oncology field turned their attention to nanotechnology, with the aim of finding more effective and efficient methodologies to fight and cure cancer. Among all the nanoparticles tested, one that proved to be the most effective was the carbon nanoparticle. Carbon nanotubes (CNT) consist exclusively of carbon atoms arranged in a series of benzene rings condensed and wrapped in a tubular way. Due to their physicochemical properties, they are internalized by endocytic cells. Moreover, they are capable of carrying drugs and organic molecules such as DNA, RNA and proteins. In this work, we report on the fabrication of carbon nanofibers by a synthesis polymer (poly-ethylene glycol) combined method using metal catalysts and rapid immersion in a hot filament system fed with ethanol highly diluted in hydrogen and argon. Additionally, these nanotubes were dissolved in P85, conjugated with PIRES plasmid and compared to the comercial transfection kit Effectene (Qiagen). The results showed that carbon nanovectors are more effective than Effectene in transfection assays, suggesting their utilization as RNAi, proteins or drugs carriers in a near future.
Material and Methods: Carbon Nanotube: The carbon nanovector has been made and characterized in the Departamento de Semicondutores UNICAMP. **Functionalization**: Carbon nanotube was suspended P85 buffer (10% w/v). **Cell line:** NIH/3T3 mice fibroblast cells were acquired from the National Institutes of Health. ***In vitro* cytotoxicity:** Cells were incubated with carbon nanovectors without the polymer in concentration range of 0.008 to 1 mg/mL for 12, 24, 48 and 72 h in 96-well plates. **The MTT assay**: was performed according to manufacturer's data. **Celular Transfection:** was in accordance with Effectne (Qiagen) guide.
Results: The carbon nanotube produced by this method and suspended in P85 copolymer solution was able to carrier pIRES into the cells showing higher fluorescent intensity than Effectene. The carbon nanotube produced was not cytotoxic to tested cell.
Conclusion: The carbon nanotube is not cytotoxic and has proved to be an excellent carrier of genomic material. This carbon nanovector is going to be used in future experiments with RNAi carrier in solid tumours.

1215 POSTER

Glyco-PEGylated R-metHuG-CSF (XM22/Lipegfilgrastim) − a Novel Long-acting Once-per-cycle Filgrastim: Pharmacokinetics and Pharmacodynamics for Body Weight Adjusted Doses and a 6 mg Fixed Dose in Healthy Volunteers

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Background: Long-acting filgrastim offers the advantage of less dosing intervals when used for reduction of neutropenia and incidence of febrile neutropenia (FN) in patients treated with cytotoxic chemotherapy for malignancy. A novel once-per-cycle filgrastim (XM22/INN lipegfilgrastim) for fixed dose administration to prevent FN was designed by attaching a 20 kD PEG to glycan at natural O-glycosylation site.
Materials and Methods: The Glyco-PEGylated r-metHuG-CSF (GPF) (XM22/INN lipegfilgrastim) was intensively studied in non-clinical models. The first clinical use was in healthy volunteers in order to study pharmacokinetic and pharmacodynamic parameter as well as safety of XM22. A single dose, dose-escalating study was performed in healthy volunteers using a body weight adjusted dosing for XM22 (25, 50 and 100 μg/kg). In another cohort of healthy volunteers a single fixed dose of 6 mg lipegfilgrastim was compared versus a single fixed dose of 6 mg pegfilgrastim using a parallel group design. Pharmacokinetic and pharmacodynamic parameters were studied after all single dose s.c. administrations. Safety was studied for all healthy volunteers. Blood samples were drawn and serum levels of XM22 were detected and measured using an immunological assay based on the Mesoscale Discovery Platform and individual and mean concentration-time profiles were plotted per treatment group. Relevant pharmacokinetic parameters are described such as area under the curve (AUC), maximal serum concentration (Cmax) and half-life for XM22. The mean ANC (absolute neutrophile count) response per treatment group was chosen as pharmacodynamic parameter.
Results: A dose dependent increase in bioavailability was observed and ANC increased comparable to the comparator long acting filgrastim pegfilgrastim. Pharmacokinetic parameters for XM22 at the dose level of 100 μg/kg and for 6 mg fixed dose showed a higher bioavailability of XM22 compared to an equivalent dose of the clinically used long acting filgrastim pegfilgrastim/Neulasta® (about 60% higher AUC). Furthermore, a higher pharmacodynamic effect of XM22 was found compared to the equivalent dose of the comparator long-acting filgrastim pegfilgrastim (about 30% higher ANC response). XM22 was well tolerated in all healthy volunteers treated.
Conclusions: The clinical data on pharmacokinetics and pharmacodynamics confirm that the novel long-acting filgrastim XM22 − developed by using a glyco-PEGylation platform technology − is suitable to be further studied for a once-per-cycle fixed dose use to prevent FN in patients. Pharmacokinetic and pharmacodynamic characteristics demonstrate a dose-dependent increase of the bioavailability of lipegfilgrastim and consequently a dose-dependent increase of the ANC. Based on this study a dose of 100 μg/kg lipegfilgrastim was selected as the optimal dose level for further studies.

