SHORT COMMUNICATION

Effect of interleukin 2 on urinary excretion of degradation products of prostacyclin and thromboxane A2 in patients with ovarian cancer

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Summary  We studied the effect of intraperitoneal recombinant interleukin 2 (rIL-2) on the production of prostacyclin (PGI2) and thromboxane A2 (TXA2) in six patients with metastatic ovarian malignancy. Time-span urine samples collected before and after 17 intraperitoneal instillations of IL-2 (6 × 10^6 IU m^-2) were assessed for 2,3-dinor-6-keto-prostaglandin F4 (dinor-6-keto; a metabolite reflecting the in vivo product of PGI2) and 2,3-dinor-thromboxane B2 (dinor-TxB2; a metabolite reflecting the production of TXA2). Analysis was by high-pressure liquid chromatography, followed by radioimmunoassay. Recombinant IL-2 administration was accompanied by a significant rise (85%; P < 0.02) in the output of dinor-6-keto within the first 2 h, and this elevation persisted for up to 6 h. Moreover, output of dinor-TxB2 also rose; this rise (30%) was significant (P < 0.02) 6 h after the instillation. These effects may, in some yet unknown manner, prove significant in the anti-cancer action of rIL-2.

Keywords: prostacyclin; thromboxane A2; interleukin 2; ovarian cancer

One way the human body resists cancer cells is through activated T lymphocytes which secrete a large number of cytokines (Borden and Sondel, 1990). One of these mediators, interleukin 2 (IL-2) (Boller et al., 1989; Borden and Sondel, 1990), can nowadays be produced in large quantities through recombinant DNA technology. Synthetic recombinant IL-2 (rIL-2) is considered to show promise as an adjuvant therapy for patients with primary or recurrent cancer (Boller et al., 1989; Boyer et al., 1989; Thomas and Sikora, 1991; Budd et al., 1992). rIL-2, when administered intravenously however (Oliver et al., 1989; Budd et al., 1992), shows a high rate of severe systemic side-effects (such as pulmonary oedema), a fact which limits the use of this approach. By giving rIL-2 intraperitoneally (i.p.), we can reduce systemic side-effects and perhaps achieve a better therapeutic response in patients with metastatic gynaecological malignancies; results are, thus far, controversial (Boller et al., 1989; Bertoglio et al., 1989; Thomas and Sikora, 1991; Lissoni et al., 1992).

The mechanism(s) by which rIL-2 operates in patients with ovarian cancer are unknown, but in view of the high production in ovarian cancer of vasoactive prostanoids such as prostacyclin (PGI2) and thromboxane A2 (TXA2) (Aitokallio-Tallberg et al., 1988), an effect of rIL-2 on PGI2 and TXA2 could be possible. We therefore studied the effect of i.p. administration of rIL-2 on production of PGI2 and TXA2 in patients with metastatic ovarian cancer.

Patients and methods

The study involved six patients with residual epithelial ovarian cancer (0.5–2 cm in pelvic serosa) documented histologically at the second-look operation (five serous adenocarcinomas stage III, and one mesonephroid carcinoma stage II according to the primary staging). All had undergone surgery for their primary carcinoma, plus treatment with 6–8 monthly cycles of chemotherapy (cisplatin 60 mg m^-2 and cyclophosphamide 1000 mg m^-2). An indwelling catheter (Port-A-Cath) for delivery of IL-2 was inserted during the second-look operation, and 3–5 weeks later the first bolus (6 × 10^5 IU m^-2) of rIL-2 (Euro Cetus, Amsterdam, The Netherlands) was given in 250 ml physiological Ringer-lactate through the catheter. The rIL-2 courses were to be repeated 16 times at one week intervals, but our study focused on the first instillation with the exception of one patient who was serially followed (see below). This study was approved by the local ethics committee.

All six patients collected urine samples (see below) at the time of the first rIL-2 injection, and one patient provided urine samples during an additional 11 courses of rIL-2. The urine samples were collected as follows: the first collection during the 3 h before the treatment, the second during the 2 h from the start of the instillation of the rIL-2 and the third from hours 2–6 after the instillation, and the fourth 3 h sample 1 week after the treatment.

Urines were kept frozen at −25°C until assayed for 2,3-dinor-6-keto-PGF2α (dinor-6-keto) and 2,3-dinor-TxB2 (dinor-TxB2) by use of high-pressure liquid chromatography (HPLC), followed by radioimmunoassay; the details of the methods have been described elsewhere (Tulppala et al., 1991).

