Side-effects of paclitaxel therapy in ovarian cancer patents

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Summary

Objective: Since premedication with H1, H2 receptor antagonists and steroids fewer side-effects of paclitaxel (PTXL) chemotherapy have been published. The authors summarize the literature and their own experience.

Materials and methods: 23 patients with stage III ovarian cancer were treated with second-line chemotherapy of PTXL and carboplatin (CRB) with the doses of 175 mg/m^2, 3 h and AUC 5 mg/ml·min, respectively. The side-effects of treatment are evaluated in a prospective non-randomized study.

Results: Rare toxicity in hemoglobin (G0-15%, G1-62%, G2-12% and G4-4%) and leukocyte levels (G0-35%, G1-25%, G2-29%, G3-11% and G4-0%) were detected. There was no definite change found in platelet count (G0-89.5%, G1-10.5%), and moreover in 15.8% of the patients the controlled platelet count was higher than the normal laboratory range. Liver enzymes, serum creatinine and carbamide levels in each case were within the normal range (G0). One patient complained of severe neuropathy (nervus oculomotorius paresis), and another one developed severe ECG abnormalities

Conclusions: When suitable premedication is applied few side-effects of PTXL therapy are reported.

Key words: Paclitaxel; Chemotherapy; Ovarian cancer; Toxicity; Side-effects.

Introduction

Paclitaxel (PTXL) containing chemotherapy has been accepted as standard first line adjuvant treatment of epithelial ovarian cancers since 1996, the year in which the famous GOG 111 protocol was published [1, 2]. PTXL treatment is applied in mono- or polychemotherapy, in the latter form mainly by a combination of cisplatin (P) or carboplatin (CRB) [3, 4]. Because of severe side-effects such as hypersensitivity reaction (HSR) and cardiotoxicity which were detected in the first PTXL treatments, effective premedication has been developed. Due to these premedications the number of toxic events have decreased. PTXL treatments of ovarian cancer patients in Hungary began in 1996 in nine gynecologic centers. The Gynecologic Oncology Department at the National Institute of Oncology in Budapest was the first of the Hungarian Gynecologic Centers that applied PTXL for chemotherapy in epithelial ovarian cancer patients. In the first treatments PTXL was applied as second-line and later in first-line chemotherapy. The present report summarizes our experience on the side-effects of PTXL chemotherapy.

Materials and Methods

Between May 1, 1996 and November 5, 1998 a total of 23 advanced stage III epithelial ovarian cancer patients were given combined PTXL and CRB chemotherapy in 122 courses in the Gynecologic Oncology Department at the National Institute of Oncology, Budapest. PTXL was applied in a 3-hour infusion in a dose of 175 mg/m^2 followed by CRB in a dose of AUC 5 mg/ml·min. The patients were premedicated by methyl-prednisolon (Medrol) given 6 and 12 hours before chemotherapy in doses of 100 mg, respectively. Thirty minutes before treatment 50 mg of ranitine (Zantac), 2 mg of clemastine (Tavegyl) and 50 mg of Di-Adreson F aquosum were applied intravenously. The average age of patients was calculated as 57,7±8 years (range 42-72). Blood tests were controlled on the 14th day after treatment - mostly at the home of the patient. The patients were requested to bring the results with them for the next treatment course. The authors summarized hematologic and non-hematologic side-effects of PTXL therapy in this prospective non-randomized study.

Results

Flushing of the face was detected as the most frequent side-effect (25/122=20%). Other adverse effects such as dyspnoea, pain in the chest or oedema developed in only one patient each, whereas dizziness or pain of the lower extremities was reported by two patients. Three patients suffered from hot flushes. Hypertonia >20% of the normal range was reported in 6/122 courses (5%). Hypotonia of a similar degree was not detected at all. Only one patient suffered serious neuropathy: nervus oculomotorius paresis appeared in the third chemotherapy course. The paresis suspended spontaneously on the following day after treatment and did not repeat in any further courses. One patient developed serious ECG abnormalities (in the beginning elevated, later on depressed ST waves). PTXL infusion was immediately stopped and a few minutes later the ECG normalized. PTXL therapy was resumed and the ST elevations started again shortly after the infusion with the onset of tachycardia. Steroid and propranolol were given and the last 30 mg of PTXL was applied successfully. As the tumor showed rapid progression with an increasing level of CA 125, and the patient refused PTXL therapy fearing cardiac events, we therefore were forced to switch to another chemotherapy protocol.

