Thrombocytosis and Anaemia in Women with Recurrent Ovarian Cancer Prior to a Second-line Chemotherapy

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Abstract. *Background: To investigate the incidence and the prognostic value of platelet count and serum haemoglobin (Hb) in patients with recurrent ovarian cancer prior to second-line chemotherapy. Materials and Methods: Clinical records were reviewed for 31 patients with recurrent ovarian cancer. Survival analysis was evaluated by univariate (Kaplan-Meier product limit method and log-rank test) analysis. We analysed the results for the overall survival. Anaemia and thrombocytosis were defined as a serum Hb level <12g/dl and as platelet count >300.000/μL, respectively. Results: Thrombocytosis and tumour anaemia were present in 55% and 42% of the patients, respectively. Tumour anaemia was of no prognostic value with respect to overall survival in our series. In patients with thrombocytosis, the median survival rate was reduced (p=0.05). Conclusion: Our data suggest that a platelet count >300.000/μL appears to be an adverse prognostic parameter in patients with recurrent ovarian cancer prior to a second-line chemotherapy.*

Ovarian cancer is the leading cause of death among gynecological malignancies (1). Although frequently performed, second-line chemotherapy in patients with recurrent ovarian cancer has not been shown to improve the patients' overall survival (2). Thus, it would be of clinical value to know which patients are most likely to benefit from second-line chemotherapy. The role of haemoglobin levels as prognosticator for response to second-line chemotherapy has been discussed controversially (3,4). Anaemia and thrombocytosis are frequently found in association with malignant diseases and have been shown to predict patients' prognosis independently in various human malignancies (5-9) including cervical (10-12), endometrial (13,14) and vulvar cancer (15). Although the role of anaemia and thrombocytosis in primary ovarian cancer (16-18) has been widely investigated, data are sparse about their incidence in patients with recurrent ovarian cancer.

The aim of our study was to investigate the incidence and the prognostic value of thrombocytosis and tumour anaemia in patients with recurrent ovarian cancer undergoing a second-line chemotherapy.

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Materials and Methods

Patients. Thirty-one patients with recurrent ovarian cancer were included in the study. The median follow-up time was 33 months (range, 17-72) after the primary operation. The median age was 56 years (range, 38-79). Patient characteristics are described in Table I.

Surgery. Surgery was performed between 1993 and 1998. Standard treatment consisted of bilateral salpingo-oophoroectomy, total abdominal hysterectomy, omentectomy and pelvic lymphadenectomy. World Health Organisation (WHO) criteria were used for histological classification (21). Histological grading was performed according to the criteria of Day *et al.* defining highly-differentiated tumours as Grade 1, undifferentiated tumours as Grade 3. The clinical stage of disease was determined according to International Federation of Gynecology and Obstetrics (FIGO).

Follow-up. All patients had been treated with a first-line platinum-containing chemotherapeutical regimen and subsequently underwent an intensive diagnostic follow-up. In the first 3 years the patients were followed every 3 months, between the 3rd and the 5th year every 6 months and afterwards annually. Each follow-up study consisted of medical history, physical examination and determination of tumour marker levels (CA 125). Chest X-ray and sonography of the abdomen was performed every 6 months, abdominal computed tomography was done every 12 months. Recurrent disease was proven histologically or by computed tomography. Patients received various types of second-line chemotherapy as shown in Table III. Fourteen patients were treated with a second debulking surgery prior to second-line chemotherapy. Hb and platelet count was routinely determined before each cycle of chemotherapy. As previously reported, anaemia was defined as Hb value <12g/dL (6-10,17) - and thrombocytosis was defined as a platelet count of >300,000/μL. (11,15).

Table I. *Patients' characteristics.*

	No. of cases	%
Total number of patients	31	100
Stage of disease (FIGO)		
I	1	3.2
II	4	12.8
III	23	74.3
IV	3	9.7
Histological grading		
G1	8	25.8
G2	7	22.6
G3	16	51.6
Residual disease after surgery		
0	7	22.6
< 2 cm	8	25.8
> 2 cm	16	51.6
Histological type		
Serous Adenocarcinoma	14	45.2
Papillary Adenocarcinoma	3	9.7
Serous-papillary Adenocarcinoma	9	29.0
Mucinous Adenocarcinoma	3	9.7
Endometroid Adenocarcinoma	2	6.5

Response criteria. Response to chemotherapy was assessed according to previously published criteria (20).

