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Acute Morphine Intoxication During High-dose Recombinant Interleukin-2 Treatment for Metastatic Renal Cell Cancer

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Tumour immunotherapy received a new stimulus after recombinant interleukin-2 (rIL-2) was introduced into clinical practice. High-dose IL-2 therapy is nevertheless encumbered by severe side-effects, mainly involving the cardiovascular, renal, pulmonary and central nervous system (CNS) [1]. The authors describe four cases of acute encephalopathy which occurred during rIL-2 treatment and morphine administration in a medical oncology unit.

Between July 1989 and October 1993, we treated 50 patients with high-dose rIL-2 according to a multicentre study [2]. All the patients were affected by metastatic renal cell cancer. IL-2 was administrated at 18×10^6 U/m^2 continuous intravenous (i.v.) infusion for two cycles as induction (5 days, 2 days rest, 5 days again, repeated twice after 3 weeks), followed by four cycles of 5 days in case of response or no change. The patients were eligible if they had organ function within 1.5 of normal values, performance status 0–2 according to WHO grading, no brain metastases and measurable parameters of disease. Toxicity was evaluated according to WHO guidelines. Of 256 cycles, 30 episodes of neurological toxicity, regarding the state of consciousness were observed. 10 patients had 24 episodes of transient lethargy or somnolence (G1–G2), but 5 patients showed six episodes of severe compromise to their state of consciousness (G3–G4). 4 patients needed opioid administration for pain treatment during therapy with rIL-2, and presented complications related to the toxic effects of morphine. When we started rIL-2 treatment, the 4 patients had already been under therapy with slow-release oral morphine for several weeks: the first developed toxicity during the second rIL-2 cycle of 5 days, the second during the first cycle. Both had renal failure which was treated with dopamine 5 γ/kg/min and plasma expanders. Toxicity was characterised by clear signs of morphine intoxication (miosis, respiratory depression, coma) and administration of naloxone was, therefore, extended for 24 h in the first case and 12 h in the second. Both patients recovered completely within 48 h. Patient 1 concluded the cycle after 3 weeks at half the previous rIL-2 dosage without needing further morphine administration. Patient 2 continued the cycle after 6 days: 2.5 mg of morphine in saline solution was administered four times a day with an epidural thoracic catheter as pain therapy. Patients 3 and 4 showed less drastic signs of renal failure. Neurological intoxication was classified as G3 and naloxone was not needed. For patient 3, the rIL-2 cycle and morphine therapy were suspended but his condition deteriorated due to respiratory distress and he died of septic shock 2 weeks later. The autopsy revealed polimicrobial pneumonia on both lungs. Patient 4 concluded the rIL-2 cycle without interrupting morphine therapy. She recovered within 48 h but was no longer treated with rIL-2 due to progression of disease (Table 1). Neither cholestasis nor increased enzyme values from hepatic toxicity were found in any of the above cases. The levels of morphine metabolites were not available.

50 patients treated with high-dosage rIL-2 received a total of 256 cycles and of these, only 5 showed neurological complications classified as G3–G4 according to WHO grading. In our opinion, there are two explanations for the events reported: pathological accumulation of morphine metabolites (mainly M-6 glucuronide) due to acute renal failure (ARF) and toxic synergy of the two treatments. During rIL-2 treatment, ARF has a characteristic evolution. It is expressed as a prerenal insufficiency due to the systemic vascular leak syndrome. Azotaemia and oliguria are observed together with low sodium excretion, intense plasmatic renin activity and hypotension [3]. The morphine 6-glucuronide, normally ultra filtered, has a reduced or absent clearance and its plasmatic concentration can therefore rise. This could explain morphine toxicity in two of our four cases. Dosages of morphine and serum creatinine values were undoubtedly lower than those reported by some authors [4] but comparable with other observations [5, 6]. Recombinant IL-2 toxicity on CNS is expressed as agitation, disorientation, deep drowsiness and coma [1]. Mental state alterations were also observed in patients treated with rIL-2 doses lower than those used in our protocol [7]. Severe alterations of the blood–brain barrier (BBB) were found after i.v. infusion of a single dose of rIL-2 [8]. Recombinant IL-2 may facilitate the passage of neurotoxic substances through the BBB [9], although a clear relationship between impaired BBB permeability, brain water content and mental state alterations was not found [10]. Saris and colleagues considered direct cytotoxic action of rIL-2 on cerebral parenchyma as a possible explanation [10]. Renal failure seems to have an important role in at least two of the cases reported, even if less so in the last two. However, in the presence of renal failure, the possibility of a synergistic CNS toxicity from rIL-2 and opioids, either through an increased permeability of the BBB to morphine metabolites, or through direct rIL-2 CNS effects, cannot be discarded. Further data on rIL-2 neurotoxicity is needed in order to evaluate the role of ARF and morphine metabolite storage. Nevertheless, the use of morphine during rIL-2 therapy is strongly correlated to a greater occurrence of neurological complications. We conclude that the most preferable and safest pain control modalities are the epidural or intrathecal route for the administration of local anaesthetic and/or low dosage opioids.

In patients with pain symptoms, we recommend that rIL-2 treatment be started only after establishing effective and safe pain control methods.