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Common Toxicity Criteria of the National Cancer Institute, USA was used for evaluating hematological toxicities [5]. There was no extreme toxicity of hemoglobin levels: G0-15%, G1-62%, G2-12% and G4-4%. Leukocytosis was detected as: G0-35%, G1-25%, G2-29% and G3-11%. The authors did not observe any G4 leukocytopenia after PTXL courses. Platelet count did not show a marked decrease: G0 and G1 was 89.5% and 10.5%, respectively; moreover thrombocytosis was reported in 15.8% of patients. Each patient showed normal levels (G0) of liver enzymes, serum creatinine and carbamide.

Discussion

Platinum-based chemotherapy was applied as the standard adjuvant treatment of epithelial ovarian cancers till the 1990's whereas PTXL therapy spread after the beginning of the 1990's. It is based on a different mechanism in the cell cycle and shows higher efficacy than previous drugs. PTXL stops mitosis by inhibiting depolymerization of microtubules.

The first PTXL treatment reports documented serious allergic reactions however with more experience researchers discovered the cause of these reactions. Cremofor (polyoxyethilated castor oil) serves as a vehicle for PTXL and produces this hypersensitive reaction (HSR) [6]. Premedication with H1, H2 receptor antagonists and steroids was developed to prevent allergic reactions and thus HSR frequency has markedly decreased. The first reports documented serious dyspnoea, bronchospasms, chest or back pain in some cases. The latter signs decreased due to the aforementioned premedication, however one can read reports of flushing or hypotension in today's literature as well. Flushing was demonstrated in 42% by Eisenhauer and in 74% by Weiss [7, 8]. The present paper shows rarer (25%) flushing as can be found in the literature. The alteration disappeared on the second day after PTXL treatment.

In PTXL chemotherapies side-effects other than HSR can be detected such as hematological and non-hematological toxicities. G3-4 leukocytopenia is the most characteristic hematological discrepancy. Decline in platelet count is not so frequently reported as in monochemotherapy with CRB; moreover a thrombocyte sparing effect is observed as well [15]. An explanation for this action is yet unidentified. A hemopoietic hormone is assumed to deliberate in bone marrow causing protection but an obscure mechanism between the CRB and Cremofor may be hypothetized as well. Similar to observations in breast cancer patients several authors have reported on G3-4 anemia of 7-11% due to PTXL chemotherapy in ovarian cancer patients (Table 1). Principally in dose escalating studies this anemia also required transfusion [16]. Summarized reports in Table I show an average G3-4 granulocytopenia of 29-68% and G3-4 thrombocytopenia of 2-5%. Noteworthy is the G3-4 thrombocytopenia of an average of 2-5% detected in combination therapy with PTXL/CRB, a rate which a small proportion of values were reported in mono CRB therapies only [4, 17, 18]. We found a similar rate of G3-4 anemia (11%) and a little bit smaller rate of G3-4 leukocytopenia (11%) as can be found in the literature.

Nausea and vomiting are frequently noted non-hematological side-effects of chemotherapies. In PTXL treatments they are very rare and mild. A mild emetogen effect of mono PTXL therapies was reported by Eisenhauer (8%) and Bolis (2%) [7, 19]. The emetic

Table 1. — *G3-4 toxicities of PTXL therapy in ovarian cancer patients in the literature (%).*

			Hematological			Non-hematological				
Author, year	Th	N	Anm	Gran	Thr	HSR	Card	Arthral/Myalgia	Neur	Alop
Tori, 2000	PTXL	116	nd	7	nd	nd	nd	nd	19	nd
Muggia, 2000	PTXL	213	6	96	3	nd	2	nd	2	48
Eisenhauer, 1994	PTXL	391	nd	46	2	1	0	5	1	87
Galardo-R, 1999	PTXL	31	nd	39	nd	nd	nd	42	nd	68
Bolis, 1999	PTXL	41	12	24	2	nd	0	0	0	100
	Average		9	42	2	1	2	24	7	76
Coeffic, 1997	PTXL/P	23	5	91	13	0	0	0	17	96
McGuire, 1996	PTXL/P	184	9	92	3	4	nd	nd	4	54
DuBois, 1999	PTXL/P	384	19	8	1	nd	nd	nd	19	nd
Piccart, 1997	PTXL/P	188	nd	56	nd	nd	nd	nd	18	nd
Piccart, 2000	PTXL/P	339	nd	64	2	4	nd	9	24	51
Muggia, 2000	PTXL/P	201	9	94	3	nd	2	nd	5	49
	Average		11	68	4	4	2	9	15	63
Markman, 1997	PTXL/CRB	92	nd	21	3	13	nd	nd	2	100
DuBois, 1999	PTXL/CRB	392	7	14	4	nd	nd	nd	8	nd
Ciruelos, 2000	PTXL/CRB	66	nd	43	7	nd	nd	nd	nd	nd
	Average		7	29	5	13	nd	nd	5	100
Present paper	PTXL/CRB	23	11	11	nd	0.8	0	0.8	0.8	nd

