The influence of lymphocyte to monocyte ratio on the postoperative outcome of patients diagnosed with advanced stage ovarian cancer

Sorin Petrea[1], Nicolae Bacalbasa[2,3], Irina Balescu[4], Claudia Stoica[5,6], Lucian Pop[7], Valentin Varlas[2,8], Cristina Martac[9], Andrei Voichitoiu[2,7], Tarig Massawi[10], Alexandru Ristea[11]

[1]Department of Surgery, "Cantacuzino" Clinical Hospital, Bucharest, Romania
[2]Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3]Department of Visceral Surgery, Center of Excellence in Translational Medicine, Fundeni Clinical Institute, Bucharest, Romania
[4]PhD Student at "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[5]Department of Anatomy, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[6]Department of Surgery, Ilfov County Emergency Hospital, Bucharest, Romania
[7]Department of Obstetrics and Gynecology, "Alessandrescu-Rusescu" National Institute of Mother and Child Care, Bucharest, Romania
[8]Department of Obstetrics and Gynecology, Filantropia Clinical Hospital, Bucharest, Romania
[9]Department of Anesthesiology, Fundeni Clinical Institute, Bucharest, Romania
[10]Department of Obstetrics and Gynecology, Ilfov County Emergency Hospital, Bucharest, Romania
[11]Department of Visceral Surgery, "Dan Setlacec" Center of Gastrointestinal Diseases and Liver Transplantation, Fundeni Clinical Institute, Bucharest, Romania

ABSTRACT

Introduction: the lymphocyte to monocyte ratio has been widely investigated in patients with different malignancies and proved to have prognostic value for both early and long-term evolution.

Aim: Current paper investigates the influence of this parameter on the perioperative course of patients submitted to surgery for advanced stage ovarian cancer. Material and methods: between 2016-2018 there were 34 patients diagnosed with advanced stage ovarian cancer who were submitted to surgery with curative intent and in whom this parameter was evaluated.

Results: a low rate of this parameter seemed to be significantly associated with a more advanced stage at diagnostic (p=0,002), with higher risk of the presence of lymph node metastases (p=0,003), with larger residual tumor (p=0,002). Meanwhile, patients with a lower lymphocyte to monocyte ratio usually had a higher level of CA 125, but this fact did not have statistical significance (p=0,87).

Conclusions: patients with a lower lymphocyte to monocyte rate are expected to present more aggressive ovarian tumors and therefore a personalized therapeutic strategy might be needed.

Keywords: lymphocyte to monocyte, advanced stage ovarian cancer, debulking surgery, aggressive tumor

INTRODUCTION

In the last decades attention was focused on identifying new prognostic factors for oncological patients in order to better organize their treatment and to increase the chances to achieve a long-term survival rate [1-3]. One of the most frequently inves- tigated parameters was represented by the lymphocyte to monocyte ratio, a lower value of this parameter being usually associated with a more aggressive tumoral biology. Recently this ratio was also investigated in ovarian cancer patients [4]. The aim of the current paper is to study the influence of lymphocyte

to monocyte ratio on the perioperative outcomes of patients submitted to primary debulking surgery between 2016-2018 in "Cantacuzino" Clinical Hospital.

MATERIAL AND METHODS

After receiving the approval of the ethics committee no 151/2021, data of patients submitted to primary debulking surgery were retrospectively reviewed, a total number of 34 such patients being identified. A cut off value of 3 was established for the lymphocyte to monocyte ratio and therefore the patients were classified accordingly.

RESULTS

The median age of the entire study group was of 57 years (range 34-78 years) while the median body mass index was of $31kg/m^2$ (range 17-42kg/m^2). All cases were initially diagnosed with advanced stage ovarian cancer, this fact being confirmed intraoperatively; therefore, there were 23 patients with FIGO stage IIIC ovarian cancer and 11 cases with FIGO stage IV lesions. As for the histopathological subtype, there were 16 cases diagnosed with serous ovarian adenocarcinoma, eight cases with mucinous adenocarcinoma and 12 cases with endometroid adenocarcinoma. Preoperative and intraoperative data are presented in Table 1.

When performing an univariate analysis in order to determine if a statistically significant correlation can be obtained between the lymphocyte and monocyte ratio and different other parameters could be obtained, we observed that a low rate of this parameter seemed to be significantly associated with a more advanced stage at diagnostic (p=0,002), with higher risk of the presence of lymph node metastases (p=0,003), with larger residual tumor (p=0,002). Meanwhile, patients with a lower lymphocyte to monocyte ratio usually had a higher level of CA 125, but this fact did not have statistical significance (p=0,87). When analyzing the correlation ship between the lymphocyte to monocyte ratio and the histopathological subtype, the presence of ascites and the degree of differentiation, no significant correlation was obtained.

