1312 POSTER

Content Analysis of Pamphlets Provided by Pharmaceutical Companies for the Medical Usage of Oncology Pharmaceuticals

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Background and purpose: Patient information pamphlets containing drug information are educational and improve knowledge on dosage, adverse effects, and drug interactions. These pamphlets are provided by pharmaceutical companies and are convenient and appropriate; they are provided free of cost. However, these pamphlets differ in content and the volume and quality of data provided for each drug. In this study, we researched the structure and content of pamphlets produced and distributed by pharmaceutical companies in Japan for chemotherapy drugs.
Material and Method: We collected pamphlets for chemotherapy drugs at 96 components and 116 pharmaceutical drugs; pamphlets for generic drugs were not included in the study. These pamphlets had been produced and distributed between March 1962 and August 2010. We analyzed the pamphlets with regard to dosage form; mechanism of action; and total number of pages, i.e., volume of data.
Results: There were published patient 74 information pamphlet of chemotherapy in 55 of the 116 drugs. The median number of content pages in the pamphlets was 31 (range, 6–101 pages). We obtained a total of 43 pamphlets for 30 of the 71 drugs in the injectable dosage form and 33 pamphlets for 25 of the 42 drugs in the oral dosage form. We obtained 41 pamphlets for 28 of the 77 drugs that had a cytotoxic mechanism of action, 25 pamphlets for 18 of the 21 molecular-targeted drugs and 8 pamphlets for 8 of the 8 hormone preparation. The content of adverse effects was included in all pamphlets. On the other hand, the content of coping strategies for the adverse effects was included 69% (51/74 pamphlets) of pamphlets. Especially, all pamphlets of the hormone preparation had no content of coping strategies for those. The content of coping strategies for those significantly correlated with the dosage form ($p < 0.05$) and mechanism of action ($p < 0.001$).
Conclusion: Our results showed that the patient information pamphlets of chemotherapy were not enough published in Japan. The contents of the patient information pamphlets are expected to be included equally regardless of dosage form or mechanism of action. Therefore it would be required to accumulate and assess clinical information of adverse effects for chemotherapy agents, especially for molecular-targeted drugs, and to reflect in the patient information pamphlets of chemotherapy.

1313 POSTER

Stability of Diluted L-asparaginase in Normal Saline Solution

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Background: L-asparaginase (L-asp; Kidrolase®) is a homotetrameric enzyme used in the treatment of leukemia. However, its practical stability and optimal storage conditions have not been studied in detail. The aim of this study was to assess physical, chemical and biological stabilities of diluted L-asp stored during 10 days at 4ºC.
Materials and Methods: The following methods were used: size exclusion chromatography (SEC), dynamic light scattering (DLS) describing submicronic populations and corresponding mean diameters (md), turbidity (350 nm), thermal aggregation curves and determination of L-asp concentration by UV at 280 nnm (chemical stability) and enzymatic activity (biological stability). Three batches were prepared under aseptic conditions in normal saline (80 μg/ml) in Feeflex® bags and stored at 4ºC during 10 days. Aliquots were taken at days D0, D1, D3, D4, D7, 9 and D10. Results were expressed as mean±SD.
Results: No significant difference was found both for chemical and biological activities after 1 week. The melting temperature was unchanged (59.0ºC). Turbidity exponentially increased from 0.08 to 0.06 absorbance unit, indicating slight aggregation. Immediately after reconstitution, 4 peaks were found by SEC. The mean peak (tetramer 133 kDa, 84% ± 1% of the total area under curve) decreased to 70.4% ± 7.9 after 10 days. These results were confirmed by DLS analysis since 3 initial submicronic populations were found: tetrameric population: md = 9.43±0.3 nm: 99.5% of the total population; highly aggregated populations: 50 < md < 200 nm; 0.5%. After 10 days, the md of main peak was unchanged but the percentage of tetramer decreased to 97.4% with an increase of the md of others populations (up to 900 nm). Percentages of aggregated enzyme (1.4%) remained unchanged during 8 days but reached to 9.5% at D10. However, the loss of enzymatic activity was only 5.1% after day 10, suggesting that aggregated enzyme should partially retain asparaginase activity. In total, our results suggest that the loss of activity was no significant modified until 8 days.
Conclusion: The results show that diluted L-asp in normal saline solution remains stable for 7 days at 4ºC. Therefore, anticipated ready-to-use bags could be prepared by centralized pharmacy units and stored during 1 week without loss of activity. However, the slight increase of aggregates observed during the storage remains questionable in terms of potentially increased immunogenic-induced side-effects.

