EJGO European Journal of Gynaecological Oncology

Parameters of blood count and tumor markers: a retrospective analysis and relation to prognostic factors in ovarian cancer

R.S. Nomelini[1], L.J. de Carvalho Oliveira[1], B.M. Tavares-Murta[2], E.F.C. Murta[1]

[1] Oncological Research Institute (IPON)/ Discipline of Gynecology and Obstetrics, Uberaba
[2] Discipline of Pharmacology; Federal University of the Triângulo Mineiro, Uberaba (Brazil)

Summary

Purpose of Investigation: The aims of study were to evaluate potential prognostic laboratory factors in ovarian cancer (blood count parameters and tumor markers) and to relate these parameters with prognostic factors. *Materials and Methods:* The authors evaluated patients that underwent surgical treatment and with confirmed histopathologic diagnosis of ovarian cancer. Age, FIGO stage, type of surgery, serum levels of tumor markers, parameters of blood count, disease-free and overall survival were recorded. Mann-Whitney test was performed. The significance level was less than 0.05. *Results:* Higher levels of CA 125, CA 15.3, and platelets were found in the group with Stage III/IV, since hemoglobin levels were higher in stage I/II ($p < 0.05$). CEA levels were higher in the group of non-serous neoplasms ($p < 0.05$). Higher levels of CA125, CA15.3 and platelets were seen in the group histological grade 2/3 ($p < 0.05$). *Conclusion:* CA 125, CA 15.3, hemoglobin, and platelets can be related prognostic factors in ovarian cancer.

Key words: Ovarian neoplasms; Blood cell count; Blood platelets; Prognosis; CA-125 antigen; CA-19-9 antigen.

Introduction

Ovarian cancer is the main cause of death among gynecological malignancies due to deficiency of effective methods for early diagnosis of this neoplasm [1, 2]. The five-year survival for patients diagnosed with Stage I ranges between 80 and 90%, whereas for patients with Stages III and IV, it ranges from 5 to 50%. Currently, about 60-65% of patients are in Stage III at diagnosis, which explains the high mortality of this neoplasm [3]. Although undergoing adequate treatment, 75% of cases have a recurrence of the disease, many of which occur within the first two years [4, 5].

Approximately 80-90% of ovarian cancers are derived from the surface epithelium [6]. The epithelial tumors are classified into well-differentiated, moderately differentiated, and poorly differentiated. Poorly differentiated epithelial tumors are associated with poor prognosis [3].

Histological type, staging, residual disease after initial surgery, and tumor grade are the most important clinical-pathological factors related to the prognosis of patients with epithelial ovarian cancer. New studies have evaluated prognostic factors in ovarian malignancies, such as hemoglobin and platelets, and tumor markers [7-10]. Salvage surgery at recurrence was independent prognostic factors in patients with recurrent early-stage ovarian cancer [11]. In borderline tumors, some studies have shown levels of CA-125 related to the prognosis of neoplasia [12, 13].

The aims of this study were to evaluate potential prognostic laboratory factors in ovarian cancer (blood count parameters and tumor markers), and to relate these parameters with clinical and pathological prognostic factors.

Materials and Methods

A retrospective study was performed at the Discipline of Obstetrics and Gynecology / Oncology Research Institute (IPON) of Federal University of the Triângulo Mineiro (UFTM). The authors evaluated the patients in the Pelvic Mass Service that underwent surgical treatment according to predetermined criteria [14, 15], and they had confirmed histopathologic diagnosis of primary malignant ovarian tumor over a period of ten years. The indication criteria for laparotomy were anechoic cysts with a maximum diameter less than seven cm, persistence of change for more than six months, altered tumor markers, anechoic cysts with a maximum greater than or equal to seven cm diameter, ovarian tumors with solid content, presence of intracystic vegetation, thick septa, two or more thin septa, and resistance index by color Doppler less than or equal to 0.4.