Comment: Th-therapy; N-number of patients; Anm-anemia; Gran-granulocytopenia; Thr-thrombocytopenia; HSR-hypersensitive reaction; Card-cardial; Arthral-arthralgia; Neur-neuropathy; Alop-alopecia; PTXL; P; CRB-as in the text; nd-no data.

effect intensifies a little in combined chemotherapies. An increased emetic effect was observed in combinations of PTXL and cisplatin compared to single PTXL therapies in the studies of Coeffic (13%), duBois (19%) and Piccart (26%) [4, 20, 21]. With a combination of PTXL and CRB the emetic effect is lowered, but duBois reported it as high as 7% [4]. The present paper reports a rare and mild emetic effect (4%).

Severe cardiac adverse effects in early PTXL treatments are rare (an average of 2%) because of adequate premedications (Table 1). Among the 23 patients we found only one who developed serious ECG changes.

One of the most common side-effects of PTXL treatment is myalgia/arthralgia on mainly the lower extremities. They are suggested to be preventable or alleviated by any of the non-steroid drugs. G3-4 myalgia/arthralgia was detected in an average of 9-24% (Table 1). We documented only one patient of the 23 with pain of the extremities in the PTXL course. Similar complaints in the period of 1-5 days following treatment should be taken into account however precise processing has not yet been accomplished.

Sensory or motor neuropathy was observed after PTXL treatments in some cases, generally as a temporary event. Sensory neuropathy is seen mainly in glove/sock- form of paresthesia. G3-4 neuropathy was recorded in an average of 5-15%. Noteworthy is the G3-4 neuropathy of 5-7% in mono PTXL or in combination therapy of PTXL/CRB compared to the almost double rate (15%) of the combination with cisplatin. The high frequency of neuropathy is produced by cisplatin. Possible encephalopathia which developed on days 3-7 after PTXL treatment and finished after two consecutive days has also been published [22]. However the probability of encephalopathia in this manner is very low because transmission of PTXL through the cerebrospinal barrier could not be confirmed till now. A more conceivable cause for the symptoms of the central neural system is permeation through the barrier by Cremofor, which has already been proven in experiments done on rats [23].

Essentially difficult for women to see is the loss of hair in the course of chemotherapy. It occurs in the majority of PTXL therapies, and reaches a full alopecia in 63-100% of patients (Table 1). A small consolation is that hair will regrow within months after the last PTXL course.

Conclusion

Summarizing, the experience the authors confirm that patients usually tolerate PTXL treatment well after adequate premedication. Considered to be the most severe side-effect HSRs are mostly observed soon after the beginning of the first course. Therefore if HSR does not develop a safe second treatment course can be considered. Lacking severe side-effects oncological specialists can also deliver PTXL treatment easily and safely in outpatient clinics.

References

[1] McGuire W. P., Hoskins W. J., Brady M. F., Kucera P. R., Partridge E. E., Look K. Y., Clarke-Pearson D. L., Davidson M.: "Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer". *N. Engl. J. Med.*, 1996, *334*, 1.

[2] Berek J. S., Bertelsen K., du Bois A., Brady M. F., Carmichael J., Eisenhauer E. A., Gore M. *et al.*: "Advanced epithelial ovarian cancer: 1998 consensus statements". *Ann. Oncol.*, 1999, *10* (Suppl. 1), 87.

[3] Ozols R. F., Bundy B. N., Fowler J., Clarke-Pearson D., Mannel R., Hartenbach E. M., Baergen R.: "Randomized phase III study of cisplatin (CIS)/paclitaxel (PAC) versus carboplatin (CARBO)/PAC in optimal stage III epithelial ovarian cancer (OC): A Gynecologic Oncology Group Trial (GOG 158)". Proc. Am. Soc. Clin. Onc., 1999, Abstract No 1373.

[4] du Bois A., Lueck H. J., Meier W., Moebus V., Costa S. D., Bauknecht T. *et al.*: "Cisplatin/Paclitaxel vs Carboplatin/Paclitaxel in Ovarian Cancer: Update of an Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Study Group Trial". Proc. Am. Soc. Clin. Onc., 1999, Abstract No 1374.

[5] Cvitkovic E., Droz J. P., Armand J. P., Khoury S. (Eds): "Handbook of Chemotherapy in Clinical Oncology". Second edition. Scientific Communication International Ltd. Channel Islands. 1993, 748.

