Clinical Research

Association between immune system parameter and clinical characteristics among patients with solid cancer

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ABSTRACT

BACKGROUND Lymphopenia has been reported to be a major predictor of chemotherapy-related toxicity. This study aimed to investigate the correlation between neutrophils, lymphocytes, CD4, and CD8 in solid cancer patients and cancer clinical characteristics.

METHODS This was a cross-sectional study of patients who will undergo chemotherapy at the Hematology and Medical Oncology Clinic, Cipto Mangunkusumo Hospital, from June to September 2023. Clinical characteristics, CD4 and CD8 levels, and neutrophil and lymphocyte counts were assessed at the first visit. A comparative test was carried out on the patients' average CD4, CD8, neutrophil, and lymphocyte counts.

RESULTS Types of cancer were associated with CD4 levels. Patients with head and neck cancer had lower CD4 levels (411.3 [119.3–1,427.5] cells/mm^3) compared with colorectal (514.7 [129.2–861.3] cells/mm^3), breast and gynecological (567.5 [180.1–939 cells/mm^3), and other cancers (681.4 [175.1–2,056.9] cells/mm^3), with p = 0.009. Patients aged ≥40 years had higher CD8 levels than those aged <40 years (376.4 [142.8–1,293.1] cells/mm^3 *versus* 565.3 [185.9–1,944] cells/mm^3, p = 0.01). Additionally, lymphocyte count was associated with cancer type, with the lowest number in head and neck cancer (1,380 [280–2,660] µl, p = 0.044).

CONCLUSIONS CD4 levels and lymphocyte counts were associated with the cancer type, whereas CD8 levels were influenced by age.

KEYWORDS CD4 lymphocyte count, malignancy

The immune system primarily performs essential tasks, such as identifying and eradicating foreign substances, establishing immune memory, and fostering tolerance towards the body's self-antigens. Lymphocytes differentiate within primary lymphoid organs, bone marrow and thymus, yielding B, T, and natural killer cells. In particular, T cells mature in the thymus to become CD4+ and CD8+ T cells, whereas immature B cells complete their development in the spleen.[1,2]

T lymphocytes carry out cell-mediated immunity and provide adaptive immunity that functions closely with the innate immune system. CD4+ T cells serve various functions, including stimulation of innate immune cells, cytotoxic T cells, B lymphocytes, and non-immune cells, and are also involved in immune response suppression.[2] Meanwhile, naive CD8 T cells are stimulated when they recognize particular peptides presented by major histocompatibility complex class I on antigen-presenting cells (APCs) in lymphatic organs. Furthermore, the differentiation of CD8+ T cells is influenced by the signals and cytokines delivered by APCs and CD4+ T cells. Following this activation, CD8 T cells become numerous effector cells that migrate

to peripheral tissues.[3] However, dysfunction of tumor-reactive CD8 T cells is linked to tumor development.[4]

Moreover, the location of head and neck tumors may influence factors such as body mass index (BMI) and reduced oral intake due to difficulties in chewing and swallowing, potentially causing a poor prognosis.[5] Low lymphocyte counts before treatment are associated with shorter overall survival (OS) and progression-free survival (PFS) in patients with solid cancer.[6]

Neutrophilia, a chronic inflammatory condition, is frequently observed in cancer. Elevated neutrophil levels have been linked to the suppression of immunity against cancer, particularly by suppressing the activity of cytotoxic T lymphocytes. An increased neutrophil count was also accompanied by relative lymphocytopenia, indicating a reduced adaptive immune response.[3]

Approximately 20% of patients with advanced cancer and 3% of those with localized disease have been reported to experience lymphopenia, which affects both T and B cells. CD4 lymphopenia is predominantly observed in advanced stages, while CD8 lymphopenia can be detected in patients with localized primary tumors.[7] Therefore, this study aimed to discuss the relationship between neutrophils, total lymphocytes, CD4, and CD8 levels in patients with solid cancer and their clinical characteristics.

METHODS

This cross-sectional study used a total sampling method for patients who underwent their first chemotherapy at the Hematology and Medical Oncology Clinic, Cipto Mangunkusumo Hospital, between June to September 2023. The inclusion criterion was patients aged >18 years with solid cancers who underwent chemotherapy. Patients who refused to have their blood samples drawn for the study were excluded. CD4 and CD8 levels in patients who underwent their first chemotherapy regimen were calculated using cytometry. Demographic data, cancer type and stage, and patient performance statuses were also recorded. Furthermore, the patient's age was divided into ≥40 and <40 years groups; BMI was divided into underweight, normal weight, and overweight; the Eastern Cooperative Oncology Group scale was divided into 0 and >0; and the stage was divided into metastatic and nonmetastatic. Subsequently, a comparative analysis was conducted using an independent *t*-test and one-way analysis of variance to assess the averages with a normal distribution. The Mann–Whitney and Kruskal–Wallis tests were applied when the data did not exhibit a normal distribution. A *p*-value of <0.05 is considered statistically significant.