Age, FIGO stage, type of surgery, chemotherapy, serum levels of tumor markers (CA-125, CA-15.3, CA-19.9, CEA, and AFP) parameters, blood count (hemoglobin, WBC, platelets), disease-free and overall survival were recorded. The parameters of blood count and tumor markers were evaluated from blood collected preoperatively.

Data were analyzed using GraphPad Instat software. Values were expressed as medians (25 - 75 percentiles). The laboratory test results were compared between groups using unpaired Mann-Whitney test. The significance level was less than 0.05.

The Research Ethics Committee of Federal University of Triângulo Mineiro (protocol number 116.1953/2011) approved

Revised manuscript accepted for publication December 14, 2015

Table 1. — *Laboratory parameters in Stages I/II and III/IV of ovarian malignancies.*

	Stage I/II	Stage III/IV	*p*
CA-125 (U/ml)	16.34 (8.55−24.16)	105.25 (54.27−519.75)	< 0.0001
CA-15.3 (U/ml)	18.7 (14.85−25.88)	47.1 (24.2−88.5)	0.0013
AFP (U/ml)	1.5 (1.21−2.07)	1.57 (1.24−2.5)	0.93
CEA (U/ml)	1.04 (0.65−1.39)	1.5 (0.89−2.5)	0.19
CA-19.9 (U/ml)	11 (4.8−21.21)	10.4 (3.95−129.25)	0.54
Haemoglobin (g/100 ml)	13.75 (12−14.3)	11.45 (10.77−13.17)	0.01
Leucocytes (/mm^3)	7,730 (5,950−9,000)	9,050 (6,800−11,000)	0.10
Platelets (/mm^3)	272,000 (245,000−326,000)	345,500 (290,250−501,250)	0.02

Mann-Whitney test. Values are medians (25−75 percentiles).

Table 2. — *Laboratory parameters in histological grades 1, 2, and 3 in ovarian malignancies.*

	Grade 1	Grades 2/3	*p*
CA-125 (U/ml)	16.5 (9.2−25.22)	238 (54.27−704.52)	0.0002
CA-15.3 (U/ml)	19.4 (15.72−23.65)	47.1 (27.25−88.5)	0.004
AFP (U/ml)	1.57 (1.22−1.17)	1.57 (1.23−1.87)	0.95
CEA (U/ml)	1.28 (0.63−1.66)	1.36 (1.02−1.69)	0.56
CA-19.9 (U/ml)	10.26 (4.15−19.36)	8.8 (3.6−68.5)	0.70
Haemoglobin (g/100ml)	12.85 (11.3−14.3)	12.4 (11.2−13.5)	0.41
Leucocytes (/ mm^3)	7,440 (5,405−9,150)	8,800 (7,540−10,200)	0.10
Platelets (/mm^3)	271,000 (237,000−318,000)	326,000 (291,000−509,000)	0.02

Mann-Whitney test. Values are medians (25−75 percentiles).

this research.

Results

The authors evaluated 54 patients with ovarian malignant neoplasms. The average age of the patients was 46.7 ± 13.8 years. Thirty-five patients (64.8%) underwent complete surgery, ten (18.5%) underwent unilateral or bilateral salpingo-oophorectomy, seven (13%) underwent optimal debulking, and one patient underwent suboptimal debulking. Fifteen patients (27.8%) were in Stage IA, one (1.8%) in Stage IB, eight (14.8%) in Stage IC, one (1.8%) in Stage IIB, two (3.7%) in Stage IIC, five (9.2%) in Stage IIIA, one (1.8%) in Stage IIIB, 16 (29.6%) in Stage IIIC, and five (9.2%) in Stage IV. Thirty-seven patients (68.5%) underwent chemotherapy. Eleven (20.3%) patients died.

Two groups are evaluated in Table 1: Stage I/II (n = 27) and Stage III/IV (n = 27), and compared with laboratory parameters. Higher levels of CA 125, CA 15.3, and platelets ($p < 0.0001$, $p = 0.0013$, and $p = 0.02$, respectively) were observed in the group in Stage III/IV, since hemoglobin levels were higher in Stage I/II ($p = 0.01$).

