

Conclusions Antifungal spending is disproportionately high considering the low number of fungal isolates, and entails a high use of empirical and prophylactic treatment.

Haematology is, by far, the main department responsible for the use of antifungal treatment. Consumption of voriconazole and liposomal amphotericin B are increasing, meanwhile caspofungin is decreasing in recent years.

No conflict of interest.

DOI-037 FINGOLIMOD IN RELAPSING REMITTING MULTIPLE SCLEROSIS: A CASE REPORT

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Background Fingolimod has recently been authorised in our country (April 2011). It is the first orally administered disease-modifying drug that has been approved for highly active relapsing remitting multiple sclerosis. So far, only one patient has been treated with it in our hospital, so we have limited experience in its use.

Purpose The case report relates to relapsing remitting multiple sclerosis (RRMS) patient with high disease activity under treatment with Fingolimod. We aim to describe the evolution of this patient during the treatment period.

Materials and Methods It was an observational, six-month prospective study.

The patient, a 32-year-old female, was diagnosed with RRMS in February 2004 after an episode of sensory deficits.

Results At first, she was treated with interferon b-1a, which was stopped in February 2006 and switched to mitoxantrone IV. The patient continued to have several relapses during the treatment with this immunosuppressant; one of these relapses required plasma exchange therapy. Her Expanded Disability Status Scale (EDSS) worsened to 6 points. Assuming a lack of efficacy, the patient started treatment with natalizumab in April 2007. During four years of treatment with natalizumab she showed remarkable clinical improvement and did not experience any new relapses. Her EDSS improved to 2.5. After this time and due to the high risk of developing progressive multifocal leukoencephalopathy (PML), she switched to fingolimod (December 2011).

Ten days after initiation, she developed a severe relapse that required hospital admission, high dose IV steroids and 3 cycles of plasma exchange therapy. Doctors concluded this relapse was in fact a rebound effect due to stopping natalizumab.

In February 2012 she restarted fingolimod; one month later she developed a new relapse, treated with high dose steroids.

In April and May 2012 she had two more relapses, with severe EDSS worsening and again managed with high dose steroids.

In May 2012, it was decided to stop treatment with fingolimod, and despite the risk of PML (JC virus +), natalizumab was restarted.

Conclusions During six months of fingolimod treatment, the patient's condition further deteriorated (four relapses in six months), her EDSS worsened and showed a high disease activity. We conclude that the treatment was not effective in this patient.

No conflict of interest.

DOI-038 GEMTUZUMAB OZOGAMICIN AS SALVAGE TREATMENT IN CHILDREN WITH ACUTE MYELOID LEUKAEMIA RELAPSE: A RETROSPECTIVE STUDY

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Background Gemtuzumab ozogamicin (GO) is a humanised anti-CD33 monoclonal antibody conjugated with calicheamicin. Several studies show its safety and efficacy in refractory/relapsed acute myeloid leukaemia (AML). Nevertheless in July 2010 it was withdrawn from the US market after a study failed to confirm the clinical benefits of GO.

Purpose Following this controversy, we conducted a retrospective study to evaluate its efficacy and safety in children with refractory/relapsed AML.

Materials and Methods The study focused on the 19 children treated after approval by the French drug safety agency, between October 2006 and June 2012.

Results The median age at initial diagnosis was 6.7 years (0.5–15.3). Three patients were refractory to first-line treatment, one patient was in refractory first relapse, three were in first relapse after stem cell transplantation (SCT), three in second relapse after SCT, one in third relapse after SCT, seven were in first relapse and one in second relapse. Patients received: one dose of 3 mg/m² with cytarabine (day 1 to 7); or 9 mg/m² fractionated dose (on days 1, 4, 7) in monotherapy or associated with cytarabine (day 1 to 7); or 4.5 mg/m² on day 6 associated with fludarabine and daunorubicin liposomal. Nine complete remissions were obtained (48%) in 32 days, leading to further curative treatment. The one year overall survival was 26% (5 patients). For the others complete remission was maintained for 6–9 months before relapse or death. Grade 3–4 haematological adverse events were identified in all children including severe thrombocytopenia requiring transfusion. Sepsis (n = 2), fever (n = 3), vomiting (n = 6) were documented. One case of sinusoidal obstruction syndrome was reported.

Conclusions Children with refractory/relapsed AML have a dismal outcome and there is a lack of effective treatments. In our cohort GO led to nearly 50% of CRs and even if the long term survival is still unsatisfactory it should remain available in this indication.

No conflict of interest.

DOI-039 GUIDE TO THE PREPARATION AND ADMINISTRATION OF INJECTABLE CYTOTOXIC DRUGS

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Background The preparation of injectable cytotoxics is a key activity of many hospital pharmaceutical services. Due to the increasing availability of cytotoxic medicines, either branded or generic, the time spent by hospital pharmacists in search of information about reconstitution and/or dilution, storage and stability of these drugs has increased. In order to effectively respond to this need for information, it would be useful to have a database that holds all that information for all cytotoxic medicines currently available in Portugal.

Purpose To prepare a guide to the preparation and administration of all parenterally administered cytotoxics available in Portugal, which provides information on the reconstitution and/or dilution, storage and stability, routes of administration, infusion rate, as well as other relevant observations.

Materials and Methods Review of the summary of product characteristics (SPC) of all injectable cytotoxic drugs currently available in Portugal; consultation with the pharmaceutical manufacturers and analysis of the responses received.

