Ref: Ro Med J. 2022;69(4)
Doi: 10.37897/RMJ.2022.4.7

The significance of preoperative thrombocytosis in ovarian cancer patients

Irina Balescu[1], Nicoale Bacalbasa[2], Iulian Brezean[2,3], Claudia Stoica[4,5], Cezar Laurentiu Tomescu[6,7], Cristina Martac[8], Andrei Voichitoiu[9,10], Bogdan Gaspar[2,11]

[1]Doctoral School, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2]Department of Surgery, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3]Department of Surgery, "Ion Cantacuzino" Clinical Hospital, Bucharest, Romania
[4]Department of Anatomy, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[5]Department of Surgery, Ilfov County Emergency Hospital, Bucharest, Romania
[6]Department of Obstetrics and Gynecology, County Hospital Constanta, Romania
[7]"Ovidius" University of Medicine and Pharmacy, Constanta, Romania
[8]Department of Anesthesiology, Fundeni Clinical Institute, Bucharest, Romania
[9]Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[10]Department of Obstetrics and Gynecology, "Alessandrescu-Rusescu" National Institute of Mother and Child Care, Bucharest, Romania
[11]Department of Visceral Surgery, Floreasca Clinical Emergency Hospital, Bucharest, Romania

ABSTRACT

The presence of an increased number of platelets has been demonstrated to be significantly associated with the presence of different types of malignancies, especially when it comes to gynecological cancers and seems to be associated with a poorer prognosis. This fact has been widely studied in order to better understand the physiopathology of the phenomenon, the impact on the overall outcomes and to validate new therapeutic lines for such cases. The aim of the current paper is to review the most important studies conducted on this issue.

Keywords: platelets, thrombocytosis, ovarian cancer

INTRODUCTION

Besides the well-known role of the platelets in providing an efficient hemostasis process and in maintaining the vascular integrity in case of injury through adhesion, activation, degranulation and wound healing they also seem to be involved in the inflammatory and immune response; meanwhile, a certain role is represented by visceral regeneration and even by tumor proliferation and dissemination [1-3].

The correlation ship between the circulating platelets and tumor proliferation and dissemination

It has been widely demonstrated so far that malignant lesions benefit from the circulating platelets in order to grow and disseminate. This fact has been widely explained so far through the fact that tumor growth factors induce platelet proliferation and activation. Meanwhile, it seems that the activated platelets play a crucial role in covering the circulating tumor cells and offering them immunity in front of natural killer cells, this process being modulated by platelet derived growth factor and by tumor growth factor beta. Meanwhile tumoral cells might mimic certain features of circulating platelets and therefore, might proliferate in the presence of platelet derived growth factors. When it comes specifically to ovarian cancer, the presence of a higher number of circulating platelets as well as a higher

Corresponding author:
Irina Balescu
E-mail: irina.balescu@drd.umfcd.ro

Article History:
Received: 26 December 2022
Accepted: 30 December 2022

amount of platelet derived growth factor seems to promote the epithelial to mesenchymal transition [4-7]. This process is modulated via multiple regulators and represents the modality through which the epithelial cells lose their adherence, increasing meanwhile the capacity to invade the surrounding structures and to induce apoptosis resistance. In the meantime, tumoral cells generate high amounts of thrombin which will further conduct to platelet degranulation inducing therefore an inflammatory, proliferative and angiogenetic effect. Therefore, this effect is especially important when the tumoral volume surpasses the limit of 2 millimeters inducing in this way a proangiogenic effect; therefore, the tumoral bed will receive a higher volume of blood and a faster growth process will be achieved [8,9]. Meanwhile, an increased number of platelets will lead to an increased serum level of thrombopoietin and proinflammatory interleukins, stimulating even more the tumoral dissemination [10]. In this respect, it is estimated that an increased number of platelets might proceed with few years the diagnosis of cancer, the presence of thrombocytosis being considered as part of the preneoplastic processes. In such cases an increased number of circulating platelets is also associated with increasing serum levels of Interleukin 6 (IL6) and thrombopoietin, establishing in this way a positive diagnostic of preneoplastic syndrome and, in the meantime, excluding a possible diagnosis of myeloproliferative disorders, cases in which normal or decreased levels of circulating thrombopoietin are encountered [11,12].