1314 POSTER

Quality of Reporting of Modern Randomized Controlled Trials in Oncology

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Background: Manuscript quality influences the knowledge translation capability of results from randomized clinical trials (RCTs). The CONSORT statement (Consolidated Standards of Reporting Trials) defines requirements for RCTs publication meant to ensure quality of reporting. The aim of this study was to assess the reporting quality of modern oncology RCTs and to identify characteristics predictive of manuscript quality.
Patients and Methods: A search of MEDLINE was conducted for all oncology phase III randomized clinical trials published in 10 leading medical journals between 2005 and 2009. The quality of every published RCT was assessed using an 18-point overall reporting quality score (OQS) based on the 2001 revised CONSORT statement. Multivariate linear regression was used to identify trial features prognostic for quality of reporting. Furthermore every RCT was assessed using an adjusted 27-item OQS based on the 2010 revised CONSORT statement to provide baseline data for future evaluations of manuscript quality.
Results: 357 RCTs with a median of 437 patients each were reviewed. The number of published RCTs decreased from 91 in 2005 to 53 in 2009. They were published in intermediate (<10: 27%), high (10−20: 59%) or very high (>20: 14%) impact factor (IF) journals. Pharmaceutical companies funded, at least partially, 61% of trials. Median 2001 OQS was 14 on a 0−18 scale while median 2010 OQS was 19 on a 0−27 scale. Just over 1/3rd (120) reported 12 or less items on the 2001 OQS. Poorly reported items included: method used to generate the random allocation (n = 104; 29%), whether and how blinding was used (n = 146; 41%), method of allocation concealment (n = 182; 51%) and participant flow (n = 212; 59%). A high IF ($p < 0.001$) and a recent publication date ($p = 0.004$) were the 2 independent favorable prognostic factors identified in a multivariate model. There was no impact of source of funding, geographical origin of RCTs, tumour site, treatment setting and positivity of trial results. Trials sample size was borderline significant if included in the multivariate analysis ($p = 0.115$).
Conclusion: The overall quality of RCT reporting improved from 2005 to 2009 according to 2001 CONSORT criteria, however, a number of items remained unreported in many trials. High IF journals were more likely to report RCTs adequately.

1315 POSTER

Content Analysis of "the Guidance for Proper Usage" That Are Distributed to Medical Oncologists for Promoting Oncology Pharmaceutical Safety

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Background and purpose: Oncology pharmaceuticals such as cytotoxic agents, molecular-targeted agents, and hormonal agents are used for treating solid and hematologic malignancies. Pharmaceutical companies often provide a unique guidance for proper usage to medical oncologists to facilitate proper usage of the approved drug. In this study, the revelation of the guidance for proper usage in clinical practice has been assessed.
Material and Method: Among approved oncology drug in Japan, we collected guidance for proper usage for oncology pharmaceuticals; these guidance had been published by pharmaceutical companies for medical oncologists in Japan. For each guidance for proper usage, we determined the total number of pages and the proportion of pages that discussed toxicity, drug information, and the results of clinical trials.

Multivariate regression analysis was performed to evaluate the impact of the establishment of the Japanese regulatory agency Pharmaceuticals and Medical Devices Agency (PMDA) in 2004 with respect to the contents of guidance for proper usage.
Results: From 91 approved oncology pharmaceuticals, we obtained 59 guidance for proper usage for 50 approved oncology pharmaceuticals. The median total number of pages in the guidance for proper usage was 48 (range, 11−98 pages). The proportions of pages in the guidance that discussed toxicity, drug information, and the results of registration trials were 30%, 26%, and 11%, respectively. After the PMDA was established, the total number of pages and the proportion of pages discussing the results of registration trials significantly increased ($p = 0.007$ and $p = 0.002$, respectively). On analyzing guidance published for different types of drugs, we observed that the total number of pages and the proportion of pages discussing toxicity in the case of molecular-targeted drugs was significantly greater ($p < 0.001$ and $p = 0.008$, respectively) than that for the other types of drugs, whereas the proportion of pages discussing indications was significantly lower ($p = 0.001$) than that for the other types.
Conclusion: The guidance for proper usage distributed to medical oncologists in Japan include drug information that is not provided in package inserts. The establishment of the PMDA and the type of drugs for which the guidance for proper usage were distributed may have influenced the contents of and trends with regard to the guidance for proper usage.

