



Is the Complete Blood Count Parameters Predict Prognosis Before Treatment in Metastatic Gastric Cancer Patients?

Metastatik Mide Kanseri Hastalarda Tedavi Öncesi Tam Kan Sayımı Parametreleri Prognozu Belirler mi?

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SUMMARY

Introduction: Gastric cancer is one of the leading cause of death both in men and women. More than two-thirds of the patients were diagnosed in advanced stage. Metastatic gastric cancer has a poor prognosis with a relative 5-years-survival rate of %7. In the previous reports, hematological parameters including leukocyte, thrombocyte counts and ratios between them had been used as prognostic indicators in several tumor types. The aim of the current study was to determine whether hematological parameters like neutrophils, lymphocyte or thrombocyte counts and thrombocyte-lymphocyte ratio (TLR), neutrophil-lymphocyte ratio (NLR) before treatment might predict survival in metastatic gastric cancer.

Patients and Methods: A total of 112 patients with metastatic gastric cancer treated and followed-up from 2004 to 2008 were analyzed. Hematological parameters measured before treatment were obtained from patients chart and evaluated retrospectively. NLR and TLR were calculated from pre-treatment complete blood counts. Correlation between parameters and survival were made by using log-rank and Kaplan-Meier tests.

Results: For 112 patients with metastatic gastric cancer, 2-years survival rate and median survival time were 17% and 12 months, respectively. Although thrombocytosis (> 300.000), TLR (> 160), lymphopenia (< 1500), NLR (> 2.56) had been found predict poor survival time, it was not shown statistically significant.

Conclusion: In present study we could not find any significant correlation between survival and hematological parameters in patients with metastatic gastric cancer, however, further studies including larger sample size may be required to clarify the prognostic value of pre-treatment peripheral blood counts.

Key Words: Gastric cancer, platelet, thrombocyte-lymphocyte ratio (TLR), neutrophil-lymphocyte ratio (NLR).

ÖZET

Giriş: Gastrik kanser, kadın ve erkekte en sık ölüme neden olan kanserlerdendir. Hastaların 2/3 den fazlasına ileri evrede tanı konabilir. Metastatik mide kanserinin beş yıllık sağkalımı %7 civarındadır. Daha önceki çalışmalarda, beyaz küre, trombosit sayısı ve aralarındaki oranlar farklı kanser türlerinde prognostik gösterge olarak kullanılmıştır. Biz çalışmamızda beyaz küre, trombosit sayısı, trombosit/lenfosit oranı (TLO), nötrofil/lenfosit (NLO) oranı gibi hematolojik parametrelerin metastatik mide kanserinde yeri olup olmadığını değerlendirdik.

Hastalar ve Yöntem: 2004-2008 yılları arasında tedavi ve takip edilen toplam 112 metastatik mide kanserli hastayı inceledik. Tedaviden önce ölçülen hematolojik parametreleri hasta kartlarından elde ettik. TLO ve LTO tedavi öncesi parametrelerden hesapladık. Parametrelerle sağkalım arasındaki ilişkiyi log-rank ve Kaplan-Meier analizleriyle değerlendirdik.

Bulgular: Metastatik mide kanserli 112 hastanın iki yıllık sağkalım oranı ve ortalama sağkalım süresi ayrı ayrı %17 ve 12 aydı.

Trombositoz, (> 300.000), TLO (> 160), lenfopeni (< 1500), NLO (> 2.56) kötü sağkalımı predikte etse de istatistiksel olarak anlamlılık saptanmadı.

Sonuç: Çalışmamızda, metastatik mide kanserli sağkalım ve hematolojik parametreler arasında istatistiksel olarak anlamlı bağlantı bulamadık. İleride tedavi öncesi hematolojik parametrelerle sağkalım arasındaki ilişkiyi gösterebilecek daha fazla hasta sayısı içeren çalışmalara ihtiyaç olabilir.

Anahtar Kelimeler: Gastrik kanser, trombosit, trombosit-lenfosit oranı (TLO), nötrof-lenfosit oranı (NLO).