In Table 2, the groups evaluated are: histological grade 1 (well-differentiated tumors) (n=40) and histological grade 2/3 (moderately-differentiated and undifferentiated tumors) (n=14). Higher levels of CA125, CA15.3, and platelets were seen in the grade 2/3 group ($p = 0.0002$, $p = 0.004$, and $p = 0.02$, respectively). The laboratory parameters were also compared between serous and non-serous subtypes. CEA levels were higher in the group of non-serous neoplasms ($p = 0.04$). CA 19.9 tended to significance ($p = 0.08$), with higher values in non-serous group. The groups were also divided into disease-free survival (DFS) greater than two years and another group with DFS less than two years. There was no statistical significance.

Discussion

The tumor marker CA125 is elevated in most cases of ovarian tumors. Lower levels are found in mucinous and borderline tumors; intermediate levels are associated with clear cell tumors and endometrioid, while high levels are found in invasive serous tumors [12, 16-19]. The levels of CA125 have relationship with disease stage, degree of tumor differentiation, and survival [17, 18, 20]. Complete surgical staging, histological grade and the preoperative levels of CA125 are independent prognostic factors and could be included as factors in the decision-making of chemotherapy [21].

One study evaluated protein expression levels of CEA in Danish ovarian cancer patients and suggested that the expression of CEA expression might be an independent prognostic factor for ovarian mucinous cystadenocarcinoma [22]. Another study evaluated the clinical significance of the use of serum tumor markers in primary epithelial ovarian cancer, and CA125 correlated with the FIGO Stage, but no correlation was demonstrated with CEA and CA19-9 [23]. The present study found higher levels of CA-125 and CA 15.3 in Stages III / IV and higher levels of CEA and

CA 19.9 in less differentiated tumors.

Another parameter associated with the progression of the tumor is the platelet count. Preoperative thrombocytosis is a frequent finding in ovarian carcinomas and there is an association with staging advanced and high-grade carcinomas, demonstrating that platelets may have a role in tumor growth and progression [7]. Preoperative platelets to lymphocyte ratio had predictive value for advanced disease or suboptimal surgery, being a better indicator of prognosis compared with thrombocytosis in patients with epithelial ovarian cancer [24]. On the other hand, another study showed that thrombocytosis was not a useful prognostic factor in patients with ovarian cancer, but it was related to elevation of platelets in the presence of ascites and anemia [25]. The present study showed higher levels of platelets in Stages III / IV.

In relation to hemoglobin levels, some studies have shown that its levels before and during chemotherapy may correlate with survival [8, 9, 26]. Hemoglobin concentration can exert a prognostic factor in oral squamous carcinoma [27] and ovarian cancer [28]. Anemia in advanced stages of ovarian cancer could be related to the levels of IL-6 [29]. Higher levels of red blood cells, hematocrit, and hemoglobin were related to initial stages in borderline ovarian tumors [30]. The present study showed lower hemoglobin levels in Stages III / IV.

Conclusion

Some tumor markers, hemoglobin, and platelets can be related prognostic factors in ovarian cancer. A limitation of the study was the relatively small number of patients. New studies of novel prognostic markers are important for better scheduling of surgical and adjuvant therapy of patients, since the treatment of these neoplasms is still a challenge in Gynecologic Oncology.

Acknowledgements

The authors wish to acknowledge the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

References

[1] Landen C.N. Jr., Birrer M.J., Sood A.K.: "Early events in the pathogenesis of epithelial ovarian cancer". *J. Clin. Oncol.* 2008, *26*, 995.

[2] Roett M.A., Evans P.: "Ovarian cancer: an overview". *Am. Fam. Physician* 2009, *80*, 609.

[3] Mironov S., Akin O., Pandit-Taskar N., Hann L.E.: "Ovarian Cancer". *Radiol. Clin. N. Am*. 2007, *45*, 149.

[4] Gadducci A., Cosio S., Zola P., Landoni F., Maggino T., Sartori E.: "Surveillance procedures for patients treated for epithelial ovarian cancer: a review of the literature". *Int. J. Gynecol. Cancer*, 2007, *17*, 21.

