Comparison of Inflammatory Indexes in Patients Treated with Sorafenib in Advanced Hepatocellular Carcinoma: A Single-Center Observational Study

Havva Yeşil Çınkır¹, Ilkay Doğan²

Objective: Sorafenib has limited survival benefits with lower tumor response rates in hepatocellular carcinoma (HCC). Many researchers have attempted to identify predictors for sorafenib. In this study, we compared the role of lymphocyte/monocyte ratio (LMR), neutrophil/monocyte ratio (NMR), platelet/neutrophil ratio (PNR), systemic inflammation response index (SIRI) and systemic immune inflammation (SII) in patients with HCC received sorafenib treatment.

Materials and Methods: In this study, we retrospectively enrolled 80 patients who used Sorafenib in advanced stage HCC between January 2011 and December 2018. Baseline neutrophil, lymphocyte, monocyte and platelet counts were recorded. Cut-off points of LMR, NMR, PNR, SIRI and SII were calculated by the receiver operating characteristic (ROC) curve analysis. Overall survival (OS) and progression-free survival (PFS) were demonstrated by Kaplan-Meier analysis, and the log-rank test was used for comparing the curves.

Results: Median OS was 29 weeks (95% CI 20.41–37.58), and PFS was 16 weeks (95% CI: 12.04–19.95). We found that only low SIRI value was associated with increased survival. OS were 19 weeks for SIRI ≥2.2 and 38 weeks (95% CI: 30.96–45.03 for patients with SIRI <2.2 (p=0.005). PFS was 12 weeks for SIRI ≥2.2 and 20 weeks for SIRI <2.2 (p=0.098). The life expectancy of patients with SIRI values less than 2.2 was 2.02 times higher than the other group.

Conclusion: To our knowledge, NMR and PNR indexes were evaluated for the first time in our study in HCC patients. Low SIRI value was related to increased survival in patients receiving sorafenib with HCC.

Keywords: Hepatocellular carcinoma, inflammation, sorafenib

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. Although surveillance programs are used more frequently, the majority of HCC patients are diagnosed at an advanced stage (1). In addition, some patients with early-to-moderate HCC progress to advanced stage disease during follow-up. Only palliative treatment options are available for this group of patients.

Sorafenib is a tyrosine kinase inhibitor with effects on tumor angiogenesis and proliferation, and two placebo-controlled randomized trials have shown that this drug prolongs survival in advanced HCC patients (2, 3). However, due to the primary and acquired drug resistance mechanisms developed when taking sorafenib treatment, the drug has limited survival benefits with lower tumor response rates than expected (4). Many researchers have attempted to identify baseline or pretreatment predictors for sorafenib because the same effect was not seen in all HCC patients and response rates were not satisfactory (2). Recently, systemic inflammation was reported to be closely related to malignancy (5). Inflammation plays a significant role in the development and progression of the tumor. Immune and inflammatory cells, such as neutrophils, monocytes and lymphocytes in the systemic circulation, may contribute to tumor cell invasion and metastasis (6). Different inflammation-based scores have been proposed and are considered useful in this respect (7).

We compared the role of lymphocyte/monocyte ratio (LMR), neutrophil/monocyte ratio (NMR), platelet/neutrophil ratio (PNR), systemic inflammation response index (SIRI) and systemic immune inflammation (SII) in patients with HCC received sorafenib treatment in this study.

