1302 POSTER

Rapid Desensitization for Rituximab Hypersensitivity: Standard Protocol and Case Report

A.R. Rubio[1], N. Cabanes[2], M.A. Cruz[3], C. Esteban[3], J.M. Martínez[1], P. Moya[1]. *[1]Hospital Virgen de la Salud, Pharmacy, Toledo, [2]Hospital Virgen de la Salud, Allergy, Toledo, [3]Hospital Virgen de la Salud, Oncology, Toledo, Spain*

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

A. Ambring[1], U. Stierner[2], A. Odén[3], I. Björholt[4]. *[1]Nordic Health Economic Research AB, Department of Outcomes Research, Gothenburg, [2]Sahlgrenska University Hospital, Department of Oncology, Gothenburg, [3]Chalmers University of Technology, Department of Mathematical Sciences, Gothenburg, [4]Nordic Health Economic Research AB, Management, Gothenburg, Sweden*

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?

T. Ogura[1], S. Morita[2], K. Yonemori[3], T. Nonaka[1], T. Urano[1]. *[1]Pharmaceuticals and Medical Devices Agency, Office of New Drug V, Tokyo, [2]Yokohama City University Medical Center, Department of Biostatistics and Epidemiology, Yokohama, [3]National Cancer Center Hospital, Breast and Medical Oncology Division, Tokyo, Japan*

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

M. Paul[1], V. Vieillard[1], E. Jaccoulet[1], A. Astier[2]. *[1]Henri Mondor Hospital Group, Department of Pharmacy, Créteil, [2]Henri Mondor Hospital Group and School of Medicine Paris 12 University, Department of Pharmacy and UMR CNRS 7054, Créteil, France*

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.