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# Immunotherapy with Interleukin-2 (IL2) and Lymphokine-activated Natural Killer Cells: Improvement of Clinical Responses in Metastatic Renal Cell Carcinoma Patients Previously Treated with IL2

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**Treatment with interleukin-2 (IL2) induces clinical responses in 15–30% of metastatic renal cell carcinoma (MRCC) patients, with mainly partial responses. In order to improve clinical response, we decided to treat partial response patients from a previous IL2 treatment with a second course of IL2 associated with lymphokine-activated natural killer (LANAK) cells. 10 patients who underwent PR after an IL2 protocol (24 × $10^6$ U/$m^2$/day, 2 days a week for 5 weeks, either alone or with interferon-γ) subsequently received a combination of high-dose IL2 (16–20 × $10^6$ U/$m^2$/day, 2 days a week) and LANAK cell infusions. Four complete responses were obtained, and 2 additional patients whose tumour mass was further reduced achieved complete response following surgery. These results support the view that initial responses obtained with primary IL2 courses can be improved by complementary treatments. The potential role of cellular immunotherapy and, more particularly, of LANAK cells as an effective procedure to further reduce tumour burden in patients responsive to IL2 will have to be assessed in randomised studies.**
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## INTRODUCTION

TREATMENT WITH interleukin-2 (IL2) alone or associated with *in vitro* IL2-activated lymphocytes (LAK cells) induces clinical responses in 15–30% of patients with metastatic renal cell carcinoma (MRCC). Despite many clinical trials, no significant improvement in response rate has been obtained [1, 2].

In murine models, experiments have unequivocally demonstrated that the addition of LAK cells to IL2 increases the response rate and improves the quality of tumour regression [3–6]. In such studies, the transfused cells are the critical effectors of the *in vivo* antitumour response, this activity being maintained by *in vivo* IL2 infusion [7]. In humans, however, the contribution of LAK cells to tumour regression has appeared less substantial than in preclinical studies [8–12].

Considering the efficacy of cell infusions in animal models, one method of improving clinical results in humans is to use suspensions with potentially improved antitumour activity on a per-cell basis. *In vitro* studies have shown that the antitumour activity of the human LAK cells is mediated in a virtually exclusive fashion by a small fraction of $CD3^-$ $CD56^+$ $CD16^+$ natural killer (NK) lymphocytes [13, 14]. *In vivo*, IL2-activated adherent lymphocytes with a NK phenotype (A-LAK) were significantly more efficient than unseparated LAK cells in improving the survival of tumour-transplanted rats [15]. To improve the efficacy of cell infusions in humans, our approach has been to generate highly purified preparations of IL2-activated NK cells derived from patients' peripheral blood. In an initial clinical study, we have been able to produce and safely transfuse suspensions of lymphokine-activated natural killer (LANAK) cells in 12 patients with MRCC [16]. The *in vitro* cytotoxicity of LANAK cells was found to be usually 10 times greater than that of LAK cells. None of these 12 patients were included in the present trial.

Results from randomised trials comparing IL2 to IL2 plus LAK cells do not show a significant change in the overall response rate. Regarding complete responses (CR), results are more discrepant. While some studies have shown no difference [10, 11], a large study suggested that the quality of response was improved in patients receiving cellular immunotherapy with a 11% CR rate versus 3% without LAK [17]. We therefore considered, as a working hypothesis, that cell infusions may contribute to further tumour reduction in those patients who are responsive to IL2. We evaluated in a pilot trial whether complementary treatment with IL2 and cellular immunotherapy using LANAK cells can improve clinical response in MRCC patients who have achieved a partial response (PR) with IL2 alone.