INTRODUCTION

Gastric cancer (GC) is the second leading cause of mortality both in men and women worldwide and 12% of cancer related death was due to gastric cancer (1). More than two-thirds of patients were unresectable when GC was diagnosed. Median survival of patients with metastatic disease remains between six and nine months (2). In advanced stage, chemotherapy is the main treatment option which improve quality of life (3). Although there is no standard treatment in advanced GC, chemotherapy has approximately six months survival advantage compared with best supportive care (3).

The role of immune system on disease progression has been investigated previously and the prognostic importance of some hematological parameters including leukocyte and thrombocyte counts, mean platelet volume (MPV) have been shown in various types of malignancy (4-8). In addition, the neutrophil to lymphocyte ratio (NLR) has been documented as a simple marker of systemic inflammatory response in cancer patients (9,10). Similarly, preoperative thrombocyte to lymphocyte ratio (TLR) has been suggested also as an significant factor predict survival in pancreatic cancer (11). Altered immune response in the gastric cancer patients have also been investigated previously (12,13). Both NLR and thrombocytosis have reported as a prognostic factors in gastric cancer (14,15). TLR and lymphocyte counts were found as prognostic factors that predict OS in locally advanced gastric cancer (16). The evaluation of hematological parameters are easy and cost-effective in determination of prognosis and response of the tumor. So in this study we investigated whether lymphocyte, neutrophil and thrombocyte counts, TLR and NLR had prognostic importance to predict the survival in the metastatic gastric cancer patients.

PATIENTS and METHODS

Between 2004 to 2008, 112 patients with histologically confirmed gastric cancer with distant metastasis

who were followed-up in the department of medical oncology in the Haydarpasa Numune Hospital, were analyzed retrospectively. The patients with chronic disease like chronic renal failure, patients who received blood transfusion and with active infection during the diagnosis of gastric cancer were excluded. Demographical features and survival data of the patients were achieved from the patient' chart. Peripheral blood had been obtained from the patients at the time of the diagnosis and neutrophil, lymphocyte and thrombocyte counts had been measured in number per cubic milimeter using differential white blood cell automatic counter. The results of the pretreatment hematological parameters were evaluated retrospectively. NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count and calculated from the full blood count. The calculated values were divided into two groups as < 2.56 and ≥ 2.56 (5). TLR was also described as the ratio between thrombocyte and lymphocyte count and categorized > 160 and ≤ 160 (6). Similarly, lymphocyte and thrombocyte counts were splinted into two groups as smaller or greater than $1500/\text{mm}^3$ versus smaller or greater than $300.000/\text{mm}^3$, respectively (6,8,9).

Statistical Analysis

Descriptive parameters are quoted as mean \pm SD with 95% confidence intervals (CI). Survival curves were estimated with the Kaplan-Meier method. Overall survival (OS) time defined as the time from the diagnosis to the death or last known alive time and measured as months. Association between the factors and the prognosis were examined with the lonk-rank test in univariate analysis. P value < 0.05 was considered significant. All analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

There were 112 metastatic gastric cancer patients with pretreatment complete blood counts were available. Of these, 75 were male and 37 were female. The mean age of the patients at the time of the diagnosis was 60.57 ± 12.56 . The mean lymphocyte and throm-

bocyte counts were 1748/mm³ and 361.633/mm³ respectively. The hematological data before treatment are shown in Table 1.

The median OS interval was 12 months (95% CI, 9-14 months) and 2-years survival rate was 17.3%. Overall 44 patients had thrombocyte counts smaller than 300.000/mm³ whose median survival time was 12 months (95% CI, 8-15 months). On the other hand, 56 patients with thrombocyte counts ≥ 300.000/mm³ had median survival of eight months (95% CI, 6-10 months). There was no statistically significant according to one year survival rate between these two groups (31% vs 18.1%, p= 0.10) (Figure 1). The median OS time for seventy patients with TLR of greater than 160 was nine months (95% CI, 7-10 months) compared to patients with TLR of smaller than 160 was 13 months (95% CI, 7-13 months). Although four months of survival advantage in patients with TLR < 160, the dif-