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RESULTS

The clinical characteristics of the study participants are presented in Table 1. Seventy-four males and females who met the inclusion criteria participated in this study, with an average age of 48.8 years. These patients had normal BMIs, followed by underweight patients. Despite most of them having good performance status, they commonly have head and neck carcinoma type of tumor, predominantly in stages III and IV. Comparison between groups can be seen in Table 2.

DISCUSSION

CD4 counts were significantly lower in patients with head and neck cancer. Tobacco and alcohol, recognized as mutagens, are associated with genetic mutations and possible alterations leading to squamous cell carcinoma of the head and neck (SCCHN).[8] Individuals with oral malignancies exhibit significantly decreased levels of CD4+ and CD3+ T cell subsets, and lower CD4/CD8 ratios. Additionally, there was a notable reduction in the proportion of CD4+ IL-2+ T cells, whereas the proportions of CD8+ IL-4+ and CD3+ IL-4+ T cells significantly increased. Reduced expression of IL-2 in both CD8+ and CD4+ subsets is associated with advanced cancer stages. Tobacco-related oral cancer seems to be linked with multiple systemic immune abnormalities, primarily affecting CD4+ and CD3+ T cells, resulting in differential regulation of IL-4 and IL-2 in CD8+ and CD4+ T-cell subsets in peripheral blood.[9] Caruntu et al[10] also found lower CD4 levels among patients with head and neck cancer, suggesting immune suppression in SCCHN tumor cells.

Table 1. Clinical characteristics of the patients

Characteristics	n (%) (N = 74)
Age (years), mean (SD)	48.8 (15)
Sex	
Male	37 (50)
Female	37 (50)
BMI	
Underweight	18 (24)
Normoweight	41 (55)
Overweight	7 (10)
Obese	8 (11)
Cancer type	
Head and neck	32 (43)
Colorectal	7 (10)
Breast and gynecology	18 (24)
Others*	17 (23)
Performance status (ECOG score)	
0	54 (73)
1	16 (22)
2	2 (3)
3	2 (3)
Cancer stage	
I	0 (0)
II	0 (0)
III	34 (46)
IV	40 (54)
CD4 level (cells/mm^3), median (range)	520.5 (119.3–2056.9)
CD8 level (cells/mm^3), median (range)	464.4 (142.8–1944)
Neutrophil count (µl), median (range)	6,410 (1,780–29,130)
Lymphocyte count (µl), mean (SD)	1,660 (682)

BMI=body mass index; ECOG=Eastern Cooperative Oncology Group; SD=standard deviation
*Others were neuroendocrine carcinoma hepar, osteosarcoma, lung adenocarcinoma, and synovial sarcoma

In the present study, the median CD8 levels in participants aged ≥40 were lower than those aged <40. Three shifts in T-cell roles have been identified in older adults. The quantity and percentage of naive T cells decreased, which was associated with a gradual decline in thymus function with age that affected the naive CD8 T-cell population. Primary T-cell responses stem from the naive T-cell compartment, which acts as a diverse reservoir of precursors that differentiate upon encountering antigens, ultimately populating the memory and effector T-cell compartments. Maintenance of the naive T-cell pool relies on thymic output. However, aging triggers thymic involution, resulting in a reduction in both size and functionality of the thymus. Consequently, there is a decline in naive T cells and increased homeostatic proliferation within this pool.[11]

The compromised efficacy of CD8+ T cell priming observed in elderly individuals is linked to the diminished size of the naive CD8+ T cell compartment and associated repertoire impairments. In addition to thymic involution, factors contributing to the reduced effectiveness of CD8+ T cells include intrinsic cellular defects that affect the activation and differentiation of primed CD8+ T cells in aging individuals. Notably, impaired T cell receptor signaling in the elderly contributes to suboptimal proliferation of naive CD8+ T cells. The diminished T cell priming efficacy associated with aging is related to the depletion of primary immune resources, including alterations in the frequency and function of both naive T cells and dendritic cells (DCs). Disturbances within the DC compartment may further disrupt the CD8+ T-cell priming capacity.[11]

This study found significantly different numbers of lymphocytes in several types of cancers, including neck cancer. Head and neck tumor, which affects the oral cavity, lips, oropharynx, nasopharynx, hypopharynx, nasal cavity, paranasal sinuses, and larynx, may influence BMI and correlate with problems in chewing and swallowing, leading to reduced oral intake.[5] Ziętarska et al[12] revealed that 5% of patients with colorectal tumors experience cachexia, a condition of >10% weight loss without noticeable appetite impairment. Leandro-Merhi et al[13] concluded a positive correlation between malnutrition incidence and total lymphocyte count among hospitalized patients.