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## PATIENTS AND METHODS

### *Experimental procedures*

*Monoclonal antibodies (MAb) used for purification.* The anti-CD3 (OKT3, Ortho Diagnostics, Raritan, New Jersey, U.S.A.) MAb was used for the first purification. The mixture used for the second purification, included anti-CD3 (OKT3), CD4 (OKT4, Ortho Diagnostics), CD5 (K39, kindly provided by Dr A. Bernard, Nice, France), CD8 (OKT8, Ortho Diagnostics), MHC class II (kindly provided by Dr S. Schlossman, Dana Farber Cancer Institute, Boston, Massachusetts, USA). All MAbs were used in excess (1/100 to 1/1000). Saturating concentrations were predetermined on relevant cells by indirect immunofluorescence and cytofluorometric analysis (EPICS ELITE, Coultronics, Hialeah, Florida, U.S.A.).

*Purification of NK cells.* Peripheral blood mononuclear cells (PBMC) from patients' cytaphereses were separated on Ficoll-Hypaque density gradient using an automatic cell separator (Stericell Processor, Dupont de Nemours, Les Ulis, France). Monocytes were removed by two cycles of adherence in tissue culture flasks (45 min, 37°C). $CD3^-$ NK cells were prepared by negative selection using two successive purification steps. Non-adherent peripheral blood mononuclear cells (PBMC) were incubated (20 min, 4°C) with anti-CD3 (OKT3) MAb ($50 \times 10^6$ cells per ml) and washed twice in washing medium (DMEM complemented with 2% human AB serum (obtained from the CNTS, Paris, France), 2 mM L-glutamine, 1 mM sodium pyruvate, 0.2% NaOH 1N, 50 U/ml penicillin and 0.05 mg/ml streptomycin. Immunorosetting with magnetic beads (Dynabeads M250, Dynal, Oslo, Norway) or the Magnetic Activated Cell Sorting (MACS) [18], were used for the first purification. For the immunorosetting procedure, cells were incubated at a ratio of $250 \times 10^6$ cells per ml of magnetic beads, and separated according to a previously described method [16]. The MACS procedure has been extensively described elsewhere [19]. The second purification was performed the same day using the immunorosetting procedure. The non-rosetted cell fraction was incubated (20 min, 4°C) with the mixture of MAb ($50 \times 10^6$ cells per ml). After washing, cells were separated using magnetic beads at an optimal predetermined ratio of $50 \times 10^6$ cells for 1 ml of beads.

*LANAK cultures.* LANAK culture procedures have been extensively described [16]. Briefly, purified NK cells were plated in V-bottom microplates (Nunc, Naperville, Illinois, U.S.A.) at $5 \times 10^4$ cells/ml, on a feeder layer including irradiated (7500 cGy) LAZ 388 lymphoblastoid cells ($2 \times 10^5$ cells/ml) and irradiated (3500 cGy) allogeneic PBMC ($5 \times 10^5$ cells/ml). The culture medium was DMEM supplemented with 8% human AB serum, 2 mM L-glutamine, 1 mM sodium pyruvate, 0.2% NaOH, 100 U/ml penicillin, 0.1 mg/ml streptomycin; rIL2 (Roussel Uclaf, Romainville, France) 200 U/ml was added to the medium as well as 1% lymphocyte-conditioned medium (LCM). Purified phyto-haemagglutinin (PHA-P) (Wellcome Foundation, London, U.K.) 1 μg/ml was added once to the culture on day 0. LANAK cultures were fed and harvested from microplates using a Biomek 1000 automate (Beckman, Gagny, France). After harvest (2–5 days before infusion), cells were centrifuged, resuspended at $10^6$ per ml in culture medium (DMEM supplemented with 4% human AB serum, glutamine, sodium pyruvate, NaOH, antibiotics and 200 U/ml rIL2) and transferred to bags (Baxter, Maurepas, France). Five hours before infusion, cells were boosted by injecting 250 U/ml rIL2 into bags. Sterility was checked under both aerobic and anaerobic conditions (direct staining and bacteriological cultures) after harvest from microplates and 5 h before infusion.