[5] Morikawa Y., Kawai M., Kano T., Kikkawa F., Oguchi H., Nakashima N., *et al.*: "Clinical remission criteria for epithelial carcinoma of the ovary". *Gynecol. Oncol.,* 1993, *48*, 342–8.

[6] Mok S.C., Kwong J., Welch W.R., Samimi G., Ozbun L., Bonome T., *et al.*: "Etiology and pathogenesis of epithelial ovarian cancer". *Dis. Markers*, 2007, *23*, 367.

[7] Crasta J.A., Premlatha T.S., Krishnan S.M., Vallikad E., Rameshkumar K.: "Significance of preoperative thrombocytosis in epithelial ovarian cancer". *Indian J. Pathol. Microbiol.*, 2010, *53*, 54.

[8] Eichbaum M.H., Weiss L.M., Bruckner T., Schneeweiss A., Sinn H.P., Gebauer G., *et al.*: "Prognostic impact of hemoglobin levels before and during carboplatin/taxane-based chemotherapy in patients with primary invasive epithelial ovarian cancer". *Med. Sci. Monit.*, 2009, *15*, CR156.

[9] Pongsanon K., Benjapibal M., Ruengkhachorn I.: "Prognostic significance of hemoglobin levels in patients with primary epithelial ovarian carcinoma undergoing platinum-based chemotherapy". *Asian Pac. J. Cancer Prev.*, 2011, *12*, 131.

[10] Gadducci A., Cosio S., Tana R., Genazzani A.R.: "Serum and tissue biomarkers as predictive and prognostic variables in epithelial ovarian cancer". *Crit. Rev. Oncol. Hematol.*, 2009, *69*, 12.

[11] Gadducci A., Cosio S., Zola P., Sostegni B., Fuso L., Sartori E.: "Prognostic factors and clinical outcome of patients with recurrent early-stage epithelial ovarian cancer: an Italian multicenter retrospective study". *Int. J. Gynecol. Cancer*, 2013, *23*, 461.

[12] Kolwijck E., Thomas C.M., Bulten J., Massuger L.F.: "Preoperative CA-125 levels in 123 patients with borderline ovarian tumors: a retrospective analysis and review of the literature". *Int. J. Gynecol. Cancer*, *2009*, *19*, 1335-8.

[13] Wu T.I., Lee C.L., Wu M.Y., Hsueh S., Huang K.G., Yeh C.J., Lai C.: "Prognostic factors predicting recurrence in borderline ovarian tumors". *Gynecol. Oncol.*, 2009, *114*, 237.

[14] Murta E.F., Silva C.S., Gomes R.A., Tavares-Murta B.M., Melo A.L.: "Ultrasonography criteria and tumor marker assay are good procedures for the diagnosis of ovarian neoplasia in preselected outpatients". *Eur. J. Gynaec. Oncol.,* 2004, *25*, 707.

[15] Murta E.F., Nomelini R.S.: "Early diagnosis and predictors of malignancy of adnexal mass". *Curr. Opin. Obstet. Gynecol.*, 2006, *18*, 14.

[16] Heeran M.C., Høgdall C.K., Kjaer S.K., Christensen L., Jensen A., Blaakaer J., et al.: "CA125 expression pattern, prognosis and correlation with serum CA125 in ovarian tumor patients. From The Danish 'MALOVA' Ovarian Cancer Study". *Gynecol. Oncol.*, 2007, *104*, 508.

[17] Cooper B.C., Sood A.K., Davis C.S., Ritchie J.M., Sorosky J.I., Anderson B., Buller R.E.: "Preoperative CA 125 levels: an independent prognostic factor for epithelial ovarian cancer". *Obstet. Gynecol.*, 2002, *100*, 59.

[18] Makar A.P., Kristensen G.B., Kaern J., Børmer O.P., Abeler V.M., Tropé C.G.: "Prognostic value of pre- and postoperative serum CA 125 levels in ovarian cancer: new aspects and multivariate analysis". *Obstet. Gynecol.*, 1992, *79*, 1002.