Results A total of 153 injectable cytotoxic medicines were investigated (88 branded and 65 generic), comprising a total of 40 active substances. Of this total, 145 have marketing authorization in Portugal and 8 are used under special-use authorization. Significant variability in the information available about the reconstitution,

dilution, storage, administration and stability was observed, when considering the different formulations of the same active substance, which depend on the manufacturer. In all, 32 manufacturers were asked to add additional relevant information that was not present in the SPC. The guide is available in electronic format and in A5 print format (handbook), which has proved to be very practical, fast and effective to use.

Conclusions The published guide is a valuable tool for all Portuguese hospital pharmacists who prepare parenterally administered chemotherapy, answering to most information needs on reconstitution, dilution, storage, stability and administration of injectable cytotoxic drugs.

No conflict of interest.

DGI-040 HUMAN LUNG CARCINOMA SENSITIVITY TO PACLITAXEL: WHICH ROLE FOR BIM?

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Background Deregulation of apoptosis is one of the causes of cancer developing. The Bcl-2 family are central regulators of apoptosis. They are subdivided into two classes, the proapoptotic members (which include Bim) and antiapoptotic members (like Bcl-2). The overexpression of Bcl-2 is generally associated with many cancers and resistance to chemotherapy, including microtubule-targeting agents (MTAs). Therefore several anti-Bcl-2 strategies are in development. Unexpectedly, several studies show that a decrease in Bcl-2 may be associated with resistance to MTAs. This paradoxical role of Bcl-2 has not yet found a clear explanation.

Purpose To show that overexpression of Bcl-2 leads to overexpression of Bim, which is responsible for increasing sensitivity to MTAs. Bim is a potential biomarker which may be included in tests to predict the response to paclitaxel treatment in human lung carcinoma. Our work also enables a better understanding of how Bim regulates genes.

Materials and Methods The techniques used to study the sensitivity of cells to MTAs are the Western Blot and immunofluorescence. To study Bim's regulation of genes, we used the technique of a reporter gene.

Results Firstly, we showed that overexpression of Bcl-2 in human lung carcinoma cells (A549 Bcl-2) in turn triggers the overexpression of Bim. Apoptosis is detected after treatment with paclitaxel at 20 nM, after 24 hours. For this, we used the anti-caspase 9 antibody to show it was being cleaved and to signal the release of the apoptosis mitochondrial pathway. To confirm this, we used immunofluorescence staining to objectify the release of cytochrome c from the mitochondria. So we showed that the overexpression of Bim in cells that overexpress Bcl-2 accounts for their increased sensitivity to paclitaxel.

We also conducted a study of gene regulation by Bim in A549 cells overexpressing Bcl-2. We highlighted the increasing transcriptional activity of Bim promoter by a factor of 2.3 ± 0.2 compared to control cells. The Bim protein level seems to be a better determinant of MTAs sensitivity than Bcl-2 status in pulmonary epithelial tumours. Thus, it appears that Bim expression may be an effective biomarker in predicting the efficiency of MTA treatment. We are currently evaluating the involvement of various transcription factors, especially by DNA microarray.

Conclusions These data suggest that Bim is a more reliable marker of the sensitivity to MTAs than Bcl-2. A test showing the level of Bim expression may be able to predict therapeutic efficacy and/or resistance based on molecular profiling of the tumours. However, the induction of Bim alone cannot be sufficient for significant cell death. Indeed, it is more likely that Bim acts in unison with the other

pro-apoptotic proteins. So the development of targeted therapies, on the Bcl-2 family in particular, must await a better understanding of the molecular mechanism involved in the regulation of apoptosis.

No conflict of interest.

DGI-041 HYPOMAGNESEMIA AS A POSSIBLE MARKER OF EFFECTIVENESS IN PATIENTS TREATED WITH PANITUMUMAB

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Background Panitumumab is a human monoclonal antibody indicated in the treatment of colorectal carcinoma (CRC) that is currently being tested in otolaryngology (ENT) tumours. Recent studies suggest that hypomagnesaemia (<1.7 mg/dL) during treatment with panitumumab may be related to greater anti-tumour efficacy.

Purpose To review the effectiveness of panitumumab and its possible relationship with hypomagnesaemia.

Materials and Methods Retrospective observational study that included all patients treated with panitumumab in a tertiary hospital. The primary endpoint of effectiveness was overall survival (OS), calculated using the Kaplan Meier method. We examined anthropometric data, diagnosis, treatment duration and, in patients whose magnesium had been determined during panitumumab treatment, we also studied the causes of termination and adverse reactions.

Results During the study period (August 2008–October 2012) 72 patients were treated, who had an average baseline age of 63 (SD:11) years and were mostly male (56%). At the end of the study 47% of patients were alive and 44% of them are still being treated with panitumumab. Diagnosis of 89% of patients was CRC, while 8 ENT cancer patients were enrolled in a clinical trial. The average length of treatment was 4.9 (SD:5.7) months and 7.7 (SD:6.4) cycles/patient were administered.

Magnesium levels were only determined in 13 patients, hypomagnesaemia being detected in 6 patients (ENT:3, CRC:3) and normomagnesaemia in the remaining 7 (ENT:5, CRC:2). Treatment with panitumumab was stopped in 6 patients due to disease progression. Two patