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CLINICAL STUDY REPORT SYNOPSIS

A phase I-IIa clinical study on the investigational anticancer drug J1in patients with advanced cancer

A prospective, single armed, open label, dose-finding phase I-IIa study

Sponsor Project No:	O-05-001
EudraCT number:	2005-002901-22
Investigational Product:	J1 (melphalan-flufenamide ethyl ester, melflufen) (concentrate for solution for infusion 25 mg/mL or 50 mg/mL)
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Date of report:	FINAL report 27 February 2013

The clinical study has been conducted, and essential documentation archived, in compliance with ICH Guideline for Good Clinical Practice.

SYNOPSIS

Title of study: A phase I-IIa clinical study on the investigational anticancer drug J1 in patients with advanced cancer.
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Investigational product: J1 (concentrate for solution for infusion 25 mg/mL or 50 mg/mL)
Sponsor/company: **Oncopeptides AB**
Coordinating investigator (Sweden): Åke Berglund (MD, PhD, Assoc prof), Dept. of Oncology, Uppsala University Hospital, Uppsala, Sweden
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Study centrer: Uppsala University Hospital, Uppsala, Sweden Karolinska University Hospital, Stockholm, Sweden State Educational Institution of Higher Professional Education "St. Petersburg State Medical University named after IP Pavlov of Roszdrav", Saint Petersburg, Russia St. Petersburg State Healthcare Institution "City Clinical Oncology Center", Saint Petersburg, Russia
Publication (reference): Not applicable
Trial period: First subject enrolled: 12 Apr 2006 Last subject completed: 23 Sep 2011
Objectives: **Primary:** • To define the recommended phase II dose (RPTD) of J1 (phase I) • To confirm RPTD and investigate tumor response (phase IIa) **Secondary:** • To establish the toxicity profile of J1 • To define the dose limiting toxicities (DLT) of J1 • To study the pharmacokinetic (PK) profile of J1 (Sweden) • To document any tumor response of J1 (phase I)

Methodology:

This was a prospective, single armed, open label, dose-finding phase I-IIa study. Phase I was performed to define the starting dose of intravenous J1 for phase II. Initially, an accelerated design was used, with 1 patient included per dose level according to a pre-defined dose-escalation scheme. When the first dose-limiting toxicity in the first treatment cycle occurred, the study switched to a conservative design in which 3-6 patients were planned to be included at each dose level. MTD was reached when at least 2 patients in a cohort experienced a DLT in their first treatment cycle, and the next lower dose was denoted RPTD and was used as a starting dose for phase IIa. The phase IIa of the study aimed to expand the knowledge on the tolerance and efficacy of J1 and confirm RPTD, and patients were included at RPTD with individual dose adjustment at subsequent doses.

The study started at 1 study site in Sweden (Uppsala, phase I) and thereafter a second study site (Stockholm, phase IIa) was added. Prior to the addition of 2 study sites in Russia (Saint Petersburg), the protocol was amended and updated to a version that did not include blood sampling for PK analysis. This version of the protocol was only intended for the part IIa-part of the study performed at the study sites in Russia.

Number of patients (planned and analysed):

A maximum of 40 patients were planned to be included in the study. After addition of the study sites in Russia (with a planned number of patients of 16), the number of patients were 29 in Sweden and 16 in Russia. The total number of patients in the study was therefore 45.

Phase I: 7 patients were included in phase I of which 7 patients were included in the safety analysis set and 5 in the efficacy analysis set

Phase IIa (Sweden): 22 patients were included in phase IIa of which 22 patients were included in the safety analysis set and 12 in the efficacy analysis set

Phase IIa (Russia): 16 patients were included in phase IIa, 16 patients were included in the safety analysis set and 10 in the efficacy analysis set

Diagnoses and main criteria for inclusion:

Adult patients with different solid tumors and hematological malignancies were included in this study. All patients fulfilled the criteria to be in good performance status (Karnofsky performance status ≥70%) and with preserved major organ functions (neutrophils $>1.5x10^9$/L, platelets $>100x10^9$/L, bilirubin <30 μmol/L, glomerular filtration rate >50 mL/min and normal prothrombin complex/international normalized ratio unless treated with warfarin), not amenable to standard anticancer therapies but in need of medical cancer treatment.

