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High-dose Recombinant Interleukin-2/Verapamil Combination in Advanced Cancer

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rIL-2-BASED IMMUNOTHERAPY is a promising approach for patients with advanced melanoma and renal cell carcinoma [1]. IL-2 generates lymphokine-activated killing activity (LAK) by peripheral blood lymphocytes (PBL) which acquire the capacity of MHC-unrestricted killing of tumour cells [2–4]. We have demonstrated that human tumour cell lines, resistant to LAK-cytotoxicity *in vitro*, become sensitive to cytotoxic lymphocytes after 24–48 h exposure to the calcium channel blocker verapamil [5]. Verapamil is active at concentrations (10–100 nM) which can be reached *in vivo* [6]. Therefore, we designed a Phase I clinical study on rIL-2/verapamil combination. After committee approval, written informed consent was obtained from each patient before study entry.

All patients enrolled in the study were given the same verapamil dose, while the dose of rIL-2 given by continuous infusion for 72 h starting day 2 was escalated in the different cohorts of patients (Table 1). Dose escalation was allowed if a minimum of 3 patients had been treated at each dose level of infusional rIL-2 without grade 3–4 toxicities in 2 of 3 patients. Dose escalation over 18 IMU/m^2/day, which can be considered a standard dose [7] and close to the maximum tolerated dose (MTD) [8] of rIL-2 by continuous infusion, was not planned. 10 IMU/m^2/day rIL-2 were given by subcutaneous administration on days 6–10 to all patients who entered the study. Verapamil was administered at the dose of 0.2 mg/kg/h for 3 consecutive days by continuous infusion after a loading bolus dose of 0.15 mg/kg. 18 patients—8 males, 10 females, 10 with malignant melanoma, 7 with renal cell carcinoma, 1 with colon cancer—were enrolled in the study and completed the two planned courses of rIL-2/verapamil. Median age was 49 years (range 22–72). 3 additional patients were treated with 9 IMU/m^2 rIL-2 to further explore the rIL-2 dose which we considered, on the basis of biological activity (see below), as the recommended one for Phase II trials (Table 1).

Grade 1 elevation of BUN and creatinine occurred in 5 patients (28%), respectively, while grade 2 increase of creatinine occurred in 1 patient (6%). Oliguria occurred in 11 patients (61%) and inversion of urine electrolyte in 13 patients (72%). 2 patients experienced grade 2–3 hypotension which resulted in only temporary suspension of therapy. Grade 1 hypotension occurred in 9 patients (50%), but did not result in discontinuation of drug infusion. Synus tachicardia was observed in 7 patients (39%), first degree atrioventricular (AV) heart block in 2 patients (11%), AV dissociation in 1 (6%) and premature ventricular beats in 1. 1 patient had synus bradycardia immediately after bolus verapamil injection which resolved spontaneously with temporary discontinuation of verapamil infusion. Fever occurred in 14 (78%) patients, dyspnoea in 1 (6%), abdominal pain in 13 (72%), anaemia in 10 (56%), nausea and vomiting in 4 (22%), constipation in 4 (22%), increase of serum bilirubin in 5 (28%), diarrhoea in 1 (6%).

We also evaluated the immunomodulatory properties of the rIL-2/verapamil combination by determining the number of circulating eosinophils and induction of cytotoxic activity against the human leukaemia K562 cells. Both peripheral blood lymphocytes cytotoxic activity and circulating eosinophils were maximally increased at the rIL-2 dose of 9 IMU/m^2/day. We observed 1 complete remission in a patient with renal cell carcinoma, lasting 30+ months, and 2 partial remissions (renal cell carcinoma and melanoma), lasting 6 and 9 months. Minor objective responses were recorded in 4 patients (1 with melanoma and 3 with renal cell carcinoma). Disease progressed in 5 patients (Table 1). In conclusion, we demonstrated that a rIL-2 dose of 18 IMU/m^2 could be administered in combination with high-dose verapamil in absence of cumulative toxicity. Furthermore, this combination has biomodulatory properties and antitumour activity and deserves evaluation in Phase II clinical studies.

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Table 1. Tumour types and responses to rIL-2/verapamil combination therapy

rIL-2 (IMU/m²/day)	Tumour type	Sites of disease	Clinical response
1.2	Renal cell carcinoma	Liver, nodes	PD
1.2	Melanoma	Liver, bone	NC
1.2	Melanoma	Skin, nodes	NC
2.4	Colon carcinoma	Liver, lung	NC
2.4	Melanoma	Liver, breast	NC
2.4	Melanoma	Liver, spleen, bone, lung	NC
4.8	Melanoma	Nodes	PD
4.8	Melanoma	Pleura, lung, liver, nodes Uterus	PD
4.8	Renal cell carcinoma	Mediastinal nodes	CR
9	Melanoma	Adrenal gland, nodes	MR
9	Renal cell carcinoma	Lung	MR
9	Melanoma	Liver	PR
9	Renal cell carcinoma	Lung	MR
9	Melanoma	Nodes	NC
9	Renal cell carcinoma	Lung, nodes	PD
18	Melanoma	Lung, skin, nodes	PD
18	Renal cell carcinoma	Lung, bone	MR
18	Renal cell carcinoma	Lung	PR

CR, complete remission; PR, partial remission; MR, minimal response; NC, no change; PD, progression of disease.

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Activity of Gemcitabine in Platinum-resistant Ovarian Germ Cell Cancer

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OVARIAN GERM cell cancer (OGCT) is a rare disease accounting for less than 5% of all ovarian carcinomas. The importance of the disease is due to its relatively high incidence among children and young adults and the potential for cure by the use of platinum-containing chemotherapy [1]. The current recommendation of the Gynecologic Oncology Group (U.S.A.) for the treatment of advanced OGCT consists of cytoreductive surgery followed by three to six cycles of chemotherapy with bleomycin, etoposide and cisplatin (BEP) resulting in a 75% cure rate for advanced stage disease [1]. However, treatment of platinum-refractory OGCT remains difficult [2]. Paclitaxel is among the few drugs that have shown activity in platinum-resistant ovarian and testicular germ cell cancer [3, 4]. We report here the case of a patient with

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