*Immunofluorescence analysis of LANAK cells.* Immunophenotyping was performed by flow cytofluorimetry using an EPICS ELITE (Coultronics, Hialeah, Florida, U.S.A.). The following MAb were tested to assess the purity of the LANAK cultures: anti-CD2 (Coulter Clone, Hialeah, Florida, U.S.A.), CD3 (OKT3), CD4 (OKT4), CD5 (K39), CD8 (OKT8), CD56 (NKH1), TCR1 α/β (BMA031, kindly provided by Dr R. Kurrle, Behring Co., Marburg, West Germany) and (T cell receptor) TCR γ/δ (TCRδ1, kindly provided by Dr M. Brenner, Dana Farber Institute). Fluorescinated goat antimouse was obtained from Coulter Clone.

### *Patients*

*Selected population and eligibility requirements.* 10 patients entered the study from September 1989 to March 1991. All patients had histologically proven metastatic renal cell adenocarcinoma with clinically measurable disease, and fulfilled criteria for IL2 administration as previously reported [20]. All patients were required to give informed consent prior to participation in the study.

Patients were eligible for this protocol when partial response (PR) had been previously obtained with a high-dose IL2 induction protocol. Two different induction protocols were successively used in our institution where IL2 (Roussel Uclaf) was infused by continuous intravenous infusion at a daily dose of $24 \times 10^6$ U/m$^2$ for 2 consecutive days, for 5 consecutive weeks. Initially, IL2 was associated with interferon-γ (Roussel Uclaf) given subcutaneously at a daily dose of $5 \times 10^6$ U/m$^2$ on the same days as IL2 during the 5 weeks of treatment. Among 33 patients included in this protocol, 7 patients underwent PR [20]. As there was no evident benefit due to the addition of interferon-γ, a new study was performed where IL2 was given alone on the same 2 days a week schedule [21]. 3 patients (among the first 20 patients included) were included in this IL2–LANAK protocol. Characteristics of the patients are shown in Table 1. The IL2–LANAK treatment was started only 6–10 weeks after PR had occurred to ensure that PR would not later turn into CR without complementary treatment.

All patients had staging evaluation before the therapy including CT scans of the chest and the abdomen, and a technetium pyrophosphate bone scan when necessary. Radiological evaluation for determination of tumour measurements was repeated 4 and 8 weeks after completion of therapy.

### *Protocol*

IL2 was obtained from Roussel Uclaf. All patients were scheduled to receive four cycles of IL2. During the first two cycles, given at 1-week intervals, IL2 was infused alone for 48 h at a daily dose of $16–20 \times 10^6$ U/m$^2$ according to individual tolerance of the IL2 induction protocol. Cytaphereses were performed 2 days after the end of each course of IL2 for isolation of PBMC and *in vitro* preparation of LANAK cells (see above). LANAK cells were scheduled to be reinfused 2 weeks after each cytapheresis, during a 3-day cycle of IL2, given at the same daily dose as previously. LANAK cells were infused over 15–30 min on the first day of each cycle, and IL2 was started immediately after the cell infusion.

*Table 1. Characteristics of the patients*

| Patients | Sex | Age | Metastatic sites | Delay to metastasis | SR | Initial treatment |
|---|---|---|---|---|---|---|
| 1 | M | 62 | Lu | 4 | 45 | IL2 + γIFN |
| 2 | M | 56 | Lu | 112 | 45 | IL2 + γIFN |
| 3 | M | 44 | Lu,Med | 35 | 4 | IL2 + γIFN |
| 4 | F | 57 | Lu | 0 | 106 | IL2 + γIFN |
| 5 | M | 49 | Lu,Med,Li | 102 | 32 | IL2 + γIFN |
| 6 | M | 56 | Bo,Soft T | 0 | 6 | IL2 + γIFN |
| 7 | M | 67 | Lu,Ln,Bo | 30 | 4 | IL2 + γIFN |
| 8 | M | 57 | Lu,1° | 0 | 40 | IL2 alone |
| 9 | M | 63 | Li,Ln | 60 | 32 | IL2 alone |
| 10 | F | 52 | Lu,Li | 2 | 85 | IL2 alone |

M, male; F, female; SR, sedimentation rate; Lu, lung; Med, mediastinum; Li, liver, Bo, bones; Soft T, soft tissue; Ln, lymph node; 1°, primary tumour; γIFN, interferon-γ.

