

## Chemoimmunotherapy with low dose vinorelbine and interleukin-2 in treatment of patients with metastatic renal cell carcinoma

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Systemic therapies employed in patients with metastatic renal cell carcinoma (MRCC) include chemotherapy to immunomodulatory cytokines (interleukin 2 [IL-2], interferon alpha [INF $\alpha$ ]), chemoimmunotherapy, adoptive immune therapy and anti-angiogenic therapy. Despite this range of treatment alternatives, the optimal therapy for MRCC patients is far from being established. Thus, attempts with novel therapeutic approaches implementing new drug combinations are justified. We conducted a phase II evaluation of a combination of vinorelbine and IL-2, both at low doses, in 30 patients with MRCC. The rationale of the combination was to damage the tumor tissue to the extent necessary to make it more immunogenic while, at the same time, to obtain an efficient immune response through the concomitant administration of IL-2. The treatment, given in different dose combinations and administration times, resulted feasible, with no renal, neurological or hematological toxicity. The overall survival of the whole group of patients is higher than that usually observed following treatment with immunotherapies (18.2 versus 13.3 months, respectively). While the limited number of treated patients does not allow advancing conclusions on the effective activity of the adopted protocol, the results observed are encouraging.

*Key words: advanced renal carcinoma, chemo-immunotherapy*

Systemic therapies used in patients with metastatic renal cell carcinoma (MRCC) range from chemotherapy to immunomodulatory cytokines (interleukin 2 [IL-2], interferon alpha [INF $\alpha$ ]), chemoimmunotherapy, adoptive immune therapy and anti-angiogenic therapy. Most MRCC patients, however, do not respond to any of these treatment alternatives [1]: median survival time was 12.7 months for patients treated after 1999 [2] and 13.3 months for patients undergoing a variety of immunotherapies [3].

Response rates to chemotherapy are generally low. Chemotherapy is mainly based on fluoropyrimidines, with combinations of gemcitabine and 5-fluorouracile or capecitabine yielding response rates of 17–20%. Combined gemcitabine and oxaliplatin therapy showed a limited level of activity, as did irinotecan alone [4, 5]. The combination of vinblastine with estramustine phosphate or IFN gamma showed minimal activity in MRCC patients [6].

Control of cancer progression by an immune response has

been suggested by the spontaneous regression of synchronous metastases seen after nephrectomy, by the presence of T lymphocytes within renal tumors and by tumor regression obtained with cytokines [7]. Cytokine based immunotherapy for renal cancer, now considered standard [8], relies on IL-2, INF $\alpha$  or combination of the two. The regression rates documented in several large trials range from 12 to 20% [9–11]. Standard systemic cytokine therapy is usually performed on a high dose basis, and toxicity is significant [10, 12, 13]. However, long-term treatment with low dose IL-2 and INF $\alpha$  has also been attempted [14–16].

Chemoimmunotherapy combining 5-fluorouracile, IL-2 and INF $\alpha$  resulted in response rates ranging from 10 to 40% [9, 17], suggesting the opportunity for further trials [18]. In other experiences, however, it appeared to exert no significant antitumor activity [19, 20]. The response rate to vinblastine combined with INF $\alpha$  was 16.5% [19], while the combination of 5-fluorouracile with IL-2 and INF $\alpha$  led to

still better results than another vinblastine plus INF $\alpha$  [13] association. Capecitabine plus INF $\alpha$  yielded a response in 24% of patients [21]. On the other hand, combining cytotoxic, immunodepressive drugs with modifiers of immune response to cancer opens a wide array of delicate problems [22].

Therapies targeted to VEGF and related pathways are justified by the high vascular nature of renal cancer. Studies with anti-angiogenic factors also hold promise, with objective response rates ranging from approximately 20 to 40%, report a significant clinical activity with bevacizumab treatment, while therapy with the proteasome inhibitor bortezomib achieved partial response in only a small percentage of patients [23].

Despite the range of therapeutic options, the best treatment approach for MRCC patients is far from being established. Thus, attempts with novel therapeutic approaches implementing new drug combinations and different treatment schedules seem to be justified.

We treated 30 patients with MRCC using a combination of vinorelbine and IL-2, both at low dose. The rationale of the combination was to damage the tumor tissue to the extent necessary to make it more immunogenic while, at the same time, to obtain an efficient immune response through the concomitant administration of IL-2.

## Patients and methods

**Patients.** Thirty patients were enrolled in this study. Subjects' demographics and features are reported in Table 1.

**Study design** (Tab. 2). Patients received vinorelbine 25 mg/m<sup>2</sup> intravenously every 15 days for eight weeks and IL-2 4,000 000 MIU subcutaneously twice/day, five days/week, for 12 weeks. At the end of this period they received IL-2 4,000 000 MIU once/day (five days/week) for three weeks. Following a rest week, IL-2 treatment at 4,000 000 sc once a day was started again for three weeks, followed by a rest week. The last schedule of IL-2 treatment was continued until CT control, performed every three months, showed signs of progression. At that time the patients were taken off the protocol. The protocol allowed for the administration of palliative therapy, exclusive of steroids or radiotherapy.

Vinorelbine (Navelbine, Pierre Fabre Chemicals) was diluted in 250 of saline and infused over 45 minutes. IL-2 was diluted with sterile water and injected subcutaneously in the arm.

Primary end point of the paper was the feasibility of this two drug combination, recording of toxicities assessed by NCI-CTC criteria.