Table 1. The hematological parameters before treatment.

| | Mean ± SD | Minimum | Maximum |
|---------------------------|---------------------|---------|---------|
| Leucocyte (n= 99) | 8213.4 ± 3517.8 | 2000 | 17620 |
| Neutrophil (n= 98) | 5390.5 ± 2992.2 | 960 | 15100 |
| Monocyte (n= 56) | 593.3 ± 323.0 | 4 | 1490 |
| Platelet (n= 100) | 361633.3 ± 161346.7 | 61000 | 855000 |
| Lymphocyte (n= 98) | 1748.6 ± 1013.5 | 300 | 8800 |

SD: Standard deviation.

ference was not significant (p= 0.14) (Figure 2). The median OS time was higher in patients with a lymphocyte counts < 1500/mm³ (n= 46) than those with lymphocyte counts greater than or equal to 1500/mm³ (8 vs 11 months), but this difference was not statistically significant (p= 0.17) (Figure 3). There were 39 patients with NLR were smaller than 2.56, other 59 had NLR ≥ 2.56. The OS rates for patients with NLR ≥ 2.56 were lower than those with NLR smaller than 2.56, but not significant (p= 0.21) (Figure 4). In our study pretreatment hematological parameters in metastatic gastric

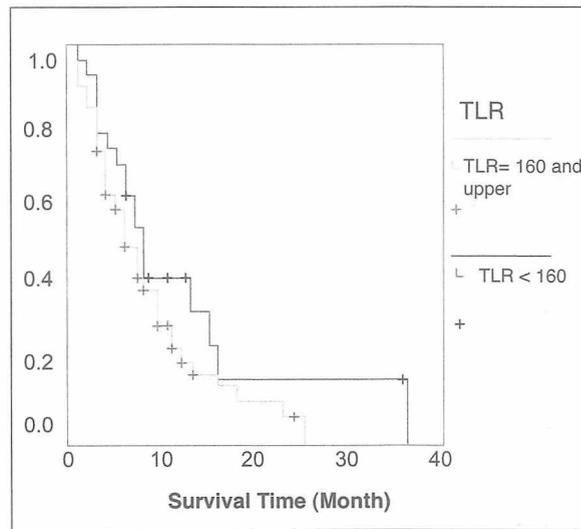


Figure 2. Kaplan-Meier cumulative survival curves for metastatic gastric cancer patients stratified by platelet-lymphocyte ratio (PLR).

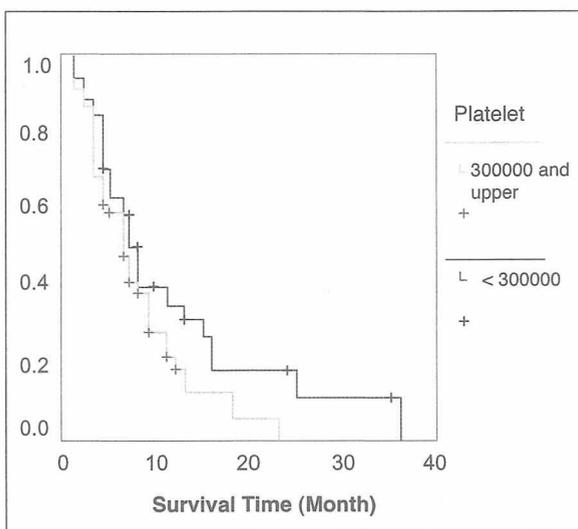


Figure 1. Kaplan-Meier cumulative survival curves for metastatic gastric cancer patients according to platelet counts.