MATERIALS and METHODS

Study Populations and Design

We retrospectively recorded the patients who were followed up with the diagnosis of HCC at Gaziantep University School of Medicine between January 2011 and December 2018. The number of patients who were prescribed sorafenib treatment was 98. However, 80 patients who had used sorafenib treatment for at least four weeks
were analyzed. This study was approved by the Ethics Committee of Gaziantep University (Decision no: 2019/02, 09.01.2019). This was a retrospective study. Thus, patients were not consented before being included in this study. The inclusion criteria were as follows: HCC diagnosis based on histologically proven or dynamic imaging and underlying chronic liver disease, good performance status (ECOG level <2) and liver function tests consistent with Child-Pugh class A or B-7. Exclusion criteria were as follows: Another history of malignant disease in the past five years, renal and/or hepatic insufficiency, acute coronary syndrome, autoimmune diseases, or systemic inflammatory diseases. The following variables were collected for analysis: age and gender; date of HCC diagnosis; treatment history; date of death or last follow-up; blood test results (baseline neutrophil, lymphocyte, monocyte and platelet counts) were recorded. Prognostic indexes were calculated according to the following formula:

LMR: Peripheral lymphocyte count/Peripheral monocyte count
NMR: Peripheral neutrophil count/Peripheral monocyte count
PNR: Peripheral platelet count/Peripheral neutrophil count
SIRI: Peripheral neutrophil count x Monocyte count/Lymphocyte count,
SII: Peripheral platelet count x Neutrophil count/Lymphocyte count

Statistical Analysis
Frequency and percentage distribution values were used for demographic variables. Cut-off points of LMR, NMR, PNR, SIRI and SII were calculated by the receiver operating characteristic (ROC) curve analysis (Youden statistic). For the comparison of them and demographic variables, one-sample t-test and analysis of variance were used. Overall survival (OS) was defined as the time interval between the onset of treatment and death or final follow-up. Progression-free survival (PFS) was defined as the time between the onset of treatment and disease progression or death or last follow-up. OS and PFS were demonstrated by Kaplan-Meier analysis, and the log-rank test was used for comparing the curves. The survival durations were presented as weeks. Cox regression method was used in univariate analysis to determine important variables in OS and PFS durations. A p-value of <0.05 was accepted for statistical significance. SPSS 22.0 software (SPSS, Chicago, IL, USA) was used for statistical analysis.

RESULTS
Patient Characteristics
The mean age was 69 (range 29–83) years and 83.8% were male gender. Etiology of HCC were infection of hepatitis B (n=49, 61%), infection of hepatitis C (n=8, 10%), non-alcoholic fatty liver disease (n=10, 12.5%), alcoholic liver disease (n=4, 5%) and cryptogenic (n=9, 11.25%). 15% of patients had extra-hepatic metastases.

Median follow up time was 31.5 weeks (range 5–155 weeks). There were 72 (90%) deaths in total. At the time of analysis, eight (10%) patients were actively receiving sorafenib. A summary of the distribution of clinical variables is outlined in Table 1.

In our study, the OS of patients according to HCC diagnosis was 34 weeks (95% CI: 29.22–38.77); OS based on the use of sorafenib treatment was 29 weeks (95% CI: 20.41–37.58); the PFS value was 16 weeks (95% CI: 12.04–19.95).

LMR, NMR, PNR, SIRI, SII and Clinical Outcome
Median PFS and OS, according to LMR, NMR, PNR, SIRI and SII, are shown in Table 2, Figure 1 and Figure 2.

The cut-off point of LMR was determined by the ROC analysis. The cut-off point was 1.4 for LMR [p=0.737; AUC=0.535; sensitivity=29.17% (95% CI: 19.0–41.1); specificity=100.0% (95% CI: 63.1–100.0)]. The PFS value for both LMR ≤1.4 and >1.4 was 16 weeks and there was no statistically significant difference (p=0.601). Median OS were 31 weeks (95% CI: 24.61–37.38) for LMR >1.4 and 18 weeks (95% CI: 20.41–37.58) for LMR ≤1.4 (p=0.155).

The cut-off point for NMR was 5.2 [p=0.005; AUC=0.805; sensitivity=81.94% (95% CI: 71.1–90); specificity=87.5% (95% CI: 47.3–99.7)]. Median PFS were 19 weeks (95% CI: 11.31–26.68) for NMR <5.2 and 14 weeks (95% CI: 8.53–19.46) for NMR ≥5.2 (p=0.126). Median OS were 31 weeks (95% CI: 17.86–44.13) for patients with NMR <5.2 and 26 weeks (95% CI: 15.47–36.52) for ≥5.2 (p=0.150).