*Supportive care*

All the patients were hospitalised in the intensive care unit. IL2 infusion was given through a central venous catheter which had been previously inserted for the induction protocol. No prophylactic antibiotherapy was given. Heart rate was monitored continuously and blood pressure was checked every 15 min. Careful monitoring was performed during cell infusions. Patients systematically received aspirin (1 g every 6 h) and paracetamol (1 g every 6 h) to prevent excessive fever. Loperamide was usually given for diarrhoea and metochlopramide for nausea. Hypotension with systolic blood pressure less than 80 mmHg was first treated with macromolecular fluid infusion. In case of persistent hypotension, dopamine (5–20 μg/kg/min) was used; IL2 was stopped if hypotension persisted despite dopamine.

*Response and toxicity evaluation*

CR was defined as the disappearance of the tumour. PR was defined as >50% reduction in the sum of the products of the largest perpendicular diameters in all measurable lesions without any new lesion or lesion increasing in size; progressive disease (PD) was defined as an increase >25% in the same sum of products, or the appearance of one or more new lesions; stable disease (SD) was defined as less than 25% change in measurable lesions without any new lesion.

Duration of the response was assessed from the time of occurrence of the response to the time when progression was first noticed. Survival time was calculated from the first day of the induction treatment.

Toxicity was graded according to the WHO criteria. Treatment was discontinued according to previously reported criteria [20].

## RESULTS

*Generation of LANAK cells*

Cytaphereses were performed on days 5 and 12 (i.e. at the first and second lymphocytic rebounds). $CD3^-$ NK lymphocytes were isolated from non-adherent PBMC by negative selection using two successive purification steps. A mean of $117 \pm 44 \times 10^6$ (mean ± S.D.) purified NK cells was generated for the first culture and $116 \pm 39 \times 10^6$ for the second culture (Table 2). After culture in microplates (mean time 12.5 ± 6.6 days), $2.6 \pm 0.9 \times 10^9$ LANAK cells were recovered. At this step, cells were harvested from microplates and transferred to bags for a mean of 4 additional days until infusion. The length of the cultures was essentially dependent of the time required by the LANAK lymphocytes to grow in microplates. Therefore, the third and fourth IL2 cycles were scheduled according to the length of the cultures. In 2 patients (5 and 7), the second cytapheresis was not performed and LANAK cells from the first culture were used to start the second one. Bacteriological cultures were negative in all but one cases (in patient 8, the first culture contaminated with *Acinetobacter* was not injected).

*Table 2. LANAK cultures*

| | Culture 1 | | | Culture 2 | | |
|---|---|---|---|---|---|---|
| Patients | PBL Day 0 ($\times 10^9$) | NK Day 0 ($\times 10^6$) | LANAK Days 13–21 ($\times 10^9$) | PBL Day 0 ($\times 10^9$) | NK Day 0 ($\times 10^6$) | LANAK Days 14–20 ($\times 10^9$) |
| 1 | 1.5 | 50 | 3.2 | 2 | 67 | 0 |
| 2 | 2.6 | 130 | 2.8 | 2.5 | 140 | 12.2 |
| 3 | 2.3 | 85 | 5.3 | 2.5 | 95 | 15.1 |
| 4 | 2.5 | 60 | 5.3 | 2.5 | 123 | 2.6 |
| 5 | 4.2 | 200 | 1.8 | — | 160* | 2.1 |
| 6 | 2.5 | 140 | 7.7 | 3.1 | 98 | 8.6 |
| 7 | 2.5 | 145 | 6.8 | — | 71* | 5.8 |
| 8 | 3.0 | 110 | 1.8 | 2.5 | 83 | 12.3 |
| 9 | 2.5 | 140 | 2.7 | 2.5 | 181 | 11.0 |
| 10 | 2.5 | 114 | 4.9 | 2.5 | 143 | 1.9 |

*Cells were recovered from the first LANAK cultures. PBL, peripheral blood lymphocyte; NK, natural killer; LANAK, lymphokine-activated natural killer cells.

