The objective of this study was to assess physical, chemical and biological stabilities of diluted rtx (1 and 4 mg/ml) for six months at 4ºC.
Materials and Methods: Three batches were prepared under aseptic conditions in normal saline for each concentration in Feeflex® bags and stored at 4ºC during 6 months. Samples were withdrawn and analysed at days D0, D14, D30, D90 and D180. Results obtained at different times of storage were compared to those at day 0. Various complementary qualitative and quantitative analytical methods were used to determine changes in physicochemical properties of rtx including size exclusion (SEC) and cation exchange HPLC (CEX), dynamic light scattering (DLS) and turbidimetry, UV spectrometry and peptide mapping HPLC after trypsin/ endopeptidase digestion. Tertiary structure destabilisation was studied by examining aggregation vs temperature curves and determining the corresponding melting point. Biological stability was assessed by comparison of the rtx-induced cytotoxicity curves using CD-20 expressing RAJI lymphoma cells.
Results: No modification of chemical, physical and biological properties of rtx was observed after 6 months of storage whatever the methods used. By CEX, SEC and peptide mapping, no significant change in chromatographic profiles was detected. The mean hydrodynamic diameter stayed unchanged (11.5±1.0 nm) without additional populations. The melting point remained unchanged at 72.6ºC. No increase in absorbance at 350 nm was noticed indicating the absence of aggregation. The IC_{50} and the area under the cytotoxicity curves (AUC) were not significantly different (IC_{50}: 137 vs 126 μg/ml; AUC: 25334 vs 25077 $\mu g/ml.days^{-1}$; D0 and D180 respectively).
Conclusion: Contrary to the manufacturer claims, diluted rtx is stable up to 6 months at 4ºC. This longer stability could authorize the anticipated preparation or batches by pharmacy centralized units which could also induce an important decrease of costs.

1306 POSTER

Accuracy of Clinical Judgment of Progressive Disease in Phase II Trials

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Background: The diagnosis of progressive disease (PD) is a key element for assessment of clinical activity of new drugs in contemporary phase II trials. In some cases, PD is assessed by the physician before the planned imaging. In this study, we attend to analyze the value of the PD based on clinical judgment.
Materials and Methods: We have conducted a single-center retrospective study to analyze the diagnostic performance of clinical judgment compared to planned imaging with respect with PD. The medical records of all patients enrolled in our institution in phase II trials investigating systemic treatments for advanced solid tumours between January 2008 and November 2010 were independently reviewed. Diagnostic accuracy of the clinical judgment of PD was examined as a diagnostic test, in comparison to PD diagnosed by imaging according to RECIST.
Results: 84 from 129 patients (65%) included in 32 different and consecutive phase II trials experienced PD during trials and 27 discontinued trials for reasons other than PD. Eighteen patients are currently treated according to these phase II trials. 47 PDs were documented by planned imaging without clinical signs of progression. One patient experienced biological PD without radiological confirmation. Out of the 36 patients who experienced clinical PD, imaging was not available at clinical progression in 7 cases. In 29 cases where imaging was available at clinical PD, radiologic PD was confirmed in 28 cases. The positive predictive value (PPV) and the specificity of clinical judgment of progression was very high (>90%). Conversely, sensibility and the negative predictive value (NPV) were low (<40%). As a result, and since most PDs were asymptomatic, the accuracy of clinical judgment of PD was 49%. We have conducted a sensitivity analysis (worst-case and best-case scenario) to take into account the 6 clinical suspicion of PD without confirmatory imaging; the PPV range from 77% to 97% and the NPV range from 33% to 46%.
Conclusions: According to this study, the clinical judgment of PD is highly predictive of radiological PD assessed by RECIST. By default, clinical judgment of PD appears as an acceptable criteria defining tumour progression.

1307 POSTER

European Consensus Conference on the Practical Stability of Anticancer Drugs

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Background: Stability studies performed by the pharmaceutical industry are only designed to fulfill licensing requirements. Thus, post-dilution or -reconstitution stability data are frequently limited to 24h only for bacteriological reasons regardless of the true chemical stability which could be largely longer. In practice, the pharmacy-based centralized preparation may require in advance preparations for several days, filling of ambulatory devices for continuous infusions or batch preparations for dose banding. Furthermore, a non justified limited stability for expansive products is obviously very costly. Thus, there is a strong need for additional stability data covering practical uses of anticancer drugs.
Method: A European conference consensus was held in France, May 2010, under the auspices of the French Society of Oncology Pharmacy (SFPO) to propose adapted rules on stability in practical situations and guidelines to perform corresponding stability studies.
Results: For each anticancer drug, considering their therapeutic index, PK/PD variability, specific clinical use and risks related to degradation products, the limit of 10% of degradation can be inappropriate. Therefore, acceptance limits must be clinically relevant and should be defined drug by drug. Design of stability studies has to reflect the different needs of the clinical practice (preparation for the week-ends, outpatient transportations, implantable devices, dose banding. . .). It is essential to use validated stability-indicating methods, separating degradation products being formed in the practical use of the drug. Sequential temperatures design should be encouraged to mimic problems seen in daily practice such as rupture of the cold-chain. Stressed conditions are recommended to evaluate not only the role of classical variability factors (i.e. pH, temperature, light) but also the mechanical stress. Physical stability (particles formation) should be systematically evaluated. Consensus conference focused on the need to perform more studies on the stability of biotherapies including a minimum of 3 complementary separative methods, careful evaluation of sub-micronic aggregates. The determination of the biological activity could be useful.
Conclusion: A guideline on the practical stability of anticancer drugs has been proposed to covert the current clinical and pharmaceutical practices. It should contribute to improve their security of use, to optimize centralized handling and to reduce costs.

1308 POSTER

Paclitaxel-related Interstitial Lung Disease − Implication of Mediastinal Lymphadenopathy

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Background: Drug-related interstitial lung disease (ILD) is rare but serious adverse reaction in patients with solid tumours treated with cytotoxic systemic chemotherapy. Paclitaxel (PTX) is widely used worldwide against solid tumours, including lung, breast, gastric, and ovarian cancer. However little is known about PTX in regard to the risk factors for developing ILD.
Material and Methods: We reviewed patients treated with PTX at our institute between January 2007 and December 2008. Clinicopathological data was retrieved from medical records. Chest CT prior to the administration of PTX was reviewed and evaluated whether the patient had pre-existing ILD and mediastinal lymphadenopathy. PTX-related ILD was defined as the bilateral interstitial shadow developed during the course of PTX administration and lack of evidence for other cause. Correlation with PTX-related ILD and clinicopathological data was investigated.
Results: A total of 192 patients were included. Median age was 66 years (range 33–86) and 99 patients (52%) were female. Primary site of disease was lung (n = 83; 43%), breast (n = 34; 18%), stomach (n = 31; 16%), ovary (n = 30; 16%), and others (n = 14; 7%). Median number of PTX administration was 8.5 doses (1−56). PTX was administered weekly in