Secondary end points were to explore time to treatment failure and overall survival.

Follow up was performed by standard clinical controls and blood analysis every week, by CT control every three months. Median follow-up was 44 months (from 0.6 to 72).

All patients gave their informed consent, according to the rules of our Institutions' Ethics Committees.

## Results

Overall, the 30 patients treated showed a median survival of 18.2 months.

At the moment, 55% of patients have died, while 45% are still alive. A group of 17 patients (non-responders) had a mean survival of 14.8 months; a second group of 13 subjects (responders) had a mean survival of 43.7 months. The difference between these two groups of patients was statistically significant ( $p > 0.001$ ; CI 21.57–39.17). The range and statistical analysis of survival times are reported in Table 3.

According to more accepted risk factor score [24, 25] responder group had 0 score; among non responders, ten patients had a score of 2 and seven patients a score of 3 or more.

Time to treatment failure (TTF) (by CT control) took place after a mean of 8.1 months in the non-responder group and after a mean of 40.69 months in the responder group. The difference in TTF between the two groups was statistically significant, with  $p < 0.001$  (CI 22.58–41.69) (Tab. 3). We recorded some differences in blood parameters between the two groups.

Responders differed from non-responders in some blood parameters at enrollment (Tab. 4). PCR values were 4.18 and

**Table 1. Patient's general features**

Age (mean and range)	56 (52–75)
Sex	M 60%; F 40%
Mean time since diagnosis of renal cancer	3 months
Nephrectomy	100%
Mean time from nephrectomy	5 weeks
Synchronous metastasis	100%
Metastases	Lung only 66%; Bone only 16%; Lung + bone 9%; retroperitoneal only 9%
PS (ECOG)	all enrolled patients 0=65%; 1=15%; 2= 20%. 13 responders: 0=100%; 17 non responders 0=25%; 1=40%; 2= 35%
Previous treatments	IL-2 0%; IFN alfa 0%; CT 0%

**Table 2. Treatment schedule**

IL-2 sc	4,000 000 IU BID for 8 weeks
Vinorelbine 25 mg/m <sup>2</sup> iv	Q14 for 8 weeks
IL-2 sc (maintenance) (from week 9)	4,000 000 IU until progression* or toxicity
*Progression	Assessed with CT every 3 months

**Table 3. Survival and time to treatment failure**

	Responders	Non-responders	All Patients	p
OS	43.7	14.8	18.2	<0.001
TTF	40.69	8.1		<0.001

Variance analysis test

**Table 4. Hematological values (All values in mean)**

	All patients	Responders	Non-responders	p
PCR (basal)	2.84/normal	1.5	4.18	NS
Hb (basal)	12.8 gr	13	11.8	NS
WBC (basal)	6946	7460	6350	NS
Lymphocytes (basal)	1503	1856	1150	<0.001
WBC(3 weeks)	8314	9543	7085	<0.001
Lymphocytes (3 weeks)	2600	4003	1198	<0.001

Variance analysis test

1.5 times normal levels in non-responders and in responders, respectively.

At the beginning of treatment the lymphocyte level was 1150/mm<sup>3</sup> in non responders and 1850/mm<sup>3</sup> in responders. These lymphocyte count differences were statistically significant ( $p < 0.001$ ). On the whole, treatment was satisfactorily tolerated. During the first three weeks of treatment all patients had grade 2-3 fever, which prompted antipyretic drug administration. One patient had a pulmonary edema ten days following the first IL-2 administration, which resolved with usual treatment, but IL-2 administration was not resumed. No renal, neurological or hematological toxicity was observed.

## Discussion

We have conducted a phase II evaluation of a combination of vinorelbine and IL-2, both at low doses, in 30 patients with metastatic renal cell carcinoma (MRCC). Collected data appear encouraging.

The treatment resulted feasible, with no renal, neurological or hematological toxicity; one developed a pulmonary edema, which was possibly not related to the anticancer treatment. At the beginning of the trial, however, all patients had grade 2-3 fever, which was easily controlled.

Although the limited number of treated patients does not allow definitive conclusions on the effectiveness of the applied protocol, the results observed are encouraging. The overall survival of our patients is higher than that usually achieved following immunotherapies (18.2 months versus 13.3 [3], respectively) and compares favorably with findings obtained with the newest anti-angiogenic drugs [22]. One possible explanation for the observed activity is, that apart from having an additive effect, the combination of vinorelbine and IL-2 may be synergistic. The antitumor efficacy of IL-2 seems to be related to the activation of cytotoxic lymphocytes. One might therefore speculate that the tumor tissue damaged by vinorelbine constitutes a better target for these cells.

In our study the response to the vinorelbine-IL-2 combination seems to have differed according to patients' characteristics. We were able to single out two groups of patients, one with an OS of 14.8 months (non-responders), and a second,

smaller, group with an OS of 43.7 months (responders). This may reflect the well known variability of the natural history of MRCC, in which survival is contingent on many variables, including response to treatment. We believe it is important that, at least in our group of patients, some simple clinical data, such as PS, and some laboratory variables allowed us to predict the response to therapy: specifically, lymphocyte values, both basal and at three weeks following the start of treatment, were significantly lower in patients who subsequently did not fare as

well as patients with a higher lymphocyte count. This finding, were it confirmed in a larger group of patients (and in subjects treated with different therapeutic protocols), would in all likelihood allow the selection during an early management phase of patients requiring more challenging, toxic and costly therapies.

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