P107 STABILITY OF TRIPLE INTRATHECAL STANDARDIZED PREPARATION OF METHOTREXATE, CYTARABINE AND METHYLPREDNISOLONE SODIUM SUCCINATE

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Abstract - Introduction
Central nervous system involvement is a serious complication of acute leukemia and lymphomas. Several strategies to treat and prevent this localization of disease have been used such as intrathecal (IT) chemotherapy. A triple intrathecal combination of methotrexate, cytarabine, and corticosteroid administered simultaneously is frequently prescribed. The stability of the mixture has not yet been established and additional studies seemed necessary. Hence, the short-term stability of extemporaneously prepared triple IT therapy was evaluated.

Abstract - Material and method
The preparation was composed of 12.5 mg of Methotrexate sodium, 50 mg of Cytarabine and 40 mg of Methylprednisolone Sodium Succinate. 1 ml of water for injection was added in order to reach a final volume of 5 ml. The IT mixture was stored at 25°C, protected from light. Triplicate samples were taken after preparation and at 3, 6, 24, 48 hours (h). pH values were assessed and the solution was visually inspected. The samples were analyzed for drug content using triplicate high-performance liquid chromatography (HPLC) determinations. The microbiological stability of the preparation was tested.

Abstract - Results and discussion
The mixture was prepared in a polypropylene syringe system and was stored at 25 °C for up to 48 h after extemporaneous preparation. No variation greater than 10% of the initial concentration of Methotrexate, Cytarabine, and Methylprednisolone Sodium Succinate was observed at any time. Physical instability was defined as change in color and/or appearance and/or precipitation and pH values outside the range 7–7.5. The pH values remained close to the physiologic range. No change in color or appearance and no precipitation were observed. The concentrations after 48 h were not inferior to 90% of the initial concentration. Methylprednisolone sodium succinate was found to be the most labile component in the triple intrathecal solution. The microbiological stability test was performed by seeding on different substrates after 48 hours from the preparation, to determine if the sterility was preserved. After incubation at a temperature of 37°C for 14 days, no microbiological growth was detected.

Abstract - Conclusion
Triple intrathecal solution of cytarabine, methotrexate sodium, and methylprednisolone sodium succinate proved to be physicochemically stable for up to 48 h when stored at 25 °C and protected from light. Microbiological stability was confirmed incubating the mixture solution for 14 days and no detection of mycetes, aerobic and anaerobic bacteria was reported.

P108 Study of the relevance of osmolality measurement as a criterion for evaluating drug stability

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Abstract - Introduction
Stability studies of anticancer drugs are important for the realization of preparations in advance or standardized doses. In addition to high performance liquid chromatography (HPLC) analytical methods, osmolality measurement is used by some authors as a criterion to evaluate the stability of a drug in solution. As far as we know, no scientific publication correlates osmolality with the stability of a solution. The objective is to study this analytical technique by measuring the osmolality of injectable anti-cancer solutions whose instability has been chemically demonstrated, by HPLC.

Abstract - Material and method
Selection of five anticancer drug preparations whose chemical instability has been demonstrated in the literature. Realization of three identical samples per selected preparation and measurements of the osmolality of the freshly prepared solutions, then at different storage times until a chemical degradation of the molecule, validated by HPLC, of at least 10% and up to 50%.

Abstract - Results and discussion
Selection of five cytotoxics:
- Azacitidine 2 mg/ mL in normal saline (NS),
- Bendamustine 0.25 mg/ mL in NS,
- Busulfan 0.25 mg/ mL in NS
- Fotemustine 0.8 mg/ mL in dextrose 5% in water (D5W),
- Oxaliplatin 0.1 mg/ mL in NS,

Among these molecules, osmolality varied from 0.57% to 2.04%.
Degradation of these anticancer drugs is described in the literature: fotemustine in D5W whose degradation rate reaches 30% in 8 hours, obtains a small osmolality variation (0.57% between T0 and T8h). Similarly for bendamustine which presents a degradation rate of 27.39% after 24h against a variation of osmolality of -2.04%. None of molecules mentioned above had a clear variation of osmolality.

Abstract - Conclusion
In view of these first results, osmolality does not seem to be a criterion of choice for the study of drug stability. In the majority of the cases studied, the variation of this measure does not correlate with the loss of concentration and the appearance of degradation products of the studied molecule.

P109 Extended in-use stability of the generic nab-paclitaxel medicine Pazenir®

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Abstract - Introduction
The aim of the present study is to elucidate the maximum stability of Pazenir® in its original primary packaging under refrigeration and at room temperature to reduce drug wastage while retaining full potency.

Abstract - Material and method
Stability assays were performed by dynamic light-scattering (DLS) and reported as percentage of the hydrodynamic diameter (Dh) at the onset (day 0) and the polydispersity index (PDI).