Table 1. Distribution of the clinical variables

| Variables                          | n     | R or % |
|------------------------------------|-------|--------|
| Age (years), Mean±SD               | 61.94±11.7 (29–83) |
| Gender                             |       |        |
| Female                             | 13    | 16.25  |
| Male                               | 67    | 83.75  |
| Etiology                           |       |        |
| Hepatitis B                        | 49    | 61     |
| Hepatitis C                        | 8     | 10     |
| Non-alcoholic fatty liver disease  | 10    | 12.5   |
| Alcohol                            | 4     | 5      |
| Cryptogenic                        | 9     | 11.25  |
| Metastatic sites                   |       |        |
| Liver-multifocal                   | 70    | 75     |
| Extra-hepatic                      | 20    | 25     |
| Previously applied treatments      |       |        |
| Transplantation                    | 2     | 2.5    |
| TACE                               | 11    | 13.75  |
| TARE                               | 1     | 1.25   |
| None                               | 66    | 82.5   |
| Neutrophil count, Mean±SD (x10⁹/l)| 4918±1835 (880–11210) |
| Monocyte count, Mean±SD (x10⁹/l)   | 717±285 (250–1980) |
| Lymphocyte count, Mean±SD (x10⁹/l)| 1395±488 (470–3300) |
| Platelet count, Mean±SD (x10⁹/l)  | 202±82 (56–427)  |

R: Range; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; SD: Standard deviation
For PNR, the determined cut-off point was 44.8 (p=0.127; AUC=0.630; sensitivity=63.89% (95% CI: 51.7–74.9); specificity=75.0% (95% CI: 34.9–96.8). Median PFS were 15 weeks (95% CI: 9.90–20.09) for ≤44.8 and 17 weeks (95% CI: 10.52–23.48) for PNR >44.8 (p=0.788). Median OS were 20 weeks (95% CI: 7.55–32.44) for PNR ≤44.8 and 33 weeks (95% CI: 25.10–40.89) for PNR >44.8 (p=0.055).

The cut-off point for SIRI was 2.2 (p=0.127; AUC=0.630; sensitivity=63.89% (95% CI: 51.7–74.9); specificity=75.0% (95% CI: 34.9–96.8). Median OS were 19 weeks (95% CI: 15.76–22.23) for SIRI ≥2.2 and 38 weeks (95% CI: 30.96–45.03) for patients with SIRI <2.2 (p=0.005). Median PFS was 12 weeks (95% CI: 8.28–15.71) for SIRI ≥2.2 and 20 weeks (95% CI: 11.68–28.31) for SIRI <2.2 (p=0.098).

For SII, the cut-off point was 523 [p=0.002; AUC=0.740; sensitivity=69.44% (95% CI: 57.5–79.8); specificity=75.00% (95% CI: 34.9–96.8)]. Median PFS were 13 weeks (95% CI: 6.88–19.11) for SII ≥523 and 20 weeks (95% CI: 12.54–27.45) for SII <523 (p=0.086). Median OS were 20 weeks (95% CI: 16.52–23.47) for SII ≥523 and 31 weeks (95% CI: 26.00–35.99) for patients with SII <523 (p=0.209).

According to the univariate Cox regression analysis for OS, a statistically significant difference was found in the SIRI variable (p=0.005). Life expectancy was 2.02 times higher for SIRI <2.2 (Table 3).