As observed in the first IL2–LANAK trial [16], the LANAK cultures contained greater than 90% highly cytotoxic activated $CD3^-$ $CD56^+$ NK cells. Except for patient 8 (33% of $CD3^+$), no more than 5% of $CD3^+$ lymphocytes were detected in the infused lymphocytes (data not shown).

*Administration of treatment and toxicity.* Characteristics of IL2 and LANAK cells infusions are summarised in Table 3. 5 patients received 100% of the planned doses of IL2. In the 5 remaining patients, IL2 had to be interrupted at least once during the treatment. Reasons for IL2 discontinuation were mainly hypotension: patient 4 (four cycles), patient 5 (third cycle) and patient 8 (three cycles). In 2 patients, however, IL2 was stopped by patients' request during the last cycle despite the absence of predetermined criteria for interruption (patient 3), and neurological disturbance with agitation (patient 7).

LANAK cells were infused 18.6 ± 8.9 and 16.2 ± 3.4 days after the cytapheresis following the first and the second cycle of IL2, respectively. In 3 patients, the protocol schedule was altered. Patients 1 and 2 received only three cycles of IL2 and one infusion of LANAK cells. Cells recovered from the 2 cytapheresis were infused at the same time in patient 2 (Table 3). In patient 8, the second culture grew very slowly and was infused only 42 days after cytapheresis. A third cytapheresis was performed in this patient (without previous cycle of IL2) and cells were infused 22 days later. We found no obvious correlation between the number of infused LANAK cells (see Table 2) and the clinical response.

Usual toxicities described with high-dose IL2 occurred in all patients. Severe toxicities (grade 3 and 4) were mainly hypotension. Thus, hypotension occurred in all but 1 patient (patient 1), requiring the cessation of IL2 in 3 patients. Renal failure occurred in 1 patient and neurological disturbance in another. No chill was observed during LANAK cells infusions.

*Response to treatment and survival.* Clinical results are shown in Table 4. Clinical response was evaluated by comparison of the tumour size at the beginning of the IL2–LANAK treatment (6–10 weeks after PR had occurred) with that after treatment. All, except patient 8, improved their clinical status.

4 patients (patients 3, 4, 7, 10) went to CR after treatment. Responding sites included lung, mediastinum, liver, lymph node, bone and soft tissue. CR in bone metastasis in patient 6 was assessed by complete bone reconstruction and normal bone scan. Patient 3 relapsed in the brain after 10 months, and patients 4, 7 and 10 are still in CR (29, 25 and 14 months+).

PR were improved in 5 patients (patients 1, 2, 5, 6, 9) following IL2–LANAK therapy. Patients 1 and 2 with residual lung metastases were considered as relevant candidates for surgery, and underwent CR after lung surgery (whereas surgery had been considered as not feasible before immunotherapy); patient 1 is still in CR (32 months+); patient 2 relapsed in adrenal gland after 14 months and underwent new surgery. He is still in CR (9 months+). The 3 remaining PR patients (patients 5, 6, 9) had no surgical complementary treatment, either because of refusal (patients 5 and 6), or of unresectable residual tumour (patient 9). Patient 5 relapsed in the brain after 20 months (and is still alive), patient 6 is still in PR, while patient 9 relapsed 6 months later in the lung and died at 12 months.

Together, among the 10 patients, 4 had CR with immunotherapy alone, 2 additional patients were in CR after immunotherapy plus surgery, 3 improved their PR, and only 1 patient did not improve his clinical status.

Survival time was considered starting on the first day of IL2 induction protocol (either alone or with γ interferon). 8 patients are still alive with a median duration of 30 months (mean 27.6 ± 8.5).