Study treatment and dosage:

Test product: J1 (L-Melphalanyl-p-L-fluorophenylalanine ethyl ester hydrochloride, melflufen) formulated as a concentrate (50 mg/mL [batch 2013641] and 25 mg/mL [batches 00605 and 00526]) in the solvent dimethylacetamide (DMA). The concentrate was diluted in 5% glucose solution before infusion (maximum 60 min from preparation to end of infusion)

Study treatment: 30 min iv infusion on day 1 each treatment cycle with 21 days between treatments, and with the possibility to postpone the dose up to 3 weeks waiting for clinically relevant adverse events (AEs) to return to grade 1 or less (Sweden) or grade 2 or less (Russia). For efficacy evaluation, the patient should have received at least 3 treatment periods. Patients that had partial response (PR) or stable disease (SD) after cycle 3 could continue treatment within the study up to a maximum of 6 treatment cycles.

Criteria for evaluation:

Safety: Standard AE reporting according to National Cancer Institute Common toxicity criteria (CTC) v2.0, laboratory assessment including biochemistry, haematology, urine analysis and pregnancy test, vital signs, body temperature, body weight, Karnofsky performance status, electrocardiogram (ECG) and physical examination.

Efficacy: Tumor response according to RECIST criteria evaluated every 3rd treatment cycle.

Pharmacokinetics (PK, applicable for all patients in Sweden): Sampling was performed on day 1 of

cycles 1 and 2. Plasma concentrations of J1 and melphalan were analysed.

Statistical methods:

No hypothesis testing was planned and all endpoints were evaluated descriptively. The safety population included all patients who received any amount of J1 and the efficacy population all patients who received at least 3 treatment cycles of J1.

Results, safety:

The experience of treating humans with J1 is limited. In the phase I dose finding part of this first-in-man clinical study, J1 (25-130 mg) was administered to seven patients with advanced solid tumor disease, as a 30-min intravenous infusion every 3rd week in a total of 25 treatment cycles. Dose limiting toxicity was found to be bone marrow related, i.e. neutropenia and thrombocytopenia, mainly occurring at doses of 75 mg or above. The dose recommended for phase II was established at 50.

In the subsequent phase IIa part of the study in Sweden and Russia a total number of 38 patients (22 in Sweden, 16 in Russia) have been treated with a total of 115 infusions (SWE: 64 cycles at doses 25-75 mg + RUS: 51 cycles at doses 30-50 mg). The most common AE reported in the phase IIa part of the study were bone marrow toxicity related events such as neutropenia and leukopenia reported in roughly 75%, thrombocytopenia in 50% and anemia in 40% of the patients. Even though 28 of the 38 patients (75%) reported neutropenia at least once during the course of the phase II part of the study, only 4 cases of febrile neutropenia were reported. General symptoms commonly connected with advanced cancer disease, especially when undergoing cytotoxic chemotherapy treatment, such as nausea, fatigue and asthenia were reported in 26-45% of the patients. The majority of these general symptoms were of CTC severity of grade 1-2.

In total 140 treatment cycles (25-130 mg) were administered to 45 patients in the three parts of the study. A total of 24 patients reported 37 SAEs, of which 22 events were assessed as related to study medication. All of the related SAEs, with two exceptions, were events commonly seen in connection to treatment with alkylating agents (bone marrow related, GI events and fatigue). The exceptions were one CTC grade 2 event of subileus that occurred in patient 149 and one CTC grade 2 event of ascites that occurred in patient 307.

The most important side effects of J1 are thrombocytopenia and neutropenia. In the completed phase I and IIa study, 36 patients with solid tumors were treated with the recommended phase 2 dose (50 mg) in their first cycle. The results show that 13 of these 36 patients reported grade 3-4 neutropenia compared with 3 patients reporting grade 3 thrombocytopenia (No patient reported grade 4 thrombocytopenia). All three patients reporting grade 3 thrombocytopenia also reported grade 3-4 neutropenia during the same cycle. Previous treatment with several chemotherapy regimens appeared predictive of hematological toxicity, while patient weight did not.

