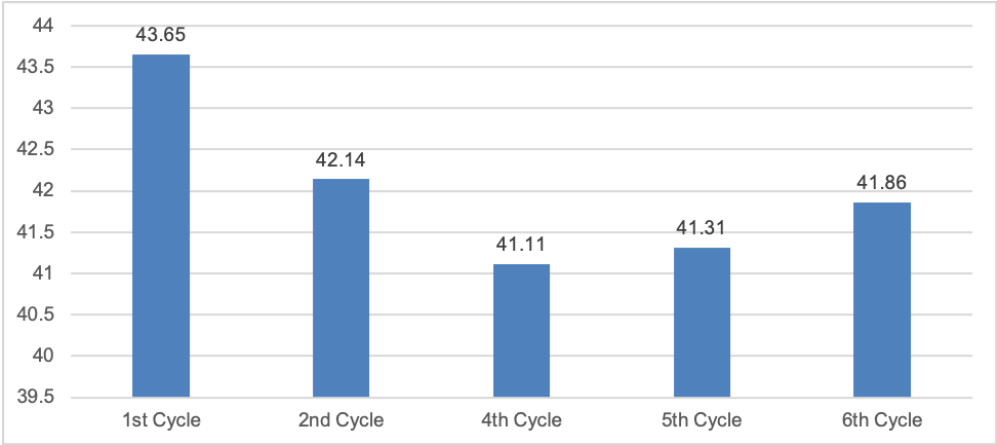
Comment: At treatment initiation, the prevalence of anemia among study patients was 16.7%. During the course of chemotherapy cycles, the rate of anemia increased progressively. The prevalence reached 86.7% at 4th Cycle and rose to 90% by 6th Cycle 6.

Table 3. Changes in white blood cell parameters during treatment

	1st Cycle	2nd Cycle	4th Cycle	5th Cycle	6th Cycle
Leukocytes (G/L)	9.3	7.0*	6.3*	5.4*	4.1*
Neutrophils (G/L)	5.6	4.6	3.9*	2.9*	2.1*
Lymphocytes (G/L)	2.8	2.0*	1.8*	1.8*	1.5*

*t-test, $p<0.05$

Comment: The total white blood cell count showed a progressive decline across chemotherapy cycles, with statistically significant differences between subsequent cycles compared to the previous ones and also compared to 1st Cycle , except for the comparison between 2nd Cycle and 4th Cycle, which was not statistically significant. Neutrophil counts also showed a gradual decrease over time. The differences were statistically significant between 4th, 5th, 6th Cycles compared with 1st Cycle, as well as between 5th Cycle and 4th Cycle, and between 6th Cycle and 5th Cycle. Lymphocyte counts demonstrated a decreasing trend as well; however, statistically significant differences were observed only between subsequent cycles and 1st Cycle.



Picture 2. Changes in body weight during chemotherapy cycles (n=27)

Comment: Among 27 patients with complete weight data across treatment cycles, body weight showed a decreasing trend up to 4th Cycle, from 43.65 kg at 1st Cycle to 41.11 kg at 4th Cycle . Subsequently, body weight showed a slight recovery, increasing to 41.86 kg at cycle 6.

Table 4. Hospital stay duration according to BMI classification (N=40)

BMI classification	Mean (days)	Standard deviation (SD)	Min - Max	Percentage (%)
Underweight	117.5*	49.1	57 - 205	15
Normal weight	91.5*	39.1	56 - 212	70
Overweight/Obesity	76*	9.5	62 - 89	15
Overall	93.1	38.9	56 - 212	100

* p> 0.05, Kruskal – Wallis test

Comment: The mean hospital length of stay among patients was 93.1 days. The undernourished group had the longest average hospitalization time (117.5 days), followed by the normal group (91.5 days), while the overweight/obesity group had the shortest duration (76 days). The difference between 3 groups was non-statistically significant.

