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

11 days for samples reconstituted by 4ºC water and 7 days for those reconstituted by 25ºC water. To evaluate how freezing can affect the physical stability, we studied the characteristics of the suspension before and after freezing (−20ºC, 48 hours) and thawing at room temperature. The sedimentation kinetics was studied by following the decrease of absorbance at 500 nm versus time. The aspect of crystals, after filtration on a 0.22 μm filter, was studied by scanning electron microscopy.
Results: The degradation of AZC followed a biphasic kinetic with a rapid initial phase strongly depending on the temperature (% of remaining AZC at 25ºC: 93.2%; 4ºC: 95.9%). Using water at 25ºC, the rate of initial degradation is higher than using cold water (0.336% hr^{-1} vs 0.162% hr^{-1}). However, regardless of the initial conditions of reconstitution, the total degradation was less than 5% after 7 days if reconstituted vial was immediately stored at 4ºC. After storage at −20ºC, no degradation of AZC was observed. The physical characteristics of suspension were not modified: sedimentation rate (4ºC: 144 s; −20ºC: 152 s); identical size and shape of crystals.
Conclusion: If syringes are stored at 4ºC immediately after reconstitution, the use of iced water permits only to slow the initial degradation step but is not essential since the total degradation remains inferior to 5% after 7 days for both reconstitution temperatures. Therefore, the in-use stability period of AZC suspension is higher than recommended by the manufacturer. Freezing should permit long term storage of the suspension without any physical and chemical alterations.

Poster Discussion Presentations (Mon, 26 Sep, 08:00−09:00)

Biomarkers / Imaging

1400 POSTER DISCUSSION

Interest of CHOI and Modified CHOI Criterion for Evaluation of Metastatic Renal Cell Carcinomas (mRCC) Patients Treated With Everolimus

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Background: Because tumour response may be underestimated by RECIST as new targeted therapies can induce more necrosis than tumour shrinkage, we studied whether CHOI and modified CHOI (mCHOI) criterion might be valuable to assess everolimus efficacy.
Materials and Methods: We, retrospectively, reviewed the computed tomography (CT) of 70 mRCC patients (pts) enrolled in the French centers participating to the randomized, double-blind, multicenter phase III study comparing Everolimus vs placebo (RECORD-1). In this trial, the primary endpoint was PFS, based on RECIST criteria assessed on CT performed at baseline and every two months. We investigated CT until first progression according to CHOI criteria where partial response (PR) was defined as $\geqslant$10% decrease in tumour size OR $\geqslant$15% decrease in attenuation; and according to mCHOI criteria where partial response (PR) was defined as $\geqslant$10% decrease in tumour size AND $\geqslant$15% decrease in attenuation. Attenuation was measured on region of interest covering at least $\frac{3}{4}$ of the surface area of the targeted lesions on the CT sections where the largest diameter could be measured.
Results: Because of renal impairment that precluded contrast injection and lesions that could not correctly be assessed for attenuation, only 50 pts were eligible for analysis. Among them 19 were in the placebo arm and 31 treated by Everolimus. PFS were 2.8 and 6 months ($p < 0.005$), respectively. In the placebo group, CHOI criteria identified 47% of PR compared to non-responders with significant differences for PFS (3.6 vs 2.0 months $p < 0.01$, respectively), while mCHOI criteria found 0% of PR.
In the Everolimus group, 55% of pts were considered PR and 45% non responders according to CHOI criteria without significant differences for PFS (6.0 and 5.9 months, respectively) while mCHOI found 26% PR compared to 74% non-responders without significant differences for PFS (7.4 and 5.5 months, $p = 0.13$, respectively).
Conclusion: The use of CHOI or mCHOI criterion could not discriminate PFS between responders or non-responders pts treated with Everolimus. In the placebo arm, CHOI criteria identified a subgroup of pts with spontaneous necrosis associated with a longer PFS.

