there is no clear data regarding the frequency and outcome of patients admitted in ICU while included in phase I clinical trials.
Methods: We conducted a retrospective study evaluating all patients admitted in ICU among the 270 consecutive patients enrolled in phase I clinical trials at Institut Gustave Roussy over a 2-year period. We assessed the characteristics and outcome of the patients admitted in ICU. The study endpoints were frequency of ICU admission and 2-month mortality rate.
Results: A total of 270 patients were enrolled in phase I clinical trial between January 2007 and January 2009. Only 11 patients required ICU admission (4.0%). Median age was 54 (48−70) and 5 (45%) were male. The most common cancer was non-small cell lung cancer (n = 5; 45%). Admission occurred within the first month following inclusion for 54% of patients (median = 26 days). The most common reason for ICU transfer was respiratory failure (6/11; 54%). The majority of patients required ventilation support (6/11; 54%) and 4 patients (36%) required vasopressors drugs. The ICU transfer was due to toxicity in 5 patients (45%). The majority of patients had progressive-disease (6/11; 54%) at the time of transfer to ICU. In-ICU mortality was 45%. The 2-month mortality rate was 54%.
Conclusion: ICU admission is rare in patients enrolled in phase I clinical trial. Around 50% of patients admitted in ICU are alive 2 months after discharge. Drug-related toxicity is the reason of admission for 45% of patients. Hence, early collaboration with ICU physicians is mandatory in this setting and ICU admission should be favourably considered for patients enrolled in phase I clinical trial.

1235 POSTER

A phase-I study of the combination of intravenous reovirus (REOLYSIN ®) and gemcitabine in patients with advanced cancer

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Background: Reovirus serotype 3 (REO) is a Dearing strain, non-enveloped virus with limited pathogenicity in humans. REO is an oncolytic virus that specifically targets cells with activated Ras signalling and gemcitabine (GEM) has shown efficacy in a wide range of tumors commonly driven by activated Ras signalling. Moreover, multiple pre-clinical experiments suggest that REO is able to synergize with GEM.
Materials and Methods: This open-label, dose-escalating phase-I trial studied the combination of intravenous (iv) REO, starting at 3×10^9 $TCID_{50}$ d1−5 and iv GEM, 1000 mg/m^2 d1 and 8 in a 3 week cycle. We planned to dose escalate Reo. Primary endpoints were: the maximum tolerated dose (MTD), dose limiting toxicity (DLT), safety profile of REO/GEM and to establish a recommended phase 2 dose (RP2D). Secondary endpoints were: evaluation of the immune response, evaluation of pharmacokinetic profiles of both REO and GEM and to describe any anti-tumor activity.
Results: Since July 2007, 16 heavily pre-treated patients entered this trial. The first 2 patients on study both had a DLT (patient 1: transaminase increase; patient 2: Troponin-I increase) probably related to both drugs. The protocol was amended and the dose of REO was adjusted to 1×10^9 $TCID_{50}$, d1 of each cycle and increased in subsequent cohorts to 3×10^9, 1×10^{10}, and 3×10^{10} $TCID_{50}$, d1. In total 47 cycles were administered resulting in multiple expected toxicities including fever, headaches, rhinorrhea, fatigue and myelosupression. In the cohort with 3×10^{10} $TCID_{50}$ we observed 1 DLT in a 3 patient cohort, being a transient grade 3 transaminase rise probably related to REO. Of the 11 pts evaluable for response, 2 pts (breast and nasopharyngeal) had PR and/or clinical response and 5 pts had SD for up to 4−8 cycles, amounting for a total disease control rate (CR+PR+SD) of 64%. Interestingly, the pharmacodynamic parameters showed significant abrogation of the neutralising anti-reoviral antibody (NARA) response (<50-fold increase) when compared to our previous experience with single agent intravenous REO.
Conclusion: REO and GEM could not be combined at full dose but after dose reduction of the REO the combination is well-tolerated and results in disease control for 64% of patients. We did not establish an MTD but REO 1×10^{10} $TCID_{50}$ d1 combined with GEM would be acceptable as RP2D.