Table 2. Kaplan–Meier analysis of median progression-free and overall survival according to LMR, NMR, PNR, SIRI and SII

|        | PFS |          | OS |          |
|--------|-----|----------|----|----------|
|        | Median (95% CI) | Log-rank P | Median (95% CI) | Log-rank P |
| LMR    | ≤1.4 (6.04–25.95) | 0.601 | 0.155 |
|        | >1.4 (11.35–20.64) | 0.126 | 0.150 |
| NMR    | ≥5.2 (8.53–19.46) | 0.086 | 0.005 |
|        | <5.2 (11.31–26.68) | 0.098 | 0.055 |
| PNR    | ≤44.8 (9.90–20.09) | 0.788 | 0.002 |
|        | >44.8 (10.52–23.48) | 0.086 | 0.0209 |
| SIRI   | ≥2.2 (8.28–15.71) | 0.098 | 0.005 |
|        | <2.2 (11.68–28.31) | 0.098 | 0.005 |
| SII    | ≥523 (6.88–19.11) | 0.098 | 0.005 |
|        | <523 (12.54–27.45) | 0.098 | 0.005 |

LMR: Lymphocyte/monocyte ratio; NMR: Neutrophil/monocyte ratio; PNR: Platelet/neutrophil ratio; SIRI: Systemic inflammation response index; SII: Systemic immune-inflammation index; PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval.
DISCUSSION

Although HCC is important among cancer-related deaths, few markers have been identified for predicting survival. Therefore, it is very significant to find inexpensive, appropriate and reliable markers to predict prognosis in HCC patients. As a prognostic marker in cancer patients worldwide, interest for systemic inflammation is increasing. In our study, only low SIRI value was found to be associated with increased survival in patients receiving sorafenib with HCC.

Activated monocytes secrete a large number of proinflammatory cytokines that cause tumor growth and progression of the tumor. Lymphocytes mediate the progression of cancer by the cell-mediated immune response. A high lymphocyte value and a low monocyte value have a positive effect on the immune-related response to the tumor. In a meta-analysis, it was shown that LMR had a good prognostic effect (8). In our study, there was no statistically significant difference for PFS and OS with values of 1.4 for LMR. However, when the LMR ≤ 1.4 and >1.4 group were compared, a positive 13-week difference in OS value was observed in favor of 1.4.

The neutrophil is the most common cell among the white blood cells and has the shortest half-life. It is the first cell to respond to trauma or attack. Therefore, it is involved in the formation of the immune response by contacting the tumor cells in the first order (9). In previous studies, NMR was examined in breast and prostate cancer patients in addition to other inflammation-related parameters in cancer (10, 11). To our knowledge, NMR was investigated first time with HCC in our study. The cut-off value was 5.2 and...
there was a numerical difference in PFS and OS values in favor of <5.2, but there was no statistically significant difference. In the light of previous studies, low levels of neutrophil and monocyte were known as good parameters. Neutrophil secretes vascular endothelial growth factor (VEGF) and proteases, such as matrix metalloproteinase and elastase enzymes, causing cancer cells to invade and metastasize. Monocytes also increase cancer cell migration and inhibit immunity to the tumor cell (12). Although there was no statistically significant difference in our study, it was thought that the high level of monocyte value might be important for the response to the tumor.

As seen in NMR, low levels of neutrophils in PNR can cause better results in response to the tumor. Platelet-derived growth factor and VEGF, which are act as main factors on cell proliferation, angiogenesis and tumor metastasis, are secreted from platelets (13). These cells contain proinflammatory molecules and cytokines. Thus, they are involved in inflammatory and immune responses (14). In our study, when compared to PNR ≤44.8 to >44.8, OS benefit was observed in favor of >44.8 (33 versus 20 weeks, p=0.055).

SIRI is another simple, noninvasive prognostic marker and more comprehensive than other markers. In the study of Xu et al. (6), the relationship between survival and HCC was investigated. According to this study, the median OS was longer with low SIRI in patients receiving local treatment or sorafenib treatment. In our study, we have shown that there was a relationship with a low SIRI value (<2.2) and OS in the unresectable or metastatic patients (18 versus 38 weeks, p=0.005). There was also a difference between a low value of SIRI (<2.2) and PFS, but not statistically significant (12 versus 20 weeks, p=0.098).