Abstract - Results and discussion
Dispersions were more stable when stored at 3,5 °C ± 1°C (refrigeration), where the paclitaxel concentration of 2.5 mg/mL was more stable (28 days) than the higher concentration of 5 mg/mL (22 days). The one with a concentration of 0.25 mg/mL was the least stable one (16 days).
Stored at 23,5 °C ± 1°C (room temperature) stability was generally markedly reduced. Again, the concentration of paclitaxel 2.5 mg/mL was slightly more stable (8 days) than the concentrations 5 mg/mL and 250 µg/mL (7 days).

Abstract - Conclusion
Pazenir® stability was influenced by storage temperature, with longer shelf-life at 2-8°C, and also by drug concentration with the highest stability at a Paclitaxel concentration of 2.5 mg/mL.
However, the results of this study for reconstituted dispersions according to the summary of product characteristics (SPC) allow a significant extension of the shelf-live avoiding costly drug wastage.

P110 Extended time of use of reconstituted and diluted anticancer drugs: an online software on chemical-physical stability data

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Abstract - Introduction
The chemical-physical stability, reported in the Summary of Product Characteristics (SPC), indicates in-use stability of drug, but is often limited. An extended time of use of the preparation would facilitate the organization of anticancer drug compounding. The project 'Stability of reconstituted and diluted anticancer medicines', was developed by SIFaCT (Italian Society for Clinical Pharmacy and Therapeutics). The objectives of the project were the creation of an online database of stability data and the development of recommendations based on the technical characteristics of the laboratories

Abstract - Material and method
A group of pharmacists gathered data to fulfill the database. The database, called "Oncostability", is divided into two sections. The first shows the brand name, the excipients, the vehicle and the concentration of the product. The second indicates information on the reconstituted/concentrated/diluted product. It reports drug's concentration, its container, diluent, and possible incompatibilities. This section also includes the stability time expressed in hours, the storage temperature, light-protection. Data relating to the organization of the compounding units were collected through a survey

Abstract - Results and discussion
Our software allows the search through 11 parameters and setup conditions that can be selected within specific filters. Each of the 3788 records contains the bibliographic reference. A constant updating of the software guarantees the data to be aligned with the latest publications. The database was evaluated by expert pharmacists through a call for test trial. 43 oncology pharmacists confirmed its ease of use, and 70% state it can be used very often during work.
55 pharmacists involved in compounding units responded to the survey on their laboratories to define the classification of the compounding area, the environmental and biological monitoring, the use of personal protection equipment and closed system transfer devices for the manipulation of hazardous drugs.

Abstract - Conclusion
The online software is useful for evaluating the in-use stability of specific branded products prepared in centralized compounding units. Next step of the project will be the drafting of recommendations, the longest possible stability of the examined drugs according to the quality standards and validation processes of the compounding laboratories.

P111 Predictive intrinsic stability of Elagolix (EGX), pertinent to drug storage and in-use condition

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Abstract - Introduction
Elagolix (EGX) is an oral GnRH antagonist developed for endometriosis pain. As a marketed drug, EGX undergoes environmental stress, especially during storage or delivery. Therefore, a thorough investigation to understand its major degradation pathways remains mandatory, as per ICH guidelines. The goals were to: a) develop a stability-indicating HPLC method for determination and quantification of EGX in presence of its degradation products (DP), b) analyse its intrinsic stability, c) characterize its DP using liquid chromatography multistage – high resolution mass spectrometry (LC-HR-MSn).

Abstract - Material and method
EGX (purity > 98%) was purchased from Sigma Aldrich (St. Quentin Fallavier, France). The working solutions ([EGX] = 100 µg/mL) were exposed to stress conditions: acid hydrolysis (HCl 0.1N and 1N), basic hydrolysis (NaOH 0.1 and 1N), oxidation (H2O2 0.1% and 0.9%), thermolysis (80°C) and photolysis (natural light or xenon test chamber 0.5 watt/m2). Method validation was assessed using a calibration range with 9 concentration points (60 to 140 µg/mL) and 3 control points (80, 100 and 120 µg/mL), 3 replicates each, over a period of 3 successive days. Stressed samples were analyzed by LC-HR-MSn.

Abstract - Results and discussion
The samples analysis by HPLC allowed to devise a stability-indicating HPLC method. Therefore, the column selected is a Symmetry® C18 (4.6x150mm; 3.5 µm) maintained at 25°C. The flow rate, the injection volume and the detection wavelength were set at 1 mL/min, 40 µL and 222 nm, respectively. The mobile phase, composed of acetonitrile (solvent A) and water (solvent B), was set in gradient mode (0-5 min: 20% A; 5-7 min: 20 to 60% A; 7-12 min: 60% A; 12-16min: 60 to 80% A; 16-17min: 80 to 20% A; 17-20min: 20% A). EGX revealed to be extremely fragile towards photolysis and oxidative conditions. Up to ten degradation products were highlighted suggested that the transformation of EGX occurred via multiple reaction pathways. These included hydrolysis, deshydratation, oxidation or photolytic and radical N-dealkylation.