[6] Olson J. K., Sood A. K., Sorosky J. I., Anderson B., Buller R. E.: "Taxol hypersensitivity: rapid retreatment is safe and cost effective". *Gynecol. Oncol.*, 1998, *68*, 25.

[7] Eisenhauer E. A., ten Bokkel Huinink W. W., Swenerton K. D., Gianni L., Myles J., van der Burg M. E. L. *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.*, 1994, *12*, 2654.

[8] Weiss R. B., Donehower R. C., Wiernik P. H., Ohnuma T., Gralla R. J., Trump D. L. *et al.*: "Hypersensitivity reactions from Taxol". *J. Clin. Oncol.*, 1990, *8*, 1263.

[9] Rowinsky E. K., Donehower R. C.: "Paclitaxel (Taxol)". *N. Engl. J. Med.*, 1995, *332*, 1004.

[10] del Priore G., Smith P. S., Warshal D. P., Dubenshter B., Angel C.: "Paclitaxel-associated hypersensitivity reaction despite high-dose steroids and prolonged infusions". *Gynecol. Oncol.*, 1995, *56*, 316.

[11] Weiss R. B.: "Hypersensitivity reactions". *Semin. Oncol.*, 1992, *19*, 458.

[12] Peereboom D. M., Donehower R. C., Eisenhauer E. A., McGuire W. P., Onetto N., Hubbard J. L. *et al.*: "Successful re-treatment with Taxol after major hypersensitivity reactions". *J. Clin. Oncol.*, 1993, *11*, 885.

[13] Ibrahim N. K., Ellerhorst J. A., Theriault R. L., Rivera E., Esmaeli B., Legha S. S. *et al.*: "Phase I study of cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel (Abi-007) in solid tumors". Proc. Am. Soc. Clin. Onc., 2000, Abstract No 609F.

[14] von Hoff D. D.: "The taxoids: same roots, different drugs". *Semin. Oncol.*, 1997, *24* (Suppl. 13), 3.

[15] van Warmerdam L. J. C., Huizing M. T., Giaccone G., Postmus P. E., ten Boekkel Huinink W. W., van Zandwijk N. *et al.*: "Clinical pharmacology of carboplatin administered in combination with paclitaxel". *Semin. Oncol.*, 1997, *24* (Suppl. 2), 97.

[16] Huizing M. T., van Warmerdam L. J. C., Rosing H., Schaefers M. C. W., Lai A., Helmerhorst T. J. M. *et al.*: "Phase I and pharmacologic study of the combination paclitaxel and carboplatin as first-line chemotherapy in stage III and IV ovarian cancer". *J. Clin. Oncol.*, 1997, *15*, 1953.

[17] Markman M., Kennedy A., Webster K., Kulp B., Peterson G., Belinson J.: "Carboplatin plus paclitaxel in the treatment of gynecologic malignancies: the Cleveland Clinic experience". *Semin. Oncol.*, 1997, *24* (Suppl. 15), 15.

[18] Ciruelos E., DeSande L., Castellano D., Oramas J., Domine M., Dorta J. *et al.*: "Phase II study of paclitaxel plus carboplatin (AUC 7,5) combination as first line chemotherapy in patients with advanced epithelial ovarian cancer (AOC). Feasibility and efficacy". Proc. Am. Soc. Clin. Onc., 2000, Abstract No 1586.

[19] Bolis G., Parazzini F., Scarfone G., Villa A., Amoroso M., Rabaiotti E. *et al.*: "Paclitaxel vs epidoxorubicin plus paclitaxel as second-line therapy for platinum-refractory and -resistant ovarian cancer". *Gynecol. Oncol.*, 1999, *72*, 60.

[20] Coeffic D., Benhammouda A., Antoine E.-C., Rixe O., Paraiso D., Auclerc G. *et al.*: "Preliminary results of a phase I/II study of paclitaxel, cisplatin, and cyclophosphamide in advanced ovarian carcinoma". *Semin. Oncol.*, 1997, *24* (Suppl. 2), 38.
[21] Piccart M. J., Bertelsen K., James K., Cassidy J., Mangioni C., Stuart G. *et al.*: "Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results". *J. Natl. Cancer Inst.*, 2000, *92*, 699.
[22] Perry J. R., Warner E.: "Transient encephalopathy after paclitaxel (Taxol) infusion". *Neurology*, 1996, *46*, 1596.
[23] Waltz R., Bianchin M. M., Kliemann F.: "Transient encephalopathy after Taxol infusion". *Neurology*, 1997, *49*, 1188.

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