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Table 1. Evolution of patients co-treated with morphine

	Patient 1 (male, 53 years old)					Patient 2 (male, 53 years old)					Patient 3 (male, 56 years old)					Patient 4 (female, 55 years old)				
Day of IL-2 Course	1	2	3	4	5*	1	2	3*	4	5	1	2*	3	4	5	1	2	3	4	5
Serum creatinine level (mg/d) (normal values 0.6–1.5)	0.8	1.0	1.3	3.1	4.9	1.5	1.3	3.2	4.4	3.9	1.2	1.3	1.6	1.5	1.8	1.0	1.2	1.9	1.6	1.4
Urea level (normal values 20–40)	25	—	—	95	—	54	—	80	86	106	52	—	—	60	59	29	—	47	—	53
Urine volume (ml)	1400	900	800	—	200	1000	900	250	1600	1200	1900	2200	1650	2100	2600	800	—	650	520	600
Blood pressure (mmHg)	130/70	130/60	100/65	80/50	80/50	110/70	110/70	85/60	100/60	110/80	140/80	105/70	95/60	115/65	100/60	120/60	110/65	115/70	120/80	130/80
Temperature (°C)	37.2	38.7	41.2	41	41	36	37	39.8	38	37	36	40	40	39	39	36	37	37	38.5	38
S.R. morphine B.I.D. (mg)	10	10	10	10	Stop	30	40	Stop	—	—	20	20	20	Stop	—	70	70	80	80	70
Weight (kg)	64.7	—	—	—	67.8	94	94.8	98.2	—	97.1	71	70.5	72.7	74	75	54	53.5	52.8	52.9	54.5

*Suspension IL-2.

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Prognostic Impact of DNA Content and a Classification System for Ploidy (AUER Classification) in Primary Fallopian Tube Carcinoma (FTC)

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Nuclear DNA content (ploidy) has been correlated with biological behaviour in ovarian cancer and other solid tumours including breast, colon, lung and prostate cancer but there appears to be no data available on ploidy status in Fallopian tube carcinoma (FTC) [1, 2]. Recently, numerous reports have described methods of ploidy determination employing image cytometry (ICM) [3–6].

The present study describes, for the first time, ploidy analysis carried out in 61 cases of primary FTC using ICM. Since the so-called AUER classification has proved to be of prognostic impact in female breast cancer we evaluated the correlation between prognostic parameters of FTC as well as the prognostic influence of this classification system for this disease [7]. Patient characteristics are shown in Table 1.

Histological evaluation and grading for FTC was according to the criteria of Hu and colleagues [8]. For the staging of FTC, the latest FIGO classification was used [9].

For DNA ploidy analysis, three to four 30-μm-thick paraffin sections were cut from a representative area of each tumour and transferred into Eppendorf microvials. The disintegration procedure used is described in Mack and Hacker [6]. A standard Feulgen procedure was used for stoichiometric DNA staining [20]. In addition, the histogram types according to the AUER classification were assessed for prognostic value [6].

The mean age of the 61 patients included into this study was 61.8 years (range 37.3–80.2). Correlation analysis of ploidy and FIGO stage did not reveal any statistically significant relationship between these two parameters (Kendall's Tau—b 0.088, *P* value 0.457).

There was no statistically significant relationship between histologic grading and ploidy (Kendall's Tau—b 0.166, *P* value 0.171) or between AUER classification and FIGO stage (Kendall's Tau b: b 0.271, *P* value 0.814). Furthermore, there was no correlation between AUER classification and histologic garding (Kendall's Tau b: b = 0.120, *P* value 0.309).

The median survival time for all stages was 29.7 months (range 0.3–126). The median survival time for all euploid cases was 33.8 months (range 1.8–126.3) compared with 24.5 months (range 0.3–103.5) for the aneuploid cases; statistically significant (log rank, $P = 0.83$). Although patients with euploid tumours

Table 1. Patients' classification of 61 primary Fallopian tube cancers

	Total		Euploid		Aneuploid	
	No.	(%)	No.	(%)	No.	(%)
Stage						
I*	22	(36)	5	(23)	17	(77)
II*	13	(21)	4	(31)	9	(69)
III	17	(28)	3	(18)	14	(82)
IV	9	(15)	1	(11)	8	(89)
Grade						
G1	16	(26)	5	(31)	11	(69)
G2	22	(36)	5	(23)	17	(77)
G3	23	(38)	3	(13)	20	(87)
Ascites						
Positive	15	(25)	3	(20)	12	(80)
Negative	46	(75)	10	(22)	36	(78)
Adjuvant therapy						
Radiation	19	(31)	5	(26)	14	(74)
Chemotherapy	32	(53)	5	(25)	24	(75)
None	10	(16)	—	—	10	(100)
Surgical procedure						
BSO + TAH + omentectomy + lymph nodes	37	(61)	10 (27)	27 (73)		
BSO + TAH + omentectomy	24	(39)	3	(14)	21	(86)
Total	61	(100)	13	(100)	48	(100)

* 15 patients showed cancer confined to the adnexa and/or the uterus but did not undergo retroperitoneal lymphadenectomy.

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