1216 POSTER

Albumin-fusion R-metHuG-CSF (Balugrastim) − a Novel Long-acting Once-per-cycle Fixed Dose Filgrastim: Pharmocokinetics and Pharmacodynamics in Breast Cancer Patients

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Background: Long-acting filgrastim offers the advantage of less dosing intervals when used for reduction of neutropenia and incidence of febrile neutropenia (FN) in patients treated with cytotoxic chemotherapy for malignancy. A novel once-per-cycle filgrastim (INN balugrastim) for fixed dose administration to prevent FN was developed using an albumin-fusion platform technology by fusing r-metHuG-CSF to human serum albumin.
Materials and Methods: The recombinant albumin-fusion protein balugrastim − composed of filgrastim and human serum albumin − was intensively studied in non-clinical models. The first clinical use was performed in breast cancer patients to study pharmacokinetic and pharmacodynamic parameters as well as observe the safety of balugrastim. In a first pilot phase a cohort of 13 breast cancer patients received escalating doses of balugrastim (50, 150, 300 and 450 μg/kg) 14 days prior to their doxorubicin + docetaxel chemotherapy. Pharmacokinetic and pharmacodynamic parameters were studied after a single dose s.c. administration. Safety was studied for all patients. Blood samples were drawn for the measurement of balugrastim serum levels. Relevant pharmacokinetic parameters are described such as area under the curve (AUC), maximal serum concentration (Cmax) and half-life for balugrastim. The mean ANC (absolute neutrophile count) response per treatment group was chosen as pharmacodynamic parameter.
Same pharmacokinetic and pharmacodynamic parameters were checked later on in cycle 1 in breast cancer patients receiving an active chemotherapy treatment of doxorubicin and docetaxel.
Results: A dose dependent increase in bioavailability was observed and ANC increased comparable to historical data for the comparator long acting filgrastim pegfilgrastim. Pharmacokinetic parameters for balugrastim at the dose level of 450 μg/kg were comparable to 6 mg fixed dose s.c. pegfilgrastim. Balugrastim was well tolerated in all patients treated.
Conclusions: The clinical data on pharmacokinetics and pharmacodynamics confirm that balugrastim − a novel recombinant albumin fusion long-acting filgrastim − is suitable for a once-per-cycle fixed dose use to prevent FN in patients. Pharmacokinetic and pharmacodynamic characteristics demonstrate a dose-dependent increase of the bioavailability of the drug and consequently a dose-dependent increase of the ANC. Based on this study a dose of 450 μg/kg was selected and recommended for the phase II study for balugrastim.

1217 POSTER

Discovery and Evaluation of 3-phenyl-1H-5-pyrazolylamine-based Derivatives as Potent, Selective and Efficacious Inhibitors of FMS-like Tyrosine Kinase-3 (FLT3)

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Preclinical investigations and early clinical trial studies suggest that FLT3 inhibitors offer a viable therapy for acute myeloid leukemia. However, early clinical data for direct FLT3 inhibitors provided only modest results because of the failure to fully inhibit FLT3. In this study, we have designed and synthesized a novel class of 3-phenyl-1*H*-5-pyrazolylamine-derived compounds as FLT3 inhibitors which exhibit potent FLT3 inhibition and high selectivity toward different receptor tyrosine kinases. The structure-activity relationships (SARs) led to the discovery of two series of FLT3 inhibitors, and some potent compounds within these two series exhibited comparable potency to FLT3 inhibitors sorafenib and ABT-869 in both wt-FLT3 enzyme inhibition and FLT3-ITD inhibition on cell growth (MOLM-13 and MV4;11 cells). In particular, one selected compound exhibited the ability to regress tumours in mouse xenograft models using MOLM-13 and MV4;11 cells.