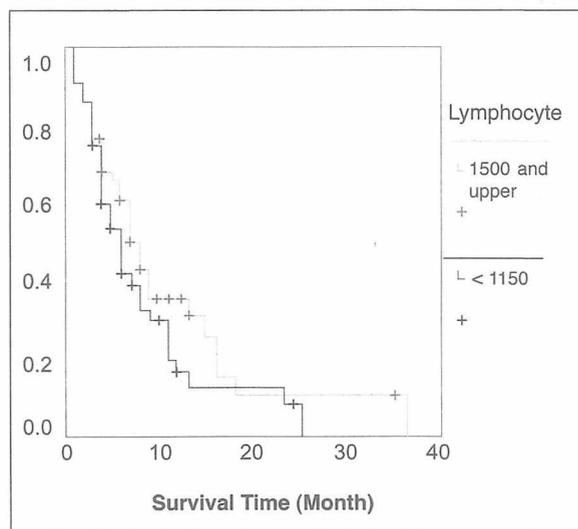


Figure 3. Kaplan-Meier cumulative survival curves for metastatic gastric cancer patients according to lymphocyte counts.

cancer patients could not be found as prognostic factor predict survival.

DISCUSSION

GC is often diagnosed in advanced or metastatic stage. When the symptoms are revealed, mostly chance of curative treatment was lost. Although various chemotherapy regimens present, the median survival of the metastatic disease remains between six and nine months (2). Inflammation plays a major role in progression of various organ tumors (17,18). Hematological parameters like neutrophil, lymphocyte included in inflammatory process are recommended as prognostic factors in several cancer types (4-8). Assessment of inflammatory response to the tumor may be easier and cost-effective in clinical practice. Thrombocytosis has been reported in patients with lung, colorectal, cervical cancer and renal cell carcinoma that can be cause poor prognosis (14,19-22). Levin and Conley previously documented that thrombocytosis was frequent in gastric cancer, but they did not investigate prognostic importance of thrombocytosis (23). In the previous study, prevalence of thrombocytosis was reported as 9.5% to 38% in gynecological malignancies, 13% to 60% for lung cancer, 56.8% for renal cell carcinoma and 33% for colon cancer patients (7). We found that 55.6% of 112 metastatic gastric cancer patients had thrombocytosis higher than 300.000/mm³, nonetheless thrombocyte counts of 35.4% patients were higher than 400.000/mm³. This results were compatible with the literature (7). Shimeda et al. reported

that thrombocytosis was present 5.1% of esophageal cancer patient and also they shown that patient with thrombocyte count higher than 295.000/mm³ had poorer prognosis than thrombocyte count < 295.000/mm³ (7). It was reported that platelets play in integral role in the metastatic process, thrombocytes protect tumor cells by shielding them from the host's immune system (14,24). Similarly Ikeda et al. indicated that thrombocytosis was an independent prognostic factor in patients with gastric cancer and it was more common among patients with advanced-stage disease. While thrombocytosis was found 3.6% of stage I patients, in advanced stage gastric cancer, frequency increased over 20% and survival was lower. In their study, 3-years-survival rates were 23.4% vs 72.9% for thrombocyte counts > 400.000/mm³ or <400.000/mm³, respectively (14). In present study we found that, patients whose platelet counts less than 300.000/mm³, had better median survival time (12 months) than those with thrombocyte counts > 300000/mm³ (8 months) (p= 0.10). There was four months of survival difference between two groups, however, it was not significant. It may be due to small population of patients included in this study.

Smith et al. defined TLR as independent prognostic factor index in patient with resected pancreatic adenocarcinoma (11). They reported that patients with TLR of greater than 300 had a poorer median survival (5.8 months), compared to a TLR of 151 to 300 (13.7 months) or less than 150 (19.7 months) (p= 0.06). In another study, Smith et al. showed that elevated pre-operative serum CA19-9 levels and TLR were associated with poorer OS of 12 months compared with lower CA 19-9 and TLR (OS over 60 months) (6). In our study, 27 patients with TLR was less than 160 had median survival of 13 months, on the other hand, 70 patients with TLR of > 160 had lower median survival as 9 months. Although this survival time compatible with the literature, the difference was not significant statistically in our study (p= 0.14).