Table 5. Hospital length of stay according to height-for-age classification (N=40)

Height-for-age classification	Mean (days)	Standard deviation (SD)	Min- Max	Percentage (%)
Stunted	67.5*	14.8	57 - 78	5
Normal	94.4*	39.4	56 - 212	95
Overall	93.1	38.9	56 - 212	100

*p>0.05, t-test

Comment: The mean hospital length of stay in the stunted group was 67.5 days, while it was 94.4 days in the normal group. However, the difference between the two groups was not statistically significant.

Table 6. Response rate (%) to neoadjuvant chemotherapy according to BMI classification (N=50)

Response to neoadjuvant chemotherapy	BMI			Total (%)
	Underweight (%)	Normal (%)	Overweight (%)	
Good	6	50	14	70
Poor	8	16	6	30
Overall	14	66	20	100

*Fisher exact test, p = 0.22

Comment: The normal BMI and overweight groups had a higher proportion of good response to neoadjuvant chemotherapy compared with poor response. In contrast, in the underwweight group, the proportion of poor response was higher than that of good response. However, these differences were not statistically significant.

4. DISCUSSION

4.1. General characteristics

At the end of the study, 50 eligible records were included in the analysis. Males accounted for the majority (62%), with a male-to-female ratio of 1.6:1. This proportion is similar to the overall epidemiology of osteosarcoma in patients under 24 years of age, where the reported male-to-female ratio is 1.43:1 [1].

Most patients were of Kinh ethnicity (94%). As a tertiary referral cancer center, K Hospital receives a large number of patients from across the country. The low proportion of ethnic minority patients in this study may be related to limited awareness of osteosarcoma among ethnic minority populations, geographical distance to major hospitals, and financial barriers to access healthcare. These factors may also negatively affect disease prognosis in osteosarcoma patients.

The tumor was predominantly located in the lower limbs (88%), which are the most common sites for osteosarcoma. All patients in this study were diagnosed at stage II or III, with nearly all cases (98%) being stage II. This is consistent with clinical practice, as patients are often diagnosed when presenting with pain and soft tissue swelling, indicating local invasion or medullary involvement.

After neoadjuvant MAP chemotherapy, patients typically underwent surgery at weeks 10-12. Surgical treatment included limb amputation or limb-sparing procedures. In this study, 86% of patients underwent limb-sparing surgery (tumor resection with endoprosthetic reconstruction). This rate is higher than that reported by Phan Đắc Phương et al. (80%) at the Pediatric Department during 2019-2022 [4]. This increase is a positive outcome, as limb-sparing surgery improves both functional outcomes and quality of life.

4.2. Nutritional status in pediatric osteosarcoma patients

Many studies have shown that malnutrition is a negative prognostic factor in pediatric cancer patients, with survival decreasing in proportion to the severity of malnutrition. Underweight children with cancer, especially those with metastatic disease, have lower survival rates. Malnutrition is also associated with reduced treatment tolerance, poorer response to chemotherapy, treatment delays, increased risk of infections, and decreased quality of life [5].

In our study, the prevalence of stunting assessed by height-for-age was 4%. Underweight status based on BMI-for-age was 14%, while overweight and obesity accounted for 20%. These results are consistent with the study by Karen Ringwald-Smith et al. in 48 children with osteosarcoma, which reported 8% underweight, 15% overweight,

and 8% obesity at diagnosis. After neoadjuvant chemotherapy, nutritional status tended to worsen, with underweight increasing to 11%, overweight decreasing to 9%, and obesity at 7%. By week 23, nutritional status further deteriorated (18% underweight, 0% overweight, and 2% obesity). However, by the end of treatment, a slight improvement was observed, with 17% underweight, 8% overweight, and 2% obesity [2].

In our study, mean body weight also decreased significantly across chemotherapy cycles, providing further evidence of nutritional decline during treatment. This deterioration may be explained by multiple factors, including tumor-related pain and metabolic effects leading to reduced food intake and increased energy expenditure, as well as chemotherapy-related side effects from the MAP regimen that impair appetite and digestion.

