GENERAL ARTICLE

The impact of thrombocytosis on the long term outcomes in relapsed ovarian cancer

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ABSTRACT

The presence of thrombocytosis has been widely associated with poor prognostic in patients diagnosed with ovarian cancer at the time of the initial diagnostic. Once this fact has been widely accepted, attention was focused on studying whether this biological parameter could be also a diagnostic tool for identifying patients with poorer outcomes at the time of secondary cytoreduction. Therefore the most commonly encountered questions are whether patients presenting thrombocytosis at the time of primary cytoreduction are expected to have also thrombocytosis at the time of relapse and if thrombocytosis at the time relapse is corelated with lower disease free intervals, with higher rates of incomplete debulking and with poorer rates of overall survival respectively. This is a literature review of the most relevant studies conducted on this issue.

Keywords: relapsed ovarian cancer, thrombocytosis, secondary cytoreduction, survival

INTRODUCTION

Ovarian cancer remains one of the most aggressive malignancies affecting women worldwide and the most commonly encountered cause of death due to gynecologic neoplastic diseases [1,2]. As expected, this fact is especially caused by the late diagnostic of patients, in advanced stages of the disease, when peritoneal, lymphatic or hematogenous metastases are already present, and therefore, the possibility of achieving complete debulking surgery is lower [3-5]. In order to improve the overall outcomes in such cases, attention was focused in identifying the cases at risk to develop recurrent disease; therefore, once identified, such cases can be successfully submitted to more aggressive chemotherapeutic and biological means in order to increase the disease free survival rate [6-9]. One of the most widely studied factors is represented by the serum levels of CA 125 [10-12]; however, attention was focused on identifying other significant prognostic factors which might predict a poorer outcome at the time of the initial diagnosis and even to predict the risk of relapse as well as the magnification of the cancer related death. In this respect, when of the most cited such factors remain the number of circulating platelets [13-15].

CAUSES OF THROMBOCYTOSIS

An increased number of circulating platelets can be encountered in primary disorders such as myeloproliferative neoplasms or essential thrombocytosis (and is considered to be primary thrombocytosis) or as an effect of inflammation, iron deficiency, infection, tissue damage, acute blood loss or of the presence of a systemic neoplastic process [16]. One of the most commonly cited neoplasms which seem to be associated with the presence of increased numbers of circulating platelets is represented by ovarian cancer [17-19]. This parameter seems to be a very important prognostic factor in order to identify patients with a poorer prognostic at the time of the initial diagnostic. However, this parameter seems to be important also in identifying patients at risk to report a lower disease free interval, a lower rate of complete debulking at the time of relapse and a poorer overall outcome [20-22].

Prognostic role of thrombocytosis at the time of relapse in ovarian cancer patients

The possible prognostic role of the number of circulating platelets at the time of relapse in ovarian cancer patients has been widely established both in cases submitted to chemotherapy or to secondary debulking surgery. A study conducted by Canzler et al. and published in 2020 in the *Archives of Gynecology and Obstetrics* included 300 patients diagnosed with recurrent disease, pretreatment thrombocytosis being encountered in 37 cases. The authors came to demonstrate that the overall response to chemotherapy among patients with pretreatment thrombocytosis was of 35.3%, significantly lower when compared to the one reported in patients with normal serum number of platelets (41.6%, p=0.046). This result was even better expressed by the overall survival, which was of 16.33 months in cases presenting pretreatment thrombocytosis and respectively 23.92 months in cases in which a normal pretreatment platelet count had been reported [23]. Therefore, these results came to underline the correctness of the supposition according to which a higher number of platelets is in fact the sign of a more aggressively biology of the tumor.

One of the first studies which came to demonstrate that thrombocytosis at the time of relapse should be considered as a negative prognostic factor in ovarian cancer patients was published by Nather in 2003; the study included 31 patients with recurrent ovarian cancer and demonstrated that cases presenting more than 300,000 platelets/microliter at the time of relapse exhibited a significantly poorer outcome in terms of survival; however, this correlation ship could not be observed when investigating the influence of decreased hemoglobin levels at the time of relapse [20].

Another important factor which should be analyzed in recurrent ovarian cancer patients is the dynamics of the number of circulating platelets at the time of relapse. Therefore, in the study conducted by Hu et al. in 2020, 104 patients with recurrent epithelial ovarian cancer were included; the authors analyzed the correlation ship between the serum levels of fibrinogen, D dimers and platelet count and the progression free and overall survival. Among these patients a decrease of the platelet count by less than 25% after the ending of the primary therapy at recurrence was associated with a significantly poorer outcome expressed through a lower disease free survival and overall survival respectively; meanwhile, this correlation could not be observed when studying the dynamics of D dimers and fibrinogen. When it comes to the dynamics of platelet count in patients with a complete response to chemotherapy at recurrence (defined by a disease free survival higher than 6 months), the authors came to demonstrate that in such cases a significant decrease of the circulating platelets was encountered (when compared to the number of the circulating platelets at the beginning of the treatment); as expected, this correlation ship failed to be demonstrated in cases in which chemo resistant disease was encountered. Moreover, the role of platelets in promoting cancer recurrence was demonstrated in a cellular culture of ovarian cells; therefore, cultures in which platelet co-cultures were associated, a protective effect against apoptosis was demonstrated. In this respect, we can conclude that a higher amount of circulating platelets has a protective role against apoptosis among ovarian cancer cells [24]. A similar conclusion was also demonstrated by Eggeman et al, an overall decrease of the number of the circulating platelets by less than 25% after chemotherapy being associated with a poorer outcome [21].

Another interesting study which aimed to investigate the correlation ship between the presence of thrombocytosis and ovarian cancer relapse was conducted by Cohen et al and included 107 patients submitted to secondary cytoreduction. The authors demonstrated the fact that the proportion of patients presenting thrombocytosis at the time of relapse was lower when compared to the proportion of patients presenting this feature at the time of the initial diagnostic, this aspect being explained through the fact that the administration of adjuvant chemotherapy after primary cytoreduction can cause a negative impact on the bone marrow. Therefore, the platelet synthesis is decreased at the time of relapse. On the other part, the same study demon-

strated that thrombocytosis can be present at the time of relapse even if it had been absent at the time of the initial diagnostic, this aspect being explained through more mechanisms: the selection of resistant cells during the adjuvant therapy at the time of the initial diagnostic, association of splenectomy at the time of the primary cytoreduction or due to the association of inflammation, myeloproliferative disorders or infections. Meanwhile the authors underlined the fact that the cut off value for thrombocytosis in such patients should be lower when compared to cases which did not undergo chemotherapy and should be established at 350,000/microliter. This fact wants to eliminate the possible influence of the chemotherapeutic agents on the bone marrow and the possible inhibition through this mechanism of platelet synthesis [25].

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CONCLUSIONS

In conclusion, thrombocytosis remains a significant prognostic factor at the time of recurrence, the presence of this parameter being associated with negative influence on the disease free and overall survival rate. Moreover, this parameter seems to be efficient in order to better identify the patients with poorer prognosis, a decrease of less than 25% of the number of circulating platelets being associated with a poorer response to chemotherapy. However, we should not omit the fact that these patients, in most cases had been also submitted to adjuvant chemotherapy at the time of the initial diagnosis and therefore, an inhibition process of platelet synthesis is to be expected at the level of the bone marrow. In this respect, a lower cut off value of the circulating platelets should be established in such cases.

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