Statistical analysis. Due to the skewed distribution of values, the median and range of values are given. Comparisons between unpaired groups were made using the Mann-Whitney *U*-test. Survival probabilities were calculated by the product limit method of Kaplan and Meier (21). Survival rates were analysed from the date of the first cycle of second-line chemotherapy to the date of the last observation. Differences between groups were tested using the Wilcoxon test. The Chi-square test was used when appropriate. *P*-values of <0.05 were considered statistically significant. The SAS statistical software system (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Results

Patients. The median disease-free interval between surgical procedure and recurrent disease was 15 months (range, 2.4-104). In 8 patients (25.8%) local recurrence, in 6 patients (19.4%) distant metastases, and in 6 patients (19.4%) local combined with distant metastases occurred. In 12 patients (38.7%) malignant ascites or malignant pleural effusion was found (Table IV). Patients' response data are described in Table II. Twenty patients (64.5%) died of cancer. The median survival of the patients was 28 months (range, 1-92).

Table II. *Response to second-line chemotherapy.*

Response	No. of cases	%
Complete Remission	11	35.5
Partial Remission	7	22.6
Stable Disease	3	9.7
Progressive Disease	10	32.2

Thrombocytosis and anaemia in patients with recurrent ovarian cancer. Anaemia was present in 13 out of 31 (42%) patients. Pre-treatment thrombocytosis was present in 17 out of 31 (55%) patients. Histological grading, tumour stage and tumour burden of the primary tumour showed no significant correlation with anaemia ($p=0.34$, $p=0.44$ and $p=0.52$, respectively) and thrombocytosis ($p=0.06$, $p=0.42$ and $p=0.07$, respectively). Anaemia and thrombocytosis were independent of grading, stage and residual disease.

Anaemia and thrombocytosis and overall survival. The median survival of patients with and without anaemia was not significantly different ($p=0.27$). The median survival in patients with thrombocytosis was 10 months compared to 17 months for patients with normal platelet counts. Thus, elevated platelet counts correlated significantly with a shortened survival ($p=0.05$). Median serum CA125 levels in patients with recurrent ovarian cancer were 296 U/mL. The median age was 56 years (range, 38-79). The patients' age and CA125 serum levels did not significantly influence the patients' survival ($p=0.17$, $p=0.12$, respectively).

Discussion

Our study demonstrated that patients with recurrent ovarian cancer prior to second-line chemotherapy had elevated platelet counts in 55% and decreased haemoglobin values in 42%. Patients with thrombocytosis showed a significantly lower survival probability compared with patients with normal platelet counts.

Several studies have described the prevalence of pre-treatment thrombocytosis or tumor anaemia in various human malignancies including stomach (7), lung (22), bladder (6), prostate (8), cervical (10-12),endometrial (13,14) and ovarian cancer (16-18). Similarly to these studies we observed thrombocytosis and anaemia in patients with recurrent ovarian cancer prior to second-line chemotherapy. The occurrence of pre-treatment thrombocytosis as well as pre-treatment tumor anaemia have been found to be independent indicators of poor survival in patients with ovarian cancer (16-18). Based on these results we investigated the possible role of thrombocytosis and tumor

Table III. *Second-line chemotherapy.*

Type of Chemotherapy	No. of cases	%
Carboplatin / Taxol	6	19.4
Carboplatin / Endoxan	1	3.2
Carboplatin	3	9.7
Taxol	7	22.6
Taxol / Cisplatin	4	12.8
Topotecan	8	25.8
Vepesid oral	2	6.5

Table IV. *Sites of recurrence.*

Sites	No. of cases	%
Pelvis (local)	14	45.2
Liver	4	12.9
Abdominal wall	3	9.7
Neck	2	6.5
Carcinosis peritonei	7	22.6
Elevated tumor marker	25	80.6
Ascites or pleural effusion	12	38.7

anaemia as prognostic parameters in patients with recurrent disease, to evaluate which patients are most likely to benefit from second-line chemotherapy.