Recently the role of immune system on cancer progression was examined and leukocytes have been proposed as a diagnostic and prognostic factor in variety of cancers (10). Previously, it was reported that pretreatment lymphocyte count had been independent prognostic factor in lung, colorectal and gastric cancer (25-28). Low lymphocyte counts (< 1500/mm³) indicate cell-mediated immunodeficiency which was common feature in cancer physiology, but also that is relevant prognostic role for survival (27). The cancer related lymphopenia occur in advanced stage cancers such as small cell lung cancer, colorectal cancer, renal cell

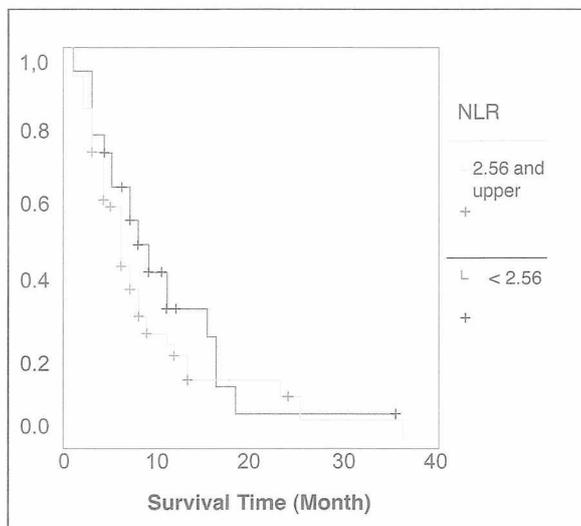


Figure 4. Kaplan-Meier cumulative survival curves for metastatic gastric cancer patients according to neutrophil-lymphocyte ratio (NLR).

cancer (27). Bruckner et al. suggested that, pre-treatment lymphocyte counts of $> 1500/\text{mm}^3$ and neutrophil counts of $< 6000/\text{mm}^3$ were independent prognostic factors for survival in the metastatic gastric cancer. In their study, 56 patients with metastatic gastric cancer had 22.5 months of overall survival however, OS of the 63 patients with lymphocyte counts were greater than $1500/\text{mm}^3$ was 46.3 months ($p= 0.02$) (29). Moreover, Elias et al. showed high percentage of lymphocyte ($> 30\%$) in patients with head and neck cancer had better survival than lower percentage of lymphocyte (30). In our study, we found that median survival time of the patients with lymphocyte count greater than $1500/\text{mm}^3$ was 11 months, on the other hand, if lymphocyte count of patients smaller than $1500/\text{mm}^3$, median OS decreased to eight months ($p= 0.17$). Although we found that three months absolute survival advantages in patients with lymphocyte counts $> 1500/\text{mm}^3$, but it was not significant statistically ($p= 0.17$).

The systemic inflammatory response features changes in relative levels of circulating leukocytes; neutrophilia is accompanied with relative lymphopenia. So NLR has been suggested as a rapid and simple parameter of systemic inflammation in cancer patients and the ratio is easily measurable parameter which may express the severity of affliction (9,10). Elevated NLR was associated with poor survival in ovarian cancer patients (10). Another study was performed by Walsh et al. indicated that in patients with colorectal cancer preoperative NLR of > 5 was together with poor survival rates (31). Yamanaka et al. found that patients with $\text{NLR} < 2.5$ had higher survival time than those with $\text{NLR} < 2.5$ in advanced gastric cancer patients (363 vs 239 days) (5). In conclusion, although we found absolute survival time advantages when patients with metastatic gastric cancer were classified according to NLR, TLR, lymphocyte or thrombocyte counts, it was not significant. It may be due to small sample size of patients in here. The documentation related to infections, biochemical, hematological or clinical parameters were limited in our database so multivariate analysis which was identified factors related prognosis could not be carried out. On the other hand, even chemotherapy lead to approximately six months of survival advantage in metastatic gastric cancer, we showed that 4 months of survival advantages in patients with thrombocyte counts $< 300.000/\text{mm}^3$ and patients with TLR < 160 . Although it was not significant, it is noteworthy clinically. In the future, our results are needed to confirm with studies including larger sample size.

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