Moreover, other studies came to demonstrate that an increased level of IL6 at the level of the peritoneal fluid or in the ovarian fluid originating from ovarian cysts is associated with a poorer prognostic and might be also associated with increased serum levels of CA 125 and increased number of circulating platelets [13-15].

The possible benefit of monoclonal antibodies, antiaggregant and anticoagulant therapies in ovarian cancer patients

While the implication of circulating platelets in tumoral proliferation and dissemination has been widely demonstrated, the next logical step was to investigate the possible role of antiaggregant and even of the anticoagulant therapies in the setting of ovarian cancer patients.

In this respect, studies have shown that administration of anti IL6 monoclonal antibodies such as Siltuximab seem to normalize the circulating levels of IL6 and therefore to inhibit tumoral proliferation. Other potential benefits of Siltuximab administration consist of decreasing the number of circulating platelets as well as of the growth factors synthetized by the tumoral cells but also by platelets themselves [16-18]. Therefore, a study conducted on mice demonstrated that cases in which Siltuximab was associated to Paclitaxel reported a 90% increase of the chemotherapeutic effect when compared to cases which received Paclitaxel alone [16]. When it comes to the possible benefit of the association of antiaggregant/anticoagulant therapies in ovarian cancer patients, it seems that these agents are able to increase the efficacy of the standard chemotherapeutic agents by inhibiting platelet induced angiogenesis and by decreasing the circulating amounts of IL6 [16,17]. Moreover, recent studies came to underline the fact that the persistence of a high number of circulating platelets after chemotherapy should be considered as a sign of poor responsive to treatment disease; this parameter, together with the post treatment levels of CA 125 seem to be at this moment the most important prognostic factors in order to predict the chemoresistance of ovarian malignancies [19]. Therefore, due to this reason a significant number of studies consider that thrombocytosis should be considered as a biological marker of aggressive ovarian lesions [19-21].

Is there a correlation ship between the preoperative number of circulating platelets at the time of relapse and the long-term outcomes in recurrent ovarian cancer?

Another significant issue which should be discussed is related to the influence of preoperative thrombocytosis at the time of relapse on the overall outcomes of ovarian cancer patients. Therefore, studies conducted so far came to demonstrate that patients presenting preoperative thrombocytosis at the time of the initial diagnosis of advanced stage ovarian cancer usually report higher numbers of circulating platelets at the time of relapse. Meanwhile, patients presenting preoperative thrombocytosis seem to have a lower disease-free survival after primary cytoreduction, a higher rate of incomplete debulking at the time of secondary cytoreduction and, as expected, a lower rate of overall survival after secondary cytoreduction [22,23]. Therefore, it is widely understood why we argue that preoperative thrombocytosis should be considered as a negative prognostic factor through all the moments of the disease in ovarian cancer patients. In this respect, maybe a more aggressive preoperative and postoperative systemic therapy should be administrated in such cases.

CONCLUSIONS

Preoperative thrombocytosis in ovarian cancer patients should be considered a significant alarm signal especially in cases in which advanced stages of the disease are suspected. In this respect, it seems that an increased number of circulating platelets is associated with a more aggressive biology of the tu-