It should be noted that the DLT criteria in the present study were conservative since a grade 3 thrombocytopenia or grade 4 neutropenia at any time during the cycle was regarded as a DLT regardless of clinical consequences or recovery to the next dose on day 22. Recovery of blood counts to the day of next treatment cycle (day 22) is most often of greater clinical interest and future studies will explore whether J1 is well tolerated also in later cycles. In the performed study in 45 patients, the hematological toxicity in the first cycle led to delay of the second dose in 8 cases. In four of these, the first cycle dose was 75 mg or higher (Patient 106, 108, 109, 110). Out of 36 patients treated with 50 mg in their first cycle, subsequent cycles were delayed because of hematological toxicity in four patients (103, 118, 303, 304), and one patient (no 117, female with ovarian cancer) was withdrawn from the study after the first dose of 50 mg J1 due to severe thrombocytopenia.

In the Swedish part of the study (Phase I and IIa), it was observed that previous chemotherapy treatment appeared predisposing to hematological toxicity. The study population was however heterogeneous with respect to diagnoses included and drugs given, and no detailed analysis was possible. The Russian phase IIa study consisted of two separate groups of patients that were different in this respect, and where all patients started with 50 mg J1. The ovarian cancer patients (n = 8) had received on average 3.9 prior chemotherapy regimens, while the NSCLC (n=8) patients only had received 2.5. It was observed that in patients having 3 or more previous regimens of chemotherapy, 90% (9 out of 10) of the patients had a bone-marrow related DLT/DHT compared to 20% (1 out of 5) of patients that had prior treatment with 2 or less chemotherapy regimens. Dose reductions were done in six of seven ovarian cancer patients receiving more than one dose of J1 (the remaining patient received only one dose), but not in any of the NSCLC patients (however, one patient discontinued after 2nd dose due to G-CSF need). Data suggest that the J1 effect on the bone marrow

is to at least some extent dependent on the size of the existing bone marrow capacity and the regenerative capacity of the bone-marrow. The J1 safety findings are not obviously different from the known melphalan adverse event profile when used at eqimolar amounts.

In summary, dose-limiting toxicity (DLT) was found to be bone marrow related, i.e. neutropenia and thrombocytopenia, mainly occurring at doses of 75 mg or above. The dose recommended for phase II was initially established at 75 mg, but later decreased to 50 mg following the execution the phase IIa part of the study in 38 patients. Grade 3-4 thrombocytopenias were less frequent than neutropenias and these only occurred in patients with severe neutropenia. Even though neutropenias were reported in roughly 75% of the 38 patients in the phase IIa part of the study, only 4 febrile neutropenias occurred. It should however be noted that a few cases with long-lasting thrombocytopenia warrants attention in future studies. The interpretation of the side effects profile is complicated by the heterogeneity of this study population of advanced cancer patients (with variable bone marrow reserves related to bone disseminated disease and different previous treatments) and the study design with frequent dose changes (between 25 and 130 mg).

Since J1 is early in its development it is advisable to design future clinical protocols with caution especially for patients who have been heavily pretreated and/or have a disease that is known to adversely affect the bone marrow.

Results, efficacy, PK:

Tumor response:

Early efficacy data based on radiology after three treatment cycles (n = 27 patients) show that there is one patient with a partial response (ovarian cancer), 18 patients (67 %) with stable disease and 8 patients (30 %) with progressive disease. Eighteen patients (40%) were not evaluated after three cycles due to earlier discontinuation from the study.

Out of 29 included patients in the phase I and IIa part in Sweden, 17 were evaluated for tumor response after 3 cycles of J1, and of these, one patient had a partial response (PR), 11 had stable disease (SD), and 5 had progressive disease (PD). Reasons for discontinuation prior to evaluation (12 patients) was disease progression after 1 (4 patients) or 2 cycles (3 patients), death (1 patient), or hematological toxicity (1 patient), best interest of the patient (2 patients), and quality problem with the study drug (1patient).

