

- (4) Lazzarino M, Corso A, Kegazzi MB, Iacona I, Bernasconi C. Modulation of all-trans retinoic acid pharmacokinetics in acute promyelocytic leukaemia by prolonged interferon- $\alpha$  therapy. *Br J Haematol* 1995;90:928-30.
- (5) Koller E, Krieger O, Kasparu H, Lutz D. Restoration of all-trans retinoic acid sensitivity by interferon in acute promyelocytic leukaemia [letter]. *Lancet* 1991;338:1154-5.
- (6) Bugge CJ, Rodriguez LC, Vane FM. Determination of isotretinoin or etretinate and their major metabolites in human blood by reversed phase high performance liquid chromatography. *J Pharm Biomed Anal* 1985;3:269-77.
- (7) Smith DC, Jacob HE, Lotze MT, Branch RA, Adedoyin A, Stiff D, et al. A phase I trial of interferon- $\alpha$ 2a (IFN- $\alpha$ ) and all-trans retinoic acid (ATRA): a pharmacokinetic assessment. *Proc ASCO* 1994;13:134.
- (8) Kalvakolanu DV, Sen GC. Differentiation-dependent activation of interferon-stimulated gene factors and transcription factor NF-kappa B in mouse embryonal carcinoma cells. *Proc Natl Acad Sci U S A* 1993;90:3167-71.
- (9) Kalvakolanu DV, Kolla V, Linder DJ, Weihau X, Freund R, Borden EC. Retinoic acid enhances IFN-regulated genes via the modulation of STAT1 protein in a breast tumor cell line. *J Interferon Cytokine Res* 1995;15 (suppl):S217.
- (10) Marth C, Doxenbichler G, Widschwendter M. Combination of retinoic acid and interferons: mechanism of synergistic interaction. *J Interferon Cytokine Res* 1995;15 (suppl):S216.
- (11) Lippman SM, Kavanagh JJ, Paredes-Espinoza M, Delgadillo-Madrueno F, Paredes-Casillas P, Hong WK, et al. 13-cis-retinoic acid plus interferon  $\alpha$ -2a: highly active systemic therapy for squamous cell carcinoma of the cervix. *J Natl Cancer Inst* 1992;84:241-5.
- (12) Athanasiadis I, Kies MS, Miller M, Ganzenko N, Joob A, Marymont M, et al. Phase II study of the all-trans-retinoic acid and  $\alpha$ -interferon in patients with advanced non-small cell lung cancer. *Clin Cancer Res* 1995;1:973-9.

## Notes

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## Myoclonus

Prednimustine is frequently used in the treatment of chronic lymphocytic leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, and ovarian and breast cancers. However, care should be taken to recognize early neurologic side effects that may have disabling consequences.

We report here a rare neurologic side effect associated with administration of prednimustine. A 79-year-old woman presented with weight loss, night sweats, asthenia, bilateral inguinal lymphadenopathy, and splenomegaly. She had had a 19-year history of low-grade follicular lymphoma, which had been treated 8 years previously by various chemotherapy regimens, including prednimustine.

A biopsy of an inguinal adenopathy disclosed Hodgkin's disease, histologically different from the previously known lymphoma. She was treated with an oral combination of lomustine at a dose of 80 mg/m<sup>2</sup> on day 1 and etoposide at a dose of 100 mg/m<sup>2</sup> and prednimustine at a dose of 60 mg/m<sup>2</sup>, both given on days 1 to 5 (corresponding to a total dose of chlorambucil of 6 mg/kg), and she was premedicated with allopurinol and ondansetron. On day 3, she noticed abnormal jerks of her hands, which increased during the subsequent days and finally involved the four limbs. On day 6, unable to stand, she fell and broke her right arm. Neurologic assessment at the emergency room disclosed severe myoclonia of the four limbs. Her mental state and conscious state were normal, and laboratory tests showed no electrolyte abnormalities. Clonazepam was introduced, and the myoclonia gradually decreased and disappeared on day 8. A medical history revealed that the patient had experienced the same hand jerks 8 years before while taking prednimustine. We replaced prednimustine with prednisone in subsequent treatment cycles, and the myoclonus did not reappear.

