1302 POSTER

Rapid Desensitization for Rituximab Hypersensitivity: Standard Protocol and Case Report

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Background: Rituximab (R) is a genetically engineered chimeric mouse/human monoclonal antibody indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy (CT).
Hypersensitivity reactions (HRs) to CT often prompt permanent discontinuation and deprive the patient of the most active regimen. In this study we evaluate the safety and effectiveness of a rapid desensitization protocol for achieving temporary tolerization to Rituximab used in a patient with HR.
Methods: We report the case of a 41-year-old male diagnosed in Sep 2009 with follicular lymphoma grade II, stage IV FLIPI IV. He was initially treated according to protocol R CHOP14, developing mild hypersensitivity reactions to R in the first two cycles, being severe during the third cycle, which led us to discontinue treatment with R and went on CT to complete eight cycles of CHOP until Jan 2010, with documented partial remission response. The patient was followed without any medical treatment until July 2010, when he presented progression of the disease and was intended to treat with the combination R-Bendamustin every four weeks, with previous desensitization to this agent in collaboration with Intensive Care Unit (ICU)and the Allergy Department. Safety and effectiveness of the protocol were assessed by review of treatment records.
Results: The patient who had HRs in response to treatment with R received rapid desensitization to this agent with a standardised 12-step protocol. Three solutions (each 250 ml of water with 5% dextrose) were delivered in 12 consecutive steps at increasing infusion rates. Solution A was a 100-fold dilution of the final target concentration (steps 1−4), solution B, 10-fold (steps 5−8), and solution C contained the total dose for the patient calculated based on his body surface. This 3-solution, 12-step protocol delivered doubling drug doses by step, infusing the target dose over 6 h.
Dexamethasone (20 mg, orally) was administered the night before and the morning of R desensitization and Montelukast (10 mg, orally) the nigth before. In addition, dexchlorpheniramine (5 mg, intravenously), ranitidine (50 mg, intravenously) and granisetron (3 mg, intravenously) were administered 30 minutes before the initiation of the protocol.
The patient was administered six courses of this protocol, with the first two administered in ICU because some mild HR, managed by slowing the infusion rate and beginning the infusion of the next course in slower rate. The patient received successfully the remaining four courses in the outpatient department, without any clinical complications nor HRs.
Conclusion: The rapid desensitization protocol was safe and effective in our patient and allowed us to continue appropriate chemotherapy for his condition.
This study warrants the incorporation of the protocol into standard clinical practise in our community.

1303 POSTER

Sequential Therapy and Immortal Time Bias in Register Studies

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Background: Metastatic renal cell cancer (mRCC) has a poor prognosis and medical treatment options were limited until a few years ago. Since then, six targeted therapies have entered the market. This raises the issue on what therapy gives the best outcome. Giving drugs in sequence has attracted particular attention, as it has been hypothesized that the order by which they are administered may have an impact on the treatment outcome. Sweden has a long-standing tradition of maintaining nationwide health-care registers, including data on all patients diagnosed with cancer. Since five years, the same has applied to the dispensation of pharmaceuticals at the pharmacy level. This means there are unique opportunities for research on how medical treatment for different diseases is used in the Swedish population.
The objective of this study is to compare two methods of analysing register data for two drugs given in sequence to patients with mRCC.
Material and Methods: National registers on prescribed drugs, cancer and cause of death were linked. Information on treatment patterns and outcomes was extracted.
The data was analyzed by two different methods. At first, the observed data from the registers were used i.e. the outcomes of patients actually subjected to sequential treatment were studied (A1). Then four hazard functions were developed, where the risk of interrupting therapy or dying during 1st line treatment was accounted for (A2). The rationale was to avoid the problem of immortal time bias, prevailing in A1, namely that only those surviving 1st line treatment had been subjected to 2nd line in the observed data set.
Results: It was possible to assess that the sequence of therapies has impact on the outcome by either A1 or A2. The last mentioned method allows an estimation of the hazard function at the end of the second therapy or death as well as the hazard function of death alone. From the hazard functions a number of quantities such as survival function, median and mean could be calculated.
Conclusion: A2 is advantageous as immortal time bias is avoided and as data from all patients having received at least one of the study drugs are considered, an aspect of particular importance in small populations.

1304 POSTER

Can We Detect Any Ethnic Differences in Toxicity in Early Phase Clinical Trials for Anticancer Drugs?

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Background: During anticancer drug development, it is important that ethnic differences in efficacy and safety are evaluated in order to determine an optimal dose and administration of the drug in a phase 3 trial and in clinical practice. The objective of this study was to explore the possibility of detecting any ethnic differences in toxicity in early phase clinical trials.
Material and Methods: We reviewed the data from phase I clinical trials of new molecular entities conducted in Japan and Western countries, which were reviewed by the Pharmaceuticals and Medical Devices Agency (PMDA) and approved by the Ministry of Health, Labour and Welfare in Japan between September 1999 and March 2011. The maximum tolerated dose (MTD), the recommended phase II dose (RP2D) and the approval dose of the Japanese were compared with those of the Western, based on the review reports of the PMDA, the published study reports and the articles. Among them, the drugs of which the MTD, RP2D or approval dose differed between the Japanese and the Western were retrospectively analyzed with the safety profile and the frequency of adverse event.
Results: Thirty-nine drugs were approved as new molecular entities in Japan. Among them, 10 drugs were ruled out from the analysis; four were not approved in both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), three were hormonal drugs, two that Phase I was not conducted for in Japan, and one that the MTD was not determined for in Phase I trials in the EU and the US. Three out of the 29 remaining drugs (capecitabine, fludarabine and topotecan) showed differences in all of the MTD, the RP2D and the approval dose between the Japanese and the Western. And, temsirolimus showed difference only in the MTD, three out of 6 patients had serious adverse events (2 had interstitial lung disease, 1 had pneumonitis) in a clinical trial which was conducted to examine the tolerability of temsirolimus for the Asian at the RP2D in the Western. Based on the radiological review of chest computed tomography scans performed retrospectively, drug-related pneumonitis were found in 45 of the 77 evaluable Asian patients (58%) compared with in 52 of the 178 evaluable Western patients (29%).
Conclusions: The differences in MTD in phase I trials were associated with some ethnic disparities in toxicity. It might be worthy to evaluate the ethnic differences in toxicity in early phase clinical trials for future anticancer drug development.

1305 POSTER

Extended Physicochemical and Biological Stability of Diluted Rituximab Solutions Stored 6 Months at 4ºC

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Background: Rituximab (rtx) is the first IgG1 monoclonal antibody successfully used in onco-hematology and also for several auto-immune diseases. According to manufacturer instructions, rtx must be prepared by dilution in a 0.9% NaCl and administrated within 36 hours. Surprisingly, rtx is available in a 10 mg/ml liquid formulation exhibiting a long term stability limit (i.e. 2 years) Thus, it could be considered that a more than 1/10 dilution step under sterile conditions was unlikely to modify drastically its stability.

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