Out of 16 included patients in the phase IIa part in Russia, 10 were evaluated for tumor response after 3 cycles of J1. These 10 included 5 ovarian cancer patients of who 4 had SD, and 1PD, and 5 NSCLC patients, where the evaluation showed SD in 3 and PD in 2. Three (3) ovarian cancer patients were non-evaluable as they discontinued the study before the third cycle due to toxicity. Two (2) of these patients were lost to follow-up and 1 received supportive G-CSF (exclusion criteria). Three (3) non-evaluable NSCLC patients discontinued the study before the third cycle due to death related to progression, hematological toxicity (and G-CSF treatment), and best interest of the patient (atrial flutter), respectively.

J1 is early in its development and it is not possible to reach a definite conclusion from this small and heterogeneous study population even though encouraging signs of tumor response have been documented.

Pharmacokinetic analyses:
In summary, administration of J1 as an intravenous infusion resulted in a rapid and extensive formation of melphalan, which was thereafter eliminated from plasma in accordance with the known pattern seen after direct administration of melphalan. Melphalan exposure increased largely in relation to dose and the interoccasion variability in exposure between treatment cycles was limited after administration of the same dose amount. Gender and body weight had no influence on the PK parameters of melphalan.

Conclusions:

The performed trial was conducted at three sites (Uppsala 19 patients phase I and IIa, Stockholm 10 patients phase IIa, St Petersburg 16 patients phase IIa), in adult patients with solid tumor malignancy not amenable to standard anticancer therapies but in need of medical cancer treatment. In total these 45 patients received 140 cycles (30-min intravenous infusion every 3rd week) of the study drug at doses ranging from 25 to 130 mg. The performed study provided information to adequately conclude on primary objectives; which were.

- **To define the recommended phase II dose (RPTD) of J1 (phase I)**
  The RPTD was set to 75 mg, and the dose limiting effect appeared to be reversible hematologic toxicity. Doses exceeding this level (6 doses at 100 mg, and 2 doses of 130 mg) generally resulted in delay of subsequent dose while recovering peripheral blood values.

- **To confirm RPTD and investigate tumor response (phase IIa)**
  The three first patients (all ovarian cancers) included in the phase IIa part started at RPTD 75 mg, and had to delay and reduce the dose in the second cycle due to hematological toxicity. This resulted in an adjustment of starting dose to 50 mg, which was better tolerated. Reversible hematological toxicity was confirmed as dose limiting, and monitoring suggests nadir values around day 13 (leukocytes), 15 (neutrophils) and 17 (platelets). Twenty-seven (27) patients were evaluated for tumor response by CT after three cycles of treatment, results showed 1 patient with a partial response (ovarian cancer), 18 patients (67 %) with stable disease and 8 patients (30 %) with progressive disease.

The conclusions in relation to the secondary objectives were:

- **To establish the toxicity profile of J1**
  A total of 22 patients (49 %) reported 37 SAEs, of which 22 were assessed as related to study medication. All of the related SAEs with two exceptions (subileus and ascites)were events commonly seen in connection to treatment with alkylating agents (bone marrow related, GI events and fatigue).
- **To define the dose limiting toxicities (DLT) of J1**
  The most important side effects of J1 were thrombocytopenia and neutropenia. In the completed phase I/IIa study, 36 patients with solid tumours were treated with the adjusted recommended phase 2 dose (50 mg) in their first cycle. The results show that a total of 13 of 36 patients reported grade 3-4 neutropenia compared with 3 patients reporting grade 3 thrombocytopenia in their first cycle. All 3 patients reporting thrombocytopenia also reported grade 3-4 neutropenia during the same cycle. Previous treatment with several chemotherapy regimens appeared predictive of hematological toxicity, while patient weight did not.
- The PK profile was assessed and results are displayed in a separate report. It was concluded that administration of J1 as an intravenous infusion resulted in a rapid and extensive formation of melphalan, which was thereafter eliminated from plasma in accordance with the pattern seen after direct administration of melphalan. Gender and body weight had no influence on the PK parameters of melphalan following administration of J1 thus supporting giving a fixed dose to patients in future studies.

Date of report:

27 Feb 2013