DISCUSSIONS

Inflammation seems to play a crucial role in tumor progression and carcinogenesis [5]. When it comes to ovarian cancer, the status of systemic inflammation seems to be strongly correlated with ovarian cancer progression and metastasizing; therefore, it seems that the circulating lymphocytes play a crucial role in preventing ovarian cancer development, inducing an antitumoral immunologi-

TABLE 1. Preoperative and intraoperative features of patients included in the current study

Variable	Value
Median age (range, years)	57 years (range 34-78 years)
Median BMI (kg/m^2)	31kg/m^2 (range 17-42kg/m^2)
Median CA 125 level (U/ml)	2830 U/ml (1233-6246 U/ml)
Stage at diagnostic : - FIGO IIIC - FIGO IV	 n=23 n=11
Histopathological subtype: - serous ovarian adenocarcinoma - mucinous adenocarcinoma - endometroid adenocarcinoma	 n=16 n=8 n=12
Degree of differentiation: - G1 - G2 - G3	 n=9 n=11 n=14
Ascites: - Yes - No	 n=31 n=3
Completeness of cytoreduction: - R0 - R1 - R2	 n=18 n=11 n=5
Lymph node metastases: - Yes - No	 n=29 n=5

n= number of cases

cal response, cytotoxic cell death and inhibition of tumoral migration. Meanwhile, increased levels of circulating monocytes will lead to the appearance of a high serum level of interleukin 6 and interleukin 10 which further contribute to a poor antitumoral response; moreover, monocytes will promote angiogenesis and will increase the metastatic potential of ovarian cancer cells [6-10]. Monocytes can also promote the metastatic potential of tumors due to the fact that they can further generate tumor associated macrophages which will further stimulate the potential of dissemination [11].

In this respect, it is evident why patients with decreased levels of lymphocytes and respectively increased levels of monocytes are more likely to develop more aggressive tumors. Therefore, it has been considered that a low rate of this parameter could be considered as a significant prognostic factor in order to identify cases with more aggressive lesions. Moreover, once identified these patients, a more personalized therapeutic strategy should be taken in consideration and therefore, a neoadjuvant therapy should be proposed in order to limit the tumoral dissemination and to increase the chances to achieve a long term survival rates.

An interesting study conducted on this issue was published by Cai et al. in 2020; the paper included nine studies conducted on this issue, six of them having a cut off value more than 3 while the other three studies having a cut off value lower than 3. The authors came to demonstrate that a higher value of this parameter was significantly associated with a poorer disease-free survival and respectively with a shorter overall survival [12].

One of the largest meta-analysis which aimed to investigate the influence of lymphocyte to monocyte ratio on the perioperative and long-term outcomes of ovarian cancer was conducted by Gong et al. in 2019; this meta-analysis included eight studies and 2259 patients and demonstrated the fact that a high value of this ratio was significantly associated with the presence of less differentiated tumors, late stage at diagnostic, high serum levels of CA 125, presence of malignant ascites and lymph node metastases. Similarly to the study of Cai et al., this meta-analysis also demonstrated that a lower value of lymphocyte to monocyte ratio is significantly correlated with poorer disease free and overall survival [13].

CONCLUSIONS

Lymphocyte to monocyte ratio seem to be a significant prognostic factor in identifying patients with aggressive ovarian malignancies. By using this parameter these patients can be easily identified preoperatively and might be selected in order to be submitted to neoadjuvant therapies followed by debulking surgery to maximize the chances for long term survival.

REFERENCES

1. Tan D, Fu Y, Tong W, Li F. Prognostic significance of lymphocyte to monocyte ratio in colorectal cancer: a meta-analysis. *Int J Surg.* 2018;55:128–38.
2. Li W, Ma G, Wu Q, Deng Y, Liu Y, Wang J. Prognostic value of lymphocyte-to-monocyte ratio among Asian lung cancer patients: a systematic review and meta-analysis. *Oncotarget.* 2017;8:110606–13.
3. Ma JY, Liu Q. Clinicopathological and prognostic significance of lymphocyte to monocyte ratio in patients with gastric cancer: a meta-analysis. *Int J Surg.* 2018;50:67–71.
4. Kwon BS, Jeong DH, Byun JM et al. Prognostic value of preoperative lymphocyte-monocyte ratio in patients with ovarian clear cell carcinoma. *J Cancer* 2018;9:1127–34.
5. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell.* 2011;144:646–74.
6. Clendenen TV, Lundin E, Zeleniuch-Jacquotte A et al. Circulating inflammation markers and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2011;20:799–810.
7. Hamanishi J, Mandai M, Iwasaki M et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci USA*. 2007;104:3360–5.
8. Santoiemma PP, Powell DJ Jr. Tumor infiltrating lymphocytes in ovarian cancer. *Cancer Biol Ther.* 2015;16:807–20.
9. Abiko K, Matsumura N, Hamanishi J et al. IFN-gamma from lymphocytes induces PD-L1 expression and promotes progression of ovarian cancer. *Br J Cancer.* 2015;112:1501–9.
10. Ishii H, Takahara M, Nagato T et al. Monocytes enhance cell proliferation and LMP1 expression of nasal natural killer/T-cell lymphoma cells by cell contact-dependent interaction through membrane-bound IL-15. *Int J Cancer.* 2012;130:48–58.
11. Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. *Cell.* 2006;124:263–266.
12. Cai L, Song Y, Zhao X. Prognostic significance of lymphocyte monocyte ratio in patients with ovarian cancer. *Medicine.* 2020;99:14.
13. Gong J, Jiang H, Shu C, Hiu MQ, Liu Q, Li RF. Prognostic value of lymphocyte-tomonocyte ratio in ovarian cancer: a metaanalysis. *Journal of Ovarian Research.* 2019;12:51.