In our analysis we found that the prevalence of thrombocytosis is associated with a poor outcome in patients with recurrent ovarian cancer. The specific pathophysiological mechanisms underlying elevated platelet counts in cancer patients are still unknown. However, there have been several hypotheses proposed on this subject. The natural history of thrombocytosis in malignant diseases has been thought to involve an increased production of thrombocytes by the megacariocytes, rather than an increased life-span (12). Tumor-related humoral factors with thrombopoietin-like activity (23) and overcompensated megacariocytopoesis because of tumor-induced disseminated intravascular coagulopathy (5) have been proposed in the ethiology of reactive thrombocytosis. Interleukin-6 (IL-6), a potent stimulator of megacariocytopoesis and maturation of megacariocytes, as well as granulocyte-macrophage colony-stimulating factor (24) have been implicated in the development of tumor-associated thrombocytosis (25). Gastl *et al.* found that IL-6 levels in patients with ovarian cancer were significantly higher in ascitic fluid than in serum and that ascitic fluid IL-6 activitiy correlated with the circulating platelet count (25).

It has been speculated that thrombocytosis may worsen the prognosis for patients with cancer and adversely affect survival by facilitating cancer cell adhesion to the endothelium, which is the first step of metastasis. Thrombospondin, an adhesive glycoprotein secreted by platelets, has been found to potentiate tumor cell metastasis in an animal model (26). High blood levels of thrombospondin are found in cancer patients and a high expression of thrombospondin receptor on tumor cells correlated with poorer survival. It is proposed that thrombospondin promotes the arrest of tumor cells in the vascular bed (27,28).

As to tumor anaemia, decreased Hb values have been reported in a variety of non-gynecological and gynecological malignancies. Though there is currently no exact explanation for the phenomenon of poorer outcome associated with decreased Hb levels in cancer patients, it has been speculated that tumor anaemia can be seen as a paraneoplastic symptom (29). Induction of haemolysis, suppression of erythropoiesis and impairment of erythropoietin response on erythroid progenitor cells caused by tumor-released cytokines have been discussed as possible pathophysiological mechanisms underlying anaemia in malignant diseases. However, our data did not provide circumstantial evidence that low pre-treatment Hb concentration is associated with an impaired survival in patients with recurrent ovarian cancer.

In summary our data show a significant relationship of elevated platelet count and shortened overall survival in patients with recurrent ovarian cancer. This supports the theory that thrombocytosis aids the establishment of metastasis. Since the pretreatment determination of platelet counts is cheap and performed routinely, the confirmation of our results obtained in a larger series of patients should be performed to evaluate whether thrombocytosis may serve as an independent prognostic factor in recurrent ovarian cancer. As for tumor anaemia our results were not statistically significant.

References

1 Boring CC, Squires TS and Tong T: Cancer statistics, 1991. CA Cancer J Clin *41*: 19-36, 1991.

2 Christian J and Thomas H: Ovarian cancer chemotherapy. Cancer Treat Rev *27(2)*: 99-109, 2001.

3 Eisenhauer EA, Vermorken JB and van Glabbeke M: Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer: a multivariate analysis of 704 patients. Ann Oncol *8(10)*:963-8, 1997.

4 Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, Gianni L, Myles J, van der Burg ME, Kerr I, Vermorken JB, Buser K and Colombo N *et al.*: European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose *versus* low-dose and long *versus* short infusion. J Clin Oncol *12(12)*:2654-66, 1994.

5 Dutcher JP: Hematologic abnormalities in patients with nonhematologic malignancies. Hematol Oncol Clin North Am *1(2)*:281-99, 1987.

6 Pollak A, Zagars GK, Dinney CP, Swanson DA and von Eschenbach AC: Preoperative radiotherapy for muscle-invasive bladder carcinoma: long term follow-up and prognostic factors for 338 patients. Cancer *74*: 2819-27, 1994.

7 Jatzko GR, Lisborg PH, Denk H, Klimpfinger M and Stettner HM: A 10-years experience with Japanese-type lymph node dissection of gastric cancer outside of Japan. Cancer *76*: 1302-12, 1995.

8 Duphy EP, Petersen IA, Cox RS and Bagshaw MA: The influence of initial hemoglobin and blood pressure levels on result of radiation therapy for carcinoma of the prostate. Int J Radiat Oncol Biol Phys *16*: 1173-8, 1998.

9 Fein DA, Lee WR, Hanlon AL, Ridge JA, Langer CJ and Curran WJ Jr. *et al.*: Pretreatment hemoglobin level inflluences local control and survival of T1-T2 squamous cell of the glottic larynx. J Clin Oncol *13*: 2077-83, 1995.