1401 POSTER DISCUSSION

Choi Response Criteria for Prediction of Clinical Outcome in Patients With Metastatic Renal Cell Carcinoma Treated With Targeted Therapies

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Background: Anticancer treatment efficacy is measured by decrease in tumour size and standardized according to the Response Evaluation Criteria in Solid Tumours (RECIST). With the advent of new targeted therapies, necrosis and cavitation rather than shrinkage were described as first response to treatment. The purpose was to evaluate whether early assessment of tumour shrinkage alone (RECIST criteria) or combined with changes in tumour density (Choi criteria) better predict clinical outcome in patients with metastatic renal cell cancer (mRCC).
Patients & Methods: In this retrospective multicenter study we included 47 patients with mRCC treated with a tyrosine kinase and/or mTor inhibitor and for whom at least two CT scans (baseline and follow-up) with measurable lesions were available. CT scans were blinded and analyzed centrally according to RECIST and Choi criteria. Patients were categorized according to both criteria into complete and partial response (CR/PR), stable disease (SD) and progressive disease (PD). A dichotomisation into responders (CR or PR) and non-responders (SD or PD) was conducted. The response to therapy was compared with clinical outcome including progression free survival (PFS) and overall survival (OS). Differences in survival of responders and non-responders were assessed with log-rank tests and Cox proportional hazards models.
Results: According to RECIST criteria, 8 patients were responders and 26 patients non-responders, whereas to Choi criteria, 17 were responders and 17 non-responders.
Responders had higher PFS and OS according to Choi criteria (log-rank test $p = 0.001$ and $p = 0.023$, respectively) than according to RECIST criteria ($p = 0.404$ and $p = 0.055$, respectively). Based on Cox proportional hazards models adjusted with prior treatment with interferon and the time between diagnosis and start of therapy, the hazard ratios for responders vs. non-responders according to Choi criteria were 0.25 for PFS (95% CI 0.10–0.61, $p = 0.002$) and 0.33 for OS (95% CI 0.12–0.90, $p = 0.030$) as opposed to the hazard ratios according to RECIST criteria of 0.59 for PFS (95% CI 0.21–1.65, $p = 0.313$) and 0.34 for OS (95% CI 0.10–1.17, $p = 0.087$).
Conclusion: Using Choi criteria in evaluating mRCC patients treated with targeted therapies will change response evaluation and better correlates with PFS and OS compared to using RECIST criteria.

1402 POSTER DISCUSSION

CT Evaluation of the Response of Colorectal Liver Metastasis After Bevacizumab Treatment − a Density Quantitative Analysis Correlated With Patient Outcome

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Context: The standard criteria used to evaluate tumour response, the Response Evaluation Criteria in Solid Tumours (RECIST), were developed to assess tumour shrinkage after cytotoxic chemotherapy and may be limited (1) in assessing response to biologic agents, which have a cytostatic mechanism of action.
Purpose: To validate novel tumour response criteria based on tumour size and density early changes observed on computed tomography (CT) in patients with colorectal liver metastases treated with bevacizumab-containing chemotherapy regimens.
Material and Methods: We performed a centralized review of the 145 patients included in ACCORD 13 prospective clinical trial (NCT00423696). Seventy one patients were excluded of the analysis because of the absence of liver metastasis (n = 19), images data not available or incomplete (n = 30), CT delay time not respected (n = 7), CT acquisition protocol not respected (n = 15). The final study population was 74 patients treated by FOLFIRI + Bevacizumab (n = 46) or XELIRI + Bevacizumab (n = 28), with a median follow up of 34.1 months [2.8–47.5 months]. Tumour size (RECIST) and density were determined objectively using a semi- automatic segmentation tools (Myran®, Intrasense) at the portal phase. We analyzed changes in tumour size and density, in patient who underwent a CT scan before and 2 months after starting treatment.
Results: There was no significant difference between the entire clinical trial population study (ACCORD 13) and the analysed patient group in terms of age, sex, PFS and OS. The RECIST response (PR or CR)