## DISCUSSION

Treatment of MRCC with IL2 has been extensively studied and the overall response rate varies from 15 to 30% [1, 2, 9]. Despite many trials where IL2 schedule was modified or associated either with other cytokines or with LAK cells, clinical results remain unchanged. However, the CR rates appear different according to the series, and vary from 0 to 11% [8–12], with a trend for 'high' CR rates in patients treated by IL2 plus LAK cells [8, 9]. Based on these findings, we hypothesised that cell infusions could improve the quality of response (i.e. CR versus PR). In light of preclinical data, it was of interest to use effector cell populations with greater cytotoxic potential (i.e. LANAK cells). In a previous study, we showed that such LANAK cells can be infused safely [16]. In the present trial, we included

*Table 3. Individual characteristics of IL2 and LANAK cells infusions*

| Patients | Interval (days) | %IL2 received/cycle | | | | Time cytapheresis/ LANAK infusion (days) | |
|---|---|---|---|---|---|---|---|
| | | First | Second | Third | Fourth | First | Second |
| 1 | 41 | 100 | 100 | 100 | ND | 15 | ND |
| 2 | 42 | 100 | 100 | ND | 100 | 22 | 16* |
| 3 | 85 | 100 | 100 | 100 | 50 | 15 | 21 |
| 4 | 61 | 76 | 54.6 | 47.5 | 52 | 14 | 15 |
| 5 | 78 | 100 | 100 | 88 | 100 | 16 | 15 |
| 6 | 82 | 100 | 100 | 100 | 100 | 15 | 15 |
| 7 | 142 | 100 | 100 | 100 | 27 | 15 | 11 |
| 8 | 81 | 100 | 60 | 44 | 36 | 43 | 22† |
| 9 | 68 | 100 | 100 | 100 | 100 | 16 | 16 |
| 10 | 61 | 100 | 100 | 100 | 100 | 15 | 16 |
| Mean | 74.1 | 97.6 | 91.5 | 88.0 | 71.0 | 18.6 | 16.2 |
| ±S.D. | 28.6 | 7.6 | 18.1 | 22.6 | 32.4 | 8.9 | 3.4 |

* LANAK recovered from the second cytapheresis were infused during the same IL2 cycle.
† LANAK were recovered from a third cytapheresis. IL2, interleukin-2; LANAK, lymphokine-activated killer cells.

*Table 4. Response to treatment with IL2–LANAK*

| Patients | Response | Duration | Further treatment | Status | Survival (months) |
|---|---|---|---|---|---|
| 1 | PR | 4 | Thoracic surgery | CR | 39+ |
| 2 | PR | 4 | Thoracic surgery | CR | |
| | | | Abdominal surgery | CR | 37+ |
| 3 | CR | 10 | Cerebral irradiation | PRO | 32+ |
| 4 | CR | 29+ | | CR | 31+ |
| 5 | PR | 20 | Cerebral irradiation | PRO | 29+ |
| 6 | PR | 23+ | | PR | 28+ |
| 7 | CR | 25+ | | CR | 30+ |
| 8 | SD | 12 | Interferon-α | Died | 20 |
| 9 | PR | 6 | Interferon-α | Died | 12 |
| 10 | CR | 14+ | | CR | 18+ |

IL2, interleukin-2; LANAK, lymphokine-activated killer cells; PR, partial response; CR, complete response; SD, stable disease; PRO, progressive disease.

patients who underwent PR with IL2 alone and attempted to further decrease the tumour burden using a second-line treatment based on the administration of IL2 and LANAK cells. Furthermore, whenever possible, surgery of residual tumour was performed in patients who improved their status after IL2/LANAK cells treatment.