Prednimustine is an ester of prednisolone and chlorambucil. Elimination of chlorambucil and its metabolite phenyl-

toxicity was dose limiting in a phase I trial of high-dose chlorambucil (1), and chlorambucil-related myoclonus has been described (2) in a 71-year-old woman treated for a lymphocytic lymphoma with a 5-day regimen of chlorambucil and dexamethasone. In this patient, the jerks appeared on day 3, culminated on day 7, and disappeared gradually after another week.

Three cases of prednimustine-induced myoclonus have also been reported (3) in women previously treated with cisplatin for an ovarian cancer. The myoclonia developed on day 4 during a 5-day regimen of prednimustine (120 mg/m<sup>2</sup> per day) and disappeared after cessation of the chemotherapy and administration of diazepam. Hypomagnesemia found in these three patients was considered a possible contributing factor.

The mechanism of chlorambucil-induced myoclonus is not known. Myoclonus arises from the central nervous system in a complex interaction between brain stem, cortex, and cerebellum. It is found in several neurologic diseases, including mitochondrial myopathies with central nervous system dysfunction, in which deficiencies of components of the respiratory chain are observed (4). Similarly, the neurotoxicity of an alkylating agent (5) is due to the interference with oxidative phosphorylation in the mitochondria by their metabolites.

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## References

- (1) Blumenreich MS, Woodcock TM, Sherrill EJ, Richman SP, Gentile PS, Epemian BE, et al. A phase I trial of chlorambucil administered in short pulses in patients with advanced malignancies. *Cancer Invest* 1988;6:371-5.
- (2) LaDelfa I, Bayer N, Myers R, Hoffstein V. Chlorambucil-induced myoclonic seizures in an adult [letter]. *J Clin Oncol* 1985;3:1691-2.
- (3) Martin M, Diaz-Rubio E, Casado A, Valverde JJ, Garcia Urra D, Lopez-Martin JA, et al. Prednimustine-induced myoclonus—a report of three cases. *Acta Oncol* 1994;33:81-2.
- (4) Hopkins LC, Rosing HS. Myoclonus and mitochondrial myopathy. *Adv Neurol* 1986;43:105-17.
- (5) Kupfer A, Aeschlimann C, Wermuth B, Cerny

## Notes

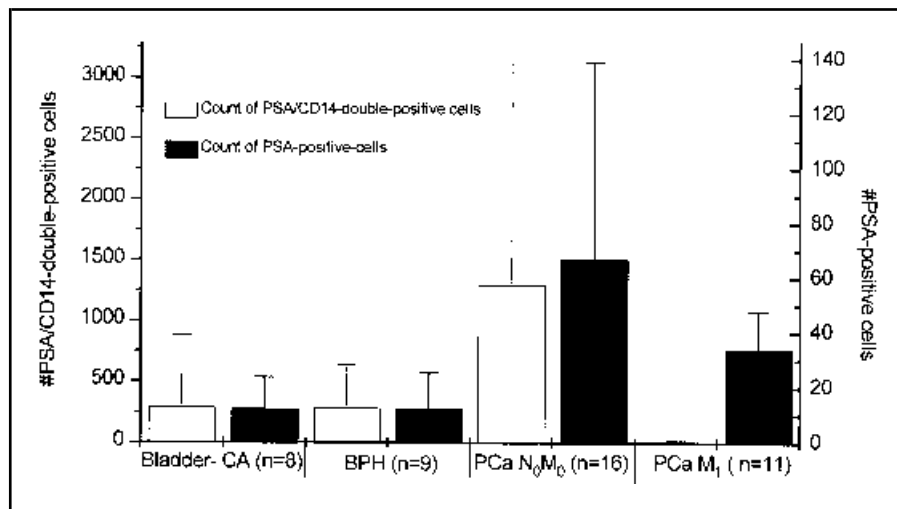
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## Circulating Prostate-Specific Antigen/CD14-Double-Positive Cells: a Biomarker Indicating Low Risk for Hematogenous Metastasis of Prostate Cancer

The presence of cells in the blood stream of prostate cancer patients that stain positively for both prostate-specific antigen (PSA) and for the monocyte marker CD14 seems to indicate a low risk of metastasis formation. This cellular biomarker might be helpful in the assessment of the prognosis for prostate cancer patients with organ-restricted disease. It could be used to define a subgroup of patients with a low risk of life-threatening bone metastasis, although these patients show evidence of circulating prostate cancer cells by flow cytometry (1) or PSA-PCR2 (2).

We describe here 16 patients with NOMO stage prostate cancer and 11 patients with prostate cancer with bone metastasis (stage M1) as well as two control groups (eight patients with bladder cancer and nine patients with benign prostatic hyperplasia). So that we could determine the number of PSA/CD14-double-stained cells in the peripheral blood of the patients by flow cytometry, 10 mL of EDTA-treated blood was drawn from the patients by venipuncture, and the erythrocytes were depleted by density-gradient centrifugation. The cells were stained simultaneously with anti-PSA-fluorescein isothiocyanate (FITC) (Coulter-Immunotech, Hamburg, Federal Republic of Germany) and an antibody labeled with CD14-phycoerythrin (PE) (Dianova, Hamburg). Controls for nonspe-



**Fig. 1.** In patients with NOMO or M1 stage prostate cancer (PCa), prostate-specific antigen (PSA)-positive cells (right Y axis) were increased compared with those in the control patients. Only in patients with stage M1 disease were the PSA/CD14-double-positively stained cells (left Y axis) significantly decreased compared with those in the control patients ( $P < .05$ , paired Wilcoxon test). A statistically significant increase in PSA/CD14-double-positive cells was measured in patients with M1 stage prostate cancer compared with patients with NOMO prostate cancer ( $P < .01$ ). BPH = benign prostatic hyperplasia. Error bars represent standard deviations.

cific binding of the antibody, negative controls with blood from healthy women, and positive controls with LNCaP cells were performed. The PSA-positive and PSA/CD14-double-positive cells were counted by a count gate discrimination procedure adjusted to the exclusion of nonspecific, stained cells in the FL1 (FITC)/FL2 (PE) plot of the negative control; two million peripheral white blood cells were analyzed for each sample after erythrocyte depletion.

The data in Fig. 1 suggest that the exclusive detection of molecular signals, either by immunologic means or by polymerase chain reaction, representing PSA-positive cells in the circulation, is not sufficient to estimate the risk of metastasis in prostate cancer.

We are entering a new period of research on circulating cancer cells. In 1991, Smith et al. (3) introduced the polymerase chain reaction for tissue-specific cell detection. Modern tools in immunology and in molecular biology now provide a means to unveil the meaning of circulating cancer cells (4).

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## References

- (1) Hamdy FC, Lawry J, Anderson JB, Parsons MA, Rees RC, Williams JL. Circulating prostate specific antigen-positive cells correlate with metastatic prostate cancer. *Br J Urol* 1992;69:392-6.
- (2) Olsson CA, de Vries GM, Raffo AJ, Benson MC, O'Toole K, Cao Y, et al. Preoperative reverse transcriptase polymerase chain reaction for prostate specific antigen predicts treatment failure following radical prostatectomy. *J Urol* 1996;155:1557-62.
- (3) Smith B, Selby P, Southgate J, Pittman K, Bradley C, Blair GE. Detection of melanoma cells in peripheral blood by means of reverse transcriptase and polymerase chain reaction. *Lancet* 1991;338:1227-9.
- (4) Brandt B, Junker R, Heidl S, Griwatz C, Semjonow A, Brinkmann O, et al. Isolation of prostate-derived single cells and cell clusters from human peripheral blood. *Cancer Res.* In press.

## Notes

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