Abstract - Conclusion
The study provided strong information on the multiple reaction pathways of EGX when subjected to various stress conditions. Understanding the main degradation pathways allows to take relevant measures to reduce or avoid active ingredient instability. This knowledge is also helpful to assess and manage the risks associated with drug degradation, thereby ensuring its safety and effectiveness.

P112 Retrospective and descriptive analysis of short stability antibodies losses, prepared in French centralized preparation unit in and out of clinical trials

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Abstract - Introduction
Daratumumab (DT) (approved), Teclistamab (TC) and Talquetamab (TQ) (in clinical trials (CT)) are multiple myeloma treatments. These drugs must be performed in aseptic preparation centralized units. Administration is mainly done in Short-Term hospitalization (STH). A 4 hours stability is required for CT monoclonal antibodies (MAb) imposing strong pharmacy/wards cooperation. The DT indications extension and an increasing Mab treated patients number contribute to STH overload. Study aim is to evaluate short stability drugs' impact on preparation and ward units in costs and organization terms.

Abstract - Material and method
Data were extracted from the pharmacy's inventory management software, quality database, patient record software and stock management file and certificates of destruction for CT. Data were analyzed for the year 2021 : March 1 to December 31 for DT used in approved indications, January 1 to September 30 for TC, TQ and DT in CT. Differences between DT used in approved indications losses and CT MAb losses were analyzed using Khi² test.

Abstract - Results and discussion
Of the 1982 DT syringes delivered in approved indications, 31 (1.6%) were returned. STH wards were the main consumers (91%). Geriatric wards, located in another hospital, have the highest rate of return (0.5 % of delivery, 33% of return). Only 23 % of returned syringes were reallocated. Loss cost is estimated at 109 200€.
For CT MAb, 185 DT, 189 TC and 65 TQ syringes were produced ; 8 DT(4.3%), 6 TC (3.2%) and 1 TQ (9.2%) were lost. CT DT losses extrapolation cost is around 36 720€. In CT, Hematology STH which use Mab the most (70%) lose the fewest syringes (33%), while wards with less MAb practice (Clinical research in oncology (11%)) lost the most syringes (67%).
Return reasons mostly reveal an organizational problem, although a specific organization has been set up (Dt 58%; CT MAb 47%), and the patient's clinical condition (Dt 39%; CT MAb 47%). More losses are observed in CT than in current practice (P<0,001). Indeed CT MAb are associated with complex preadministration procedures.

Abstract - Conclusion
Low stability MAbs cause losses from CT, needing new organization: sending MAbs 2 hours after patient arrival. This contributes to the overload of STH wards with an increasing number of patients, disorganization due to loss, and home hospitalization impossibility due to low stability. The 24 hours DT expiry extension could relieve organization circuit and reduce losses promoting reallocation.

P113 Physicochemical and biological stability study of mogamulizumab in diluted solution

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Abstract - Introduction
Mogamulizumab (M) is a monoclonal antibody used in the treatment of Sezary syndrome and mycosis fungoides. The dilution of the 4 mg/ml vial of Poteligeo® in the infusion bag is stable for 24 hours at room temperature between 0.1 to 3 mg/ml. In order to make hospital preparations in advance and optimize costs, a physicochemical and biological stability study was conducted in the pharmaceutical control laboratory.

Abstract - Material and method
4 bags of M were prepared in 0.9% NaCl 250 ml 2 at 0.14 mg/ml, 2 at 0.34 mg/ml, evaluated at 20±5°C and 5±3°C, protected from light for 28 days. Analyses are performed in triplicate by HPLC-UV, concentrations are measured by HPLC after Flow Injection Analysis (FIA). Physical stability is studied by Steric Exclusion Chromatography Biozen™SEC3 column,1.8µm 300*4.6mm.Chemical stability is evaluated by assessing acidic and basic variants proportions by Cation Exchange Chromatography 6µm 250*4.6mm WCX column.Biological activity is determined by FcyRIIIa affinity chromatography 5µm 75*4.6mm Tosoh.

Abstract - Results and discussion
At D28, the quantitative determination of mogamulizumab by FIA showed a deviation of less than 5% compared to initial concentrations. No aggregates or antibody fragments were found. The proportion of acidic, basic variants and of the main peak did not deviate by more than 5% compared to D0. For all infusion-bags studied by CEC, the main peak rates were between 79.1% and 85.8%, the acidic variant rates between 6.7% and 9.9% and the basic variant rates between 7.8% and 11.2%. The proportion of each antibody species (low, medium, high affinity) did not deviate by 5% from D0, this is correlated with the ADCC activity (Antibody Dependent Cell Cytotoxicity). The low affinity rate is between 48.2% and 52.7%, medium between 39.6% and 44.8% and high between 6.9% and 7.9%. No colonies were found on chocolate agar and heart-brain broth.

Abstract - Conclusion
Mogamulizumab is physically, chemically and biologically stable for 28 days in diluted solution between 0.14 mg/L and 0.41 mg/L at 5°C and 20°C. The four bags remained sterile during the 28 days of storage.