1236 POSTER

Assessment of pharmacodynamic effect in a Phase I study of NPI-2358, an IV administered vascular disruptive agent, using dynamic contrast-enhanced MRI

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Background: NPI-2358 is a vascular disrupting agent that inhibits tubulin polymerization, leading to endothelial cell swelling, increased vascular permeability, and disruption of blood flow. It was an aim of this study to measure this effect in humans using dynamic contrast-enhanced MRI (DCE-MRI), and to determine whether NPI-2358 shows a dose-dependent treatment effect.
Materials and Methods: DCE-MRI data were acquired at two time points (baseline and 4 hours post-dose) for 17 patients with advanced solid tumors enrolled in clinical trial NPI-2358–100 (Nereus Pharmaceuticals) using a standardized protocol at three imaging sites. Imaged subjects were arranged into 8 cohorts, with doses ranging from 2 mg/m^2 to 30 mg/m^2. A 12 slice, 10 cm slab was imaged, with spatial resolution of 2 mm in-plane and 8 mm between images. Images were acquired in the coronal plane, with TE/TR/FA of 1.3/5.3/30 and temporal resolution of approximately 8 s per slab. K^{trans} and AUCBN(90), both of which are dependent on blood flow and vascular permeability, were measured at each pixel within each target tumor, and mean and median values were reported for each parameter.
Results: Objective vascular response (reduction >20%, based on previously measured uncertainty of $\pm$10%) was seen in 0/3 patients dosed at 6 mg/m^2 and 9 mg/m^2, in 2/5 patients dosed at 13.5 mg/m^2 and 20 mg/m^2, and in 7/9 patients dosed at 30 mg/m^2. At the highest dose level a statistically significant reduction was seen in both K^{trans} (μ = −18.4%, 95% CI = −27% to −9.6%, p = 0.006) and AUCBN(90) (μ = −17.7%, 95% CI = −24% to −11%, p = 0.001). The largest decrease in K^{trans} was 82%. CT contrast enhancement disappeared in this lesion and the patient has remained with stable disease for 15 months and continuing. No reduction was seen in the lower dose cohorts in either K^{trans} (μ = 11.2%, 95% CI = −12% to 34%, p = 0.472) or AUCBN(90) (μ = 0.38%, 95% CI = −12% to 13%, p = 0.964).
Conclusions: NPI-2358 does have a measurable effect on tumor microvasculature at the 30 mg/m^2 dose, inducing a reduction in blood flow that is reflected in reductions in both K^{trans} and AUCBN(90). This effect is dose dependent, as increasing levels of reduction are seen at higher doses. It is interesting to note that the results of this study are very similar to the previously published results for other VDAs. This consistency lends additional credibility to these results, partially offsetting the fact that they are based on a small number of patients.

1237 POSTER

Is it ethical to enrol patients with advanced solid tumor in first line therapy in Phase 1 trials?

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Background: The oncology community usually perceives phase I oncology trials as associated with poor or limited benefits and substantial risks. There is limited data concerning outcome and survival of patients treated in first line therapy within phase I trials.
Patients and Methods: We reviewed all medical charts of patients with advanced solid tumors treated in fisrt line treatment within a phase 1 trial at Institut Gustave Roussy between January 2007 and January 2008.
Results: Between January 2007 and January 2008, 58 out of 250 were enrolled in first line therapy phase I trial in organ oriented phase 1 (4) or not (2). Median age was 54 years (33−73), with 35 men and 23 women. The histological cancer types were NSCLC (35 pts), breast cancer (5 pts), SCLC (5 pts), and others (pancreas, oesophagus, thyroid, cervical cancers). Patients received a median number cycles of 6 (1−23), with investigational agents (antiangiogenic therapies: 4; apoptotic induceres: 1; mTOR inhibitor: 2) in combination in standard first line chemotherapy. Partial response was observes in 19 pts and stable disease in 38 patients. Eight patients were enrolled in a further phase 1 after progression. The median PF was 5 months. According to cancer subtype, the mPFS and OS were very similar that those reported in large phase III trials.
Conclusion: This study shows that pts with advanced solid tumor treated in first line therapy enrolled in phase I trials could benefit from such trials. The PFS observed in this cohort of pts is very similar to the one reported in first line regimens.