mor, with a higher capacity of dissemination and with a poorer response to therapy. Therefore, patients presenting an increased number of thrombocytes should benefit from a personalized systemic neoadjuvant or adjuvant therapy; recent studies came to demonstrate that administration of monoclonal antibodies inhibiting IL 6, antiaggregant and anticoagulant therapies might represent a viable and efficient option of choice in order to maximize the effect of the standard chemotherapeutic therapy.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Lin RJ, Afshar-Khargan V, Schafer I. Paraneoplastic thrombocytosis: the secrets of tumor self-promotion. *Blood Spothlight*. 2014;124(2):184-7.
2. Ware J, Corken A, Khetpal R. Platelet function beyond hemostasis and thrombosis. *Curr Opin Hematol*. 2013;20(5):451-456.
3. Leslie M. Cell biology. Beyond clotting: the powers of platelets. *Science*. 2010;328(5978):562-564.
4. Nieswandt B, Hafner M, Echtenacher B, Mannel DN. Lysis of tumor cells by natural killer cells in mice is impeded by platelets. *Cancer Res*. 1999; 59(6):1295-1300.
5. Mitrugno A, Williams D, Kerrigan SW, Moran N. A novel and essential role for FcgRIIa in cancer cell-induced platelet activation. *Blood*. 2014;123(2):249-260.
6. Schumacher D, Strilic B, Sivaraj KK, Wettschureck N, Offermanns S. Platelet-derived nucleotides promote tumor-cell transendothelial migration andmetastasis via P2Y2 receptor. *Cancer Cell*. 2013; 24(3):130-137.
7. Buergy D, Wenz F, Groden C, Brockmann MA. Tumor-platelet interaction in solid tumors. *Int J Cancer*. 2012;130(12):2747-2760.
8. Egan K, Crowley D, Smyth P, O'Toole S, Spillane C, Martin C et al. Platelet adhesion and degranulation induce pro-survival and pro-angiogenic signalling in ovarian cancer cells. *PLoS ONE*. 2011;6(10):e26125
9. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. *Nat Rev Cancer*. 2011;11(2):123-134
10. Nieswandt B, Hafner M, Echtenacher B, Mannel DN. Lysis of tumor cells by natural killer cells in mice is impeded by platelets. *Cancer Res*. 1999; 59(6):1295-1300
11. Schafer AI. Thrombocytosis. *N Engl J Med*. 2004; 350(12):1211-1219.
12. Kaser A, Brandacher G, Steurer W, Kaser S et al. Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis. *Blood.* 2001;98(9):2720-2725.
13. Gastl G, Plante M, Finstad CL, Wong GY, Federici MG et al. High IL-6 levels in ascitic fluid correlate with reactive thrombocytosis in patients with epithelial ovarian cancer. *Br J Haematol.* 1993;83(3):433–41.
14. Imai T, Koike K, Kubo T, Kikuchi T, Amano Y, Takagi M et al. Interleukin-6 supports human megakaryocytic proliferation and differentiation in vitro. *Blood.* 1991;78(8):1969–74.
15. van der Zee AG, de Cuyper EM, Limburg PC, de Bruijn HW, Hollema H, Bijzet J et al. Higher levels of interleukin-6 in cystic fluids from patients with malignant versus benign ovarian tumors correlate with decreased hemoglobin levels and increased platelet counts. *Cancer.* 1995;75(4):1004–9
16. Coward J, Kulbe H, Chakravarty P, Leader D et al. Interleukin-6 as a therapeutic target in human ovarian cancer. *Clin Cancer Res*. 2011;17(18): 6083-6096.
17. Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet*. 2012; 379(9826):1591-1601.
18. Stevenson JL, Varki A, Borsig L. Heparin attenuates metastasis mainly due to inhibition of P- and L-selectin, but non-anticoagulant heparins can have additional effects. *Thromb Res*. 2007; 120(Suppl 2):S107-S111.
19. Lee M, Kim SW, Nam EJ, Yim GW, Kim S, Kim YT. The impact of pretreatment thrombocytosis and persistent thrombocytosis after adjuvant chemotherapy in patients with advanced epithelial ovarian cancer. *Gynecol Oncol*. 2011;122:238–241
20. den Ouden M, Ubachs JM, Stoot JE, van Wersch JW. Whole blood cell counts and leucocyte differentials in patients with benign or malignant ovarian tumours. *Eur J Obstet Gynecol Reprod Biol.* 1997;72(1):73–7
21. Qian X, Tuszynski GP. Expression of thrombospondin-1 in cancer: a role in tumor progression. *Proc Soc Exp Biol Med.* 1996;212(3):199–207.
22. Cohen JG, Tran AQ, Rimel BJ, Cass I, Walsh CS, Karlan BY, Li AJ. Thrombocytosis at secondary cytoreduction for recurrent ovarian cancer predicts suboptimal resection and poor survival. *Gynecol Oncol.* 2014;132:556–559
23. Allensworth SK, Langstraat CL, Martin JR, Lemens MA et al. Evaluating the prognostic significance of preoperative thrombocytosis in epithelial ovarian cancer. *Gynecol Oncol.* 2013;130(3):499–504.
24. Canzler U, Lück HJ, Neuser P, Sehouli J, Burges A et al. Prognostic role of thrombocytosis in recurrent ovarian cancer: a pooled analysis of the AGO Study Group. *Arch Gynecol Obstet*. 2020 May;301(5):1267-1274.