Nutritional deterioration during treatment is an adverse prognostic factor. Early weight loss at diagnosis is a risk factor for further malnutrition during treatment, and baseline malnutrition is associated with worse outcomes and increased mortality. Malnourished patients at the beginning of treatment have poorer survival. Malnutrition is also associated with a higher risk of infectious complications. Both low BMI at baseline and significant weight loss during treatment are strong predictors of bacterial and fungal infections and reduced survival [6]factors attributed to treatment, and specific individual risk factors in each patient. Patients with chemotherapy-induced neutropenia are at particularly high risk, and microbiological agents include viral, bacterial, and fungal agents. The etiology is often unknown in infectious complications, although adequate patient evaluation and sampling have diagnostic, prognostic and treatment-related consequences. Bacterial infections include a wide range of potential microbes, both Gram-negative and Gram-positive species, while fungal infections include both mold and yeast. A recurring problem is increasing resistance to antimicrobial agents, and in particular, this applies to extended-spectrum beta-lactamase resistance (ESBL. In particular, weight loss during the first 3 months of treatment is associated with a higher risk of sepsis [7].

4.3. Nutritional status and related factors

Nutritional deterioration during treatment may negatively affect drug tolerance, overall survival, infection risk, quality of life, and length of hospital stay. In osteosarcoma, there are still limited studies assessing the relationship between malnutrition and these outcomes.

Our study showed that the mean hospital length of stay in the malnourished group was longer than in the normal and overweight/obese groups. However, a statistically significant difference was observed only between the malnourished group and the overweight/obese group (117.5 days vs. 91.5 days). Malnourished patients were also at higher risk of chemotherapy toxicity, including hematologic toxicity and infection. The risk of leukopenia after treatment increased with the severity of malnutrition [8], leading to longer hospitalization and higher treatment costs.

In our study, height-for-age was used to classify nutritional status, and hospital length of stay was compared between the stunted and normal groups. Although the proportion of stunting was low (5%), the hospital stay in this group appeared shorter than in the normal group (67.5 days vs. 94.4 days). However, this difference was not statistically significant. This finding suggests a potential association that warrants further investigation, as few studies have evaluated the relationship between stunting and hospitalization duration in pediatric osteosarcoma.

The good response rate to neoadjuvant chemotherapy in pediatric osteosarcoma patients in our study was 70%. This result is consistent with the study by Yair Peled et al. and higher than that reported by Phan Đắc Phương (51.3% in 2019–2022) [4], [9]. This may reflect improvements in osteosarcoma treatment in recent years (2022–2024) and closer alignment with international outcomes.

This study has several limitations. First, its retrospective design relies on data extracted from medical records documented by different physicians, which may introduce variability in measurement techniques and a lack of standardized calibration of instruments. Such heterogeneity could affect the accuracy and consistency of the collected data. Second, the relatively small sample size (n = 50) limits the statistical power of the analyses, and therefore the findings should be interpreted with caution, as they may not be sufficient to draw definitive conclusions. In addition, more than 50 records were excluded from the analysis due to missing data and not meeting the inclusion criteria. This also represents a limitation of the study, as it may limit the ability to provide a comprehensive assessment of the study population.

5. CONCLUSION

This study showed that at treatment initiation, 34% of children were malnourished and 4% were stunted. During chemotherapy, patients experienced progressive weight loss and a marked increase in anemia up to 90% by 6th Cycle, followed by gradual weight recovery after the 4th Cycle. The overall good response rate to neoadjuvant chemotherapy was 70%. These findings demonstrate that children with osteosarcoma receiving the MAP regimen are at high risk of nutritional deterioration and need for early and appropriate nutritional support. Some potential association factor may be hospital length stay, response to neoadjuvant chemotherapy need to assess in future study.

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