[19] Zanaboni F., Vergadoro F., Presti M., Gallotti P., Lombardi F., Bolis G.: "Tumor antigen CA 125 as a marker of ovarian epithelial carcinoma". *Gynecol. Oncol.*, 1987, *28*, 61.

[20] Geisler J.P., Miller G.A., Lee T.H., Harwood R.M., Wiemann M.C., Geisler H.E.: "Relationship of preoperative serum CA-125 to survival in epithelial ovarian carcinoma". *J. Reprod. Med.*, 1996, *41*, 140.

[21] Paramasivam S., Tripcony L., Crandon A.: "Prognostic importance of preoperative CA-125 in International Federation of Gynecology and Obstetrics stage I epithelial ovarian cancer: an Australian multicenter study". *J. Clin. Oncol.,* 2005, *23*, 5938.

[22] Høgdall E.V., Christensen L., Kjaer S.K., Blaakaer J., Jarle Christensen I., Gayther S., *et al.*: "Protein expression levels of carcinoembryonic antigen (CEA) in Danish ovarian cancer patients: from the Danish 'MALOVA'ovarian cancer study." *Pathology*, 2008, *40*, 487.

[23] Kudoh K., Kikuchi Y., Kita T., Tode T, Takano M, Hirata J., *et al.*: "Preoperative determination of several serum tumor markers in patients with primary epithelial ovarian carcinoma". *Gynecol. Obstet. Invest.*, 1999, *47*, 52.

[24] Raungkaewmanee S., Tangjitgamol S., Manusirivithaya S., Srijaipracharoen S., Thavaramara T.: "Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer". *J. Gynecol. Oncol.*, 2012, *23*, 265.

[25] Zeimet A.G., Marth, Müller-Holzner E., Daxenbichler G., Dapunt O.: "Significance of thrombocytosis in patients with epithelial ovarian cancer". Am *J. Obstet. Gynecol.*, 1994, *170*, 549.

[26] Münstedt K., Kovacic M., Zygmunt M., Von Georgi R.: "Impact of hemoglobin levels before and during chemotherapy on survival of patients with ovarian cancer". *Int. J. Oncol.*, 2003, *23*, 837.

[27] Bryne M., Eide G.E., Lilleng R., Langmark F., Thrane P.S., Dabelsteen E.: "A multivariate study of the prognosis of oral squamous cell carcinomas. Are blood group and hemoglobin new prognostic factors?" *Cancer*, 1991, *68*, 1994-8.

[28] Chen Y., Zhang L., Liu W.X., Liu X.Y.: "Prognostic significance of preoperative anemia, leukocytosis and thrombocytosis in chinese women with epithelial ovarian cancer". *Asian Pac. J. Cancer Prev.*, 2015, *16*, 933.

[29] Allensworth S.K., Langstraat C.L., Martin J.R., Lemens M.A., McGree M.E., Weaver A.L., Dowdy S.C., *et al.*: "Evaluating the prognostic significance of preoperative thrombocytosis in epithelial ovarian cancer". *Gynecol. Oncol.*, 2013, *130*, 499.

[30] Macciò A., Madeddu C., Massa D., Mudu M.C., Lusso M.R., Gramignano G., *et al.*: "Hemoglobin levels correlate with interleukin-6 levels in patients with advanced untreated epithelial ovarian cancer: role of inflammation in cancer-related anemia". *Blood*, 2005, *106*, 362.

[31] Nomelini R.S., Silva T.M., Tavares-Murta B.M., Murta E.F.: "Parameters of blood count and tumor markers in patients with borderline ovarian tumors: a retrospective analysis and relation to staging". *ISRN Oncol.,* 2012, *2012*, 947831.

Corresponding Author:
E.F.C. MURTA, M.D.
Oncological Research Institute (IPON)
Discipline of Gynecology and Obstetrics
UFTM, Av. Getúlio Guaritá, 214
Bairro Abadia, 38025-440 Uberaba-MG (Brazil)
e-mail: eddiemurta@mednet.com.br