SII is another comprehensive marker. Gardini et al. (15) reported a prognostic effect in 56 HCC patients receiving sorafenib treatment. It had been shown that high SII values had a negative effect on survival. In our study, PFS (13 versus 20 weeks) and OS (20 versus 31 weeks) values were found to be decreased in patients with cut-off value ≥523, but there was no statistically difference (p=0.086, p=0.209, respectively).

In our study, we have shown that LMR, SIRI and SII values have a prognostic effect in accordance with the literature. NMR and PNR values were first studied in patients with HCC in our study. According to the results of these two markers, we have shown that the low neutrophil value is more effective on prognosis than low monocyte and platelet values. Although the parameters calculated using two parameters were more practical, as shown in SIRI and SII, the results may be more effective with the use of more parameters. We found numerical differences between the groups. However, statistically significant difference was not observed.

In recent years, a considerable improvement has been made in immunotherapies for all of the cancer types. There is a need for biomarkers to predict the clinical efficacy of immune checkpoint inhibitors. In patients with lung cancer receiving immunotherapy, high neutrophil/lymphocyte ratio has been shown to be associated with poor prognosis (16). In another study, the pretreatment inflammation marker was reported to be associated with decreased survival and poor treatment response (17). Chronic inflammatory status has been shown to be associated with an increase in regulatory T-cell numbers, changes in control point expression and dendritic cell function (18). In view of chronic necro-inflammatory conditions and increased expression of the programmed cell death-1 (PD-1) and the programmed cell death-ligand1 (PD-L1) in HCC tumor formation, immunotherapeutic agents have been involved in HCC treatment management (19). Increased expression and upregulation of PD-1 was shown to be associated with the progression of HBV-associated cirrhosis to HCC and recurrence of the primary tumor after surgical resection (20, 21). Validation of PD-L1 expression and inflammatory markers may be important because they are an option as a viable test to help assess the patient’s prognosis.

Our study had a few limitations, including its retrospective design and the comparatively small sample size. However, regardless of these restrictions, our results were the source of the importance of inflammatory markers. The use of these simply available and noninvasive markers in combination with others could help clinicians to predict the results.

CONCLUSION

Few markers have been identified for predicting survival. To our knowledge, NMR and PNR values were first studied in patients with HCC in our study. We found that only low SIRI value was associated with increased survival in patients receiving sorafenib with HCC. Our results showed that a simple, readily available and inexpensive biochemical marker might be useful in refining the prognosis. However, large prospective studies should be performed to verify whether inflammatory indexes have predictive and prognostic in HCC patients.