1316 POSTER

Oral Chemotherapy Administration Practices in Ireland

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Background: The use of oral chemotherapy (OC) and biologic therapy (BT) is increasing due to ease of administration compared with intravenous therapy, pressure on hospital resources and expanding indications for use. In Ireland, OC is prescribed by medical oncologists and dispensed by community pharmacies. The objective of this study was to assess procedures for OC and BT prescription, as well as patient monitoring and patient education practices for these agents in Ireland.
Materials and Methods: A cross-sectional survey was administered to all medical oncology specialist registrars and consultants in Ireland to assess OC and BT prescribing practices and efforts made to educate and monitor patients receiving these agents.
Results: Forty-one physicians were surveyed. Responses were received from physicians representing 7 of the 8 Irish cancer centres. Factors positively influencing prescription of OC or BT included ease of administration (76%) and patient travel considerations (71%). All respondents believed that BT should be prescribed only by medical oncologists and that it should be prescribed and supplied using the same procedures as OC. Baseline laboratory investigations were required by all centres prior to prescription of OC or BT. The majority of centres used hand-written prescriptions, included body surface area calculation on prescriptions and a record of the prescription in the patient's chart. Only one centre required that a second clinician check was performed.
All physicians reported questioning patients about compliance, while 24% of physicians reviewed patient diaries and 6% carried out a pill count. Errors related to OC use were reported most frequently at prescription (14%) and monitoring stages (14%).
Physicians listed company-based nurses and hospital-based specialist nurses as the most important resource for patients. Information about potential interactions and hospital-based specialist nurses were listed as the most important resources for doctors. Two centres held OC clinics, with all respondents believing these improved practice. Consultation with an oncology pharmacist was offered in one centre. Communication with community pharmacies was rated as fair by 65% and poor by 24% respondents.
Conclusions: Despite increasing use of OC, prescription and monitoring is not standardised within Ireland. The availability of specialist nurses and OC clinics were suggested as potential interventions to reduce errors and improve patient education. Improved communication with pharmacies is required. This study gives an insight into oral chemotherapy and biologic therapy prescribing and monitoring in Ireland.

1317 POSTER

Is It Possible to Contaminate Monoclonal Antibodies by Cytotoxic Drugs in Centralized Preparation Units? − a Consensus Conference From the French Society of Oncology Pharmacy

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Background: Pharmacy-centralized handling of anticancer drugs is mandatory in many countries, especially in the EU. The use of monoclonal antibodies (mAbs) in oncology is growing, mainly associated with cytotoxic drugs. Despite mAbs are not considered as hazardeous, they are anticancer drugs and often handled in the same isolators or laminar-flow hoods (LAF) as cytotoxic drugs. Nevertheless, there are no generally accepted guidelines and some national health authorities consider that mAbs should be handled in separate safety cabinets to avoid cross-contamination with cytotoxic drugs. However, this position is not scientifically based and should induce high additional costs and logistic problems for hospitals.
Method: French Society of Oncology Pharmacy (SFPO) performed a consensus conference to analyze available data and to propose guidelines. Handled drugs were classified in 4 groups: group I: cytotoxics (as listed by international safety agencies); group II: mAbs used for cancer patients also receiving cytotoxics; group III: mAbs in monotherapy used in patients for cancer or another diseases (i.e. auto-immune disorders) and group IV: others.
Results: According to the current practices, the group considered that low-level external contaminations cannot be excluded for gloves, drug containers and preparation area. Since environmental risks induced by mAbs were considered as low, the safety concern is mainly due to external cross-contamination of mAbs-containing bags by cytotoxics. No published data is available on internal cross-contamination during simultaneous preparation of drugs in the same flow LAF or isolator. Moreover, a recent experimental study from a Swiss group showed that no internal contamination occurred even if external contamination of working area and containers was present. However, the consequences of an accidental contamination of mAbs by a cytotoxic such as the use of the same needle to withdrawn both products, remain questionable and experimental works should be initiated to clarify this point. Although the risk appears of very low, a possible consequence could be the induction of mAb aggregation, leading to immunological side-effects.
Conclusion: SFPO considers there is no objective risk of internal cross contamination during simultaneous handling of different drugs in centralized units if accepted procedures for sterile preparations are respected. Therefore, there is no reason to prepare cytotoxic drugs and mAbs in separate safety equipments.

1318 POSTER

Physicochemical Stability of Diluted Azacytidine Suspensions Stored at 4ºC and −20ºC: Preliminary Results

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Background: The recommended regimen of azacytidine (AZC) in hematological diseases is a 7-days subcutaneous administration of 25 mg/ml extemporaneously prepared suspensions, noticed by the manufacturer as stable for 8 hours at 4ºC. Thus, syringes cannot be prepared in advance by hospital pharmacies, inducing non-availability during non-working days and violation of the regimen. We studied the physicochemical stability of AZC suspensions reconstituted by iced or 25ºC water and after freezing.
Materials and Methods: To test the role of iced water on the degradation kinetics, vials of lyophilizate were reconstituted with water at 4º or 25ºC (25 mg/ml). Under stirring, 100 µl samples were taken, immediately diluted at 20 ml by iced water and aliquots were analyzed by HPLC using the method of Argeni *et al*. The degradation kinetics was followed during