10 Werner Wasik M, Schmid CH, Bornstein L, Ball HG, Smith DM and Madoc Jones H: Prognostic factors for local and distant recurrence in stage I and II cervical carcinoma. Int J Radiat oncol Biol Phys *32*: 1309-17, 1995.

11 Rodriguez GC, Clarke-Pearson DL, Soper JT, Berhuck A, Synan I and Dodge RK: The negative prognostic implications of thrombocythosis in women with stage IB cervical cancer. Obstet Gynecol *83*: 445-48, 1994.

12 Hernandez E, Lavine BA, Dunton CJ, Gracely E and Parker J: Poor prognosis associated with thrombocythosis in patients with cervical cancer, Cancer *69*: 2975-2977, 1992.

13 Scholz HS, Benedicic C, Haas J, Tamussino K and Petru E: Stage IV ovarian cancer: prognostic factors and survival beyond 5 years. Anticancer Res *21(5)*:3729-32, 2001.

14 Menczer J, Geva D, Schejter E and Zakut H: Elevated platelet count in patients with endometrial carcinoma: correlation with selected prognostic factors and with survival. Int J Gynecol Cancer *6*: 463-6, 1996.

15 Hefler L, Mayerhofer K, Leibman B, Obermair A, Reinthaller A, Kainz C and Tempfer C: Tumor anemia and thrombocytosis in patients with vulvar cancer. Tumour Biol *21(5)*: 309-14, 2000.

16 Zeimet AG, Marth C, Muller-Holzner E, Daxenbichler G and Dapunt O: Significance of thrombocythosis in patients with epithelial ovarian cancer. Am J Obstet Gynecol *170(2)*: 549-54, 1994.

17 Obermair A, Handisurya A, Kaider A, Sevelda P, Kölbl H and Gitsch G: The relationship of pre-treatment serum hemoglobin level to the survival of epithelial ovarian carcinoma patients. Cancer *83*: 726-31, 1998.

18 Mencer J, Schejter E, Geva D, Ginath S and Zakut H: Ovarian carcinoma associated thrombocytosis. Correlation with prognostic factors and with survival. Eur J Gynecol Oncol *1*: 82-84, 1998.

19 Serov SF, Scully RE, Sorbin LH. Histological Typing of Ovarian Tumors. International Histological Classification. No.9. Geneva: World Health Organisation *17*: 1973.

20 Blessing JA: Design, analysis and interpretation of chemotherapy trials in gynaecologic cancer. *In*: Deppe G, editor. Chemotherapy of Gynaecologic Cancer. New York: Wiley-Liss, Inc. *63-97*, 1990.

21 Kaplan EL and Meier P: Non-parametric estimation from incomplete observations. J Am Stat Assoc *53*: 457-81, 1985.

22 Moller-Pederssen L and Milman N: Prognostic significance of thrombocythosis in patients with primary lung cancer. Eur respir J *9*: 1826-30, 1996.

23 Corbert G and Perry DJ: Significanc of thrombocythosis. Lancet I: *77*, 1983.

24 Imai T, Koike K, Kubo T, Kikuchi T, Amano Y, Okumuro M and Nakahata T: Interleucin-6 supports human megacariocyte proliferation and differentiation *in vitro*. Blood *78*: 1969-1974, 1991.

25 Gastl G, Plante M, Finstad CL, Wong GY, Federici MG, Bander NH and Rubin SC: High IL-6 levels in ascitic fluid correlate with reactive thrombocythosis in patients with epithelial ovarian cancer. Br J Haematol *83*: 433-441, 1993.

26.Tuszinsky GP, Gasic TB, Rothman VL, Knudsen KA, Gasic GJ: Thrombospondin, A potentiator of tumor cell metastasis. CancerRes *47*: 4130-4133, 1987.

27 Tusczinsky GP, Smith M, Rothmann VL, Capuzzi DM, Joseph RR, Katz J, Besa EC, Treat J and Switalska HI: Thrombospondin levels in patients with malignancy. Thromb Haemost *67*: 607-611, 1992.

28 Tusczinsky GP, Wang TN and Berger D: Adhesive proteins and the hematogenous spread of cancer. Acta Haematol *97*: 29-3, 1997.

29 Spivac JL: Cancer-related anemia: its causes and characteristics. Semin Oncol *21*: 3-8, 1994.

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