Ethics Committee Approval: This study was approved by the Ethics Committee of Gaziantep University (date: 09.01.2019, number: 2019/02).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – HYÇ, İD; Design – HYÇ, İD; Supervision – HYÇ, ID; Resource – HYÇ; Materials – HYÇ; Data Collection and/or Processing – HYÇ; Analysis and/or Interpretation – ID; Literature Search – HYÇ; Writing – HYÇ; Critical Reviews – HYÇ.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012; 379(9822): 1245–55. [CrossRef]
2. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359(4): 378–90. [CrossRef]
3. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10(1): 25–34. [CrossRef]
4. Zhu Z, Xu L, Zhang L, Ning Z, Zhang C, Yan X, et al. Role of monocyte-to-lymphocyte ratio in predicting sorafenib response in patients
with advanced hepatocellular carcinoma. Onco Targets Ther 2018;11:6731–40. [CrossRef]
5. Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin Cancer Res 2009; 15(2): 425–30. [CrossRef]
6. Xu L, Yu S, Zhuang L, Wang P, Shen Y, Lin J, et al. Systemic inflammation response index (SIRI) predicts prognosis in hepatocellular carcinoma patients. Oncotarget 2017; 8(21): 34954–60. [CrossRef]
7. Chen J, Fang A, Chen M, Tuoheti Y, Zhou Z, Xu L, et al. A novel inflammation-based nomogram system to predict survival of patients with hepatocellular carcinoma. Cancer Medicine 2018; 7(10): 5027–35.
8. Song W, Tian C, Wang K, Zhang R, Zou S. The pretreatment lymphocyte to monocyte ratio predicts clinical outcome for patients with hepatocellular carcinoma: A meta-analysis. Sci Rep 2017; 7: 46601.
9. Margetts J, Ogle LF, Chan SL, Chan AWH, Chan KCA, Jamieson D, et al. Neutrophils: driving progression and poor prognosis in hepatocellular carcinoma? Br J Cancer 2018; 118(2): 248–57. [CrossRef]
10. Losada B, Guerra JA, Malón D, Jara C, Rodriguez L, Del Barco S. Pretreatment neutrophil/lymphocyte, platelet/lymphocyte, lymphocyte/monocyte, and monocyte/lymphocyte ratios and outcome in elderly breast cancer patients. Clin Transl Oncol 2019; 21(7): 855–63. [CrossRef]
11. Ceylan Y, Günlitsoy B, Degirmenci T, Bolat D, Kozacioglu Z, Vardar E, et al. Neutrophil-to-lymphocyte and neutrophil-to-monocyte rates in the decision for a prostate re-biopsy in patients with a previous benign pathology and consistently 2.5-10 ng/ml PSA value. Arch Esp Urol 2016;69(9): 627–35.
12. Abu-Shawer O, Abu-Shawer M, Hirman N, Alhouri A, Massad A, Al-sibai B, et al. Hematologic markers of distant metastases and poor prognosis in gynecological cancers. BMC Cancer 2019; 19(1): 141.
13. Bambace NM, Holmes CE. The platelet contribution to cancer progression. J Thromb Haemost 2011; 9(2): 237–49. [CrossRef]
14. Zheng J, Cai J, Li H, Zeng K, He L, Fu H, et al. Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio as Prognostic Predictors for Hepatocellular Carcinoma Patients with Various Treatments: A Meta-Analysis and Systematic Review. Cell Physiol Biochem 2017; 44(3): 967–81. [CrossRef]
15. Casadei Gardini A, Scarpi E, Faloppi L, Scarotzi M, Silvestris N, Santini D, et al. Immune inflammation indicators and implication for immune modulation strategies in advanced hepatocellular carcinoma patients receiving sorafenib. Oncotarget 2016; 7(41): 67142–9.
16. Bagley SJ, Kothari S, Aggarwal C, Bauml JM, Alley EW, Evans TL, et al. Pretreatment neutrophil-to-lymphocyte ratio as a marker of outcomes in nivolumab-treated patients with advanced non-small-cell lung cancer. Lung Cancer 2017; 106: 1–7. [CrossRef]
17. Diem S, Schmid S, Krapf M, Platz L, Born D, Jochum W, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer 2017; 111: 176–81.
18. Martinet J, Dufeu-Duchesne T, Bruder Costa J, Larrat S, Marhu A, Leroy V, et al. Altered functions of plasmacytoid dendritic cells and reduced cytolytic activity of natural killer cells in patients with chronic HBV infection. Gastroenterology 2012; 143(6): 1586–96.e8. [CrossRef]
19. Mahipal A, Tella SH, Kommalapati A, Lim A, Kim R. Immunotherapy in Hepatocellular Carcinoma: Is There a Light at the End of the Tunnel? Cancers (Basel) 2019; 11(8): 1078. [CrossRef]
20. Shi F, Shi M, Zeng Z, Qi RZ, Liu ZW, Zhang JY, et al. PD-1 and PD-L1 upregulation promotes CD8(+) T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. Int J Cancer 2011; 128(4): 887–96. [CrossRef]
21. Makarova-Rusher OV, Medina-Echeverz J, Duffy AG, Greten TF. The yin and yang of evasion and immune activation in HCC. J Hepatol 2015; 62(6): 1420–9. [CrossRef]