Several clinical studies have indicated that pretreatment peripheral blood lymphopenia correlates with unfavorable projections in various cancers, including late-stage carcinomas and sarcomas, cervical cancer, renal carcinoma, and bladder cancer. A systematic review and meta-analysis by Zhao et al[6] evaluated lymphocyte counts before treatment in individuals with solid tumors, thus showing how low lymphocyte counts were associated with shorter OS and PFS. Furthermore, in the analysis of OS and PFS, the adverse prognostic impact of a low lymphocyte count persisted when stratified by disease stage, encompassing both stage IV and non-stage IV subgroups. This suggests that

Table 2. Associations between CD4, CD8, CD4/CD8 ratio, neutrophil, and lymphocyte counts and clinical characteristics

Clinical characteristics	CD4 (cells/mm^3), median (range)	*p*	CD8 (cells/mm^3), median (range)	*p*	CD4/CD8 ratio (cells/mm^3), median (range)	*p*	Neutrophil count (µl), median (range)	*p*	Lymphocyte count (µl), median (range)	*p*
Age (years)		0.644		**0.01**		0.06		0.398		0.476
≥40	520.5 (119.3–2,056.9)		376.4 (142.8–1,293.1)		1.16 (0.39–5.28)		6,370 (1,780–29,130)		1,530 (280–3,970)	
<40	521.5 (234.7–1,574.2)		565.3 (185.9–1,944)		0.9 (0.37–2.00)		7,360 (2,790–13,800)		1,710 (730–2,960)	
BMI		0.068		0.102		0.856		0.705		0.05
Underweight	581.6 (175.1–2,056.9)		502.5 (164.9–980.6)		1.15 (0.37–2.79)		6,270 (3,210–15,120)		1,920 (880)*	
Normoweight	416.5 (119.3–1,400.1)		373.2 (142.8–1,293.1)		1.11 (0.37–2.79)		6,080 (1,780–29,130)		1,490 (560)*	
Overweight	672.9 (211.5–1,574.2)		572.4 (199.7–1,944)		1.07 (0.54–5.28)		8,330 (2,700–11,400)		1,820 (610)*	
Cancer type		**0.009**		0.180		0.207		0.161		**0.044**
Head and neck	411.3 (119.3–1,427.5)		380.1 (142.8–905.2)		1.1 (0.37–5.28)		6,380 (1,780–26,790)		1,380 (280–2,660)	
Colorectal	514.7 (129.2–861.3)		332.8 (199.7–980.6)		1.14 (0.39–2.58)		6,400 (3,550–13,730)		990 (910–2,330)	
Breast and gynecological	567.5 (180.1–939)		507.2 (204.5–1,164.8)		1.05 (0.66–1.89)		5,040 (2,790–11,860)		1,640 (730–2,910)	
Others[†]	681.4 (175.1–2,056.9)		516.9 (185.9–1,944)		1.26 (0.77–2.79)		7,570 (3,420–29,130)		1,980 (870–3,970)	
ECOG score		0.601		0.243		0.576		0.836		0.519
0	520.5 (129.2–2,056.9)		469.2 (179.5–1,293.15)		1.12 (0.39–5.28)		6,370 (2,700–29,130)		1,540 (730–3,970)	
>0	506.9 (119.3–1574.2)		332.6 (142.8–1,944)		1.22 (0.37–3.07)		6,850 (1,780–26,790)		1,540 (280–2,490)	
Metastasis		0.126		0.143		0.782		0.058		0.196
Yes	543.5 (175.1–2056.9)		520.5 (164.9–1,944)		1.15 (0.37–2.79)		7020 (3,210–29,130)		1,760 (720)*	
No	466.1 (119.3–1427.5)		376.4 (142.8–899.3)		1.11 (0.39–5.28)		5,820 (1,780–26,790)		1550 (620)*	

BMI=body mass index; ECOG=Eastern Cooperative Oncology Group

*Data in mean (standard deviation); [†]others were neuroendocrine carcinoma hepar, osteosarcoma, lung adenocarcinoma, and synovial sarcoma

Post hoc analysis showed that head and neck *versus* others, $p = 0.001$; head and neck *versus* colorectal, $p = 0.884$; head and neck *versus* breast and gynecological, $p = 0.266$; colorectal *versus* breast and gynecological, $p = 0.397$; colorectal *versus* others, $p = 0.039$; and breast and gynecological *versus* others, $p = 0.044$

lymphocytes play a role in various phases of cancer development.

A limitation of this study was the absence of infection assessment in patients, which could have introduced a potential source of bias. Future studies could incorporate the infection status evaluation to enhance the finding's comprehensiveness. Patients with solid tumors often exhibit a predisposition to develop infections as the disease progresses. This susceptibility is linked to factors such as systemic inflammation, immunosuppression, immunosenescence, comorbidities, poor nutrition, smoking, and anatomical obstruction.[14]

In conclusion, CD4 levels and lymphocyte counts were associated with the cancer type, whereas CD8 levels were influenced by age. Lymphocyte count is associated with poor prognosis and adverse events. It is necessary to focus on improving factors such as nutrition in patients with solid cancer, particularly those experiencing lymphopenia.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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