Patients included here had initially reached a PR status with a 2 days a week IL2 schedule given over a 5-week period. This IL2 regimen appears equivalent to others with an overall 21% response rate [20, 21]. Following IL2 and LANAK cells treatment, all patients except 1 had decreased tumour mass, and 4 underwent CR. The hypothesis of a delayed response to initial IL2 treatment is unlikely because their status was stable for at least 4 weeks between initial evaluation and the complementary treatment reported here. The respective contribution of IL2 and LANAK cells in such improvement cannot be evaluated. Indeed, there are no sufficient published data to clarify whether maintenance therapy with IL2 alone does improve responses. However, it is worth noting that a comparable group of patients has been recently treated in our institution under similar conditions (unpublished results) with a maintenance therapy including $24 \times 10^6$ U IL2 alone, 2 days a week for 5 weeks. In this group of 20 patients, 5 underwent PR at the induction phase and only 1 of these initial responders reached a CR status following maintenance therapy. This, together with the present results, indicates a potential beneficial effect of LANAK cells. Demonstration of this hypothesis will require a randomised trial.

In addition to the 4 CR obtained after IL2 plus LANAK cells therapy, our approach allowed complementary surgery (leading to CR) in 2 patients. This supports the view that combination of immunotherapy and subsequent surgery may be proposed to achieve CR [22, 23]. Together, the present data showing achievement of 6 CR in a group of 10 partial responders sustain the hypothesis that MRCC patients responding to IL2 induction courses may benefit from complementary treatments.


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# A Double-blind, Randomised, Crossover Comparison of Granisetron and Ondansetron in 5-day Fractionated Chemotherapy: Assessment of Efficacy, Safety and Patient Preference

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**We report the first double-blind, randomised, crossover study comparing granisetron and ondansetron as antiemetics in cancer chemotherapy. Patients receiving two cycles of identical chemotherapy fractionated over 5 days were given either granisetron (3 mg/day) or ondansetron (24 mg/day) on each day of chemotherapy, using a double-dummy technique to preserve study blindness. Patients then crossed over to the other therapy. 309 patients (237 male) completed the crossover: 260 received cisplatin (mean dose 19.2 mg/m²/day) and 49 received ifosfamide (mean dose 1415 mg/m²/day). Primary efficacy variables were prospectively defined as complete response (no vomiting and mild or absent nausea) over 5 days, and patient preference. Both agents achieved good control of emetic symptoms with 5-day complete response rates of 44.0% on granisetron and 39.8% on ondansetron [95% confidence interval (CI) for odds ratio 0.8, 1.9]. Complete response rates were very similar in patients receiving either cisplatin (40.8% granisetron, 37.6% ondansetron) or ifosfamide (61.2% granisetron, 51.0% ondansetron). There was a statistically significant difference in patient preference in favour of granisetron, 105 patients preferred granisetron, 79 preferred ondansetron, 121 had no preference ($P = 0.048$: 95% CI for odds ratio 1.00, 1.84). Single daily doses of granisetron (3 mg/day) appeared similarly effective and well tolerated to three daily doses of ondansetron (8 mg three times daily) in prevention of emesis induced by 5-day fractionated chemotherapy, however, significantly more patients preferred granisetron.**

**Key words: granisetron, ondansetron, fractionated chemotherapy, emesis, patient preference**
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## INTRODUCTION

POWERFUL CHEMOTHERAPEUTIC agents, such as cisplatin and ifosfamide, are associated with multiple, potentially serious, side-effects including emesis, bone marrow suppression and nephrotoxicity, many of which are related to chemotherapy dose. Dividing the dose and spreading the cytotoxicity over several days (i.e. fractionating) can reduce toxicity whilst maintaining therapeutic efficacy. These fractionated chemotherapy regimens are in common use for specific tumour types such as testicular germ cell tumours [1], achieving cure rates in excess of 90% [2]. Despite administration of lower daily chemotherapy doses, nausea and vomiting occur in up to 100% of patients treated with these regimens [3]. Inadequate control of these symptoms can result in poor compliance with further curative treatment, as well as other distressing and hazardous complications such as malnutrition and dehydration [4]. All of these factors adversely impact on daily activities and detract from quality of life.

Conventional antiemetic treatments such as dopamine antagonists have met with limited success in this therapeutic setting.