Prostanoid excretions, given as medians and ranges, are in pg min^-1.

The significance of the difference was analysed by Student's t-test for paired data.

Results

No significant changes in platelet or white-cell count, haemoglobin, liver enzymes or any other laboratory tests appeared following the rIL-2 injection (data not shown). In peritoneal lavage 1 week after the first injection, no malignant cells could be found in any patient. One patient reported transient arthalgia and another one slight itching the day after the injection; no other side-effects were seen. The baseline output of dinor-6-keto ranged from 22 to 141 pg min^-1 (median 47 pg min^-1). It rose by 85% (P < 0.02) within the first 2 h of the injection of rIL-2 (median 87.0 pg min^-1, range 33–298), and remained elevated for the next 4 h (median 87 pg min^-1, range 15–209). For the one patient studied during an additional 11 courses of rIL-2, dinor-6-keto output returned to the baseline output 1 week after each injection (median 47.0 pg min^-1, range 28–110) (Figure 1).

Dinor-TxB2 output rose (25%) from a median of 143 pg min^-1 (range 51–250) to 179 pg min^-1 (range 100–355) in 2 h after the injection. The rise continued for the next 4 h (median of 186 pg min^-1, range 64–456, P < 0.02). The dinor-TxB2 excretion had returned to the baseline level (median 141.0, range 52–197) within 1 week after treatment (Figure 2).
The ratio of dinor-6-keto output to dinor-TxB₂ output did not change significantly during the treatment (P > 0.07).

Discussion

The intraperitoneal instillation of rIL-2 for patients with metastatic gynaecological cancer has limited cancer growth according to many studies (Rosenberg et al., 1987; Budd et al., 1992; Lissomi et al., 1992) although not in all (Beller et al., 1989; Steis et al., 1990). We explored whether such a treatment affects the production of PGI₂ and TXA₂, which are excessively produced by ovarian cancer (Aitokallio-Tallberg et al., 1988) and which are certainly involved in tumour and immunological processes (Xiao and Levine, 1986; Gibbons et al., 1987; Janninger and Racis, 1987; Ruiz et al., 1988, 1992; Moore et al., 1989).

It is clear from our data that i.p. administration of rIL-2 led to a significant increase in PGI₂ synthesis, as assessed by urinary 2,3-dinor-6-keto-PGF₆ output, which is regarded as the most representative method to assess PGI₂ production in vivo (FitzGerald et al., 1983, 1987; Ylikorkala et al., 1986; Oates et al., 1988). Our findings are in general agreement with data on the increased levels of 6-keto-PGF₁α in plasma in sheep which were inferred intravenously with rIL-2 (O’Neill et al., 1991), although the value of plasma 6-keto-PGF₁α measurement as an index of PGI₂ can be questioned. Our data do not allow us to deduce the origin of the PGI₂ increase, but most probably it came from the endothelial cells, with which rIL-2 may interfere, or from stimulated T lymphocytes (Damle et al., 1987). Of course we must also consider the cancer tissue as a possible source, especially as it is known to produce PGI₂ (Aitokallio-Tallberg et al., 1988), but in view of the small size of the residual tumour and the huge rise in PGI₂, this explanation is not likely. The significance of rIL-2-induced stimulation in PGI₂ synthesis in tumour behaviour or prognosis remains open in our study with its rather small number of patients, but in theory, such stimulation could prove beneficial (Honn et al., 1981, 1983).

rIL-2 is known to stimulate TXA₂ production in different animal models (Ferro et al., 1989; Klausner et al., 1989; O’Neill et al., 1991; Rabinović et al., 1992; Ruiz et al., 1992). We have provided the first human data indicating that i.p. administration of rIL-2 stimulates TXA₂ synthesis, as seen from a significant rise in the urinary output of 2,3-dinor-TXB₂, a reliable index for systemic TXA₂ synthesis (FitzGerald et al., 1983, 1987; Ylikorkala et al., 1986; Oates et al., 1988). As in the case of PGI₂, we do not know the source of TXA₂ stimulation in these patients, but immune cells (Schoultze et al., 1984; Remick et al., 1987), cancer tissue (Aitokallio-Tallberg et al., 1988) or stimulated platelets are probable candidates. The significance of rIL-2-induced TXA₂ stimulation remains open in our study.

In summary, the i.p. administration of rIL-2 leads to profound rises in PGI₂ and TXA₂ synthesis in patients with metastatic ovarian cancer, rises which may be of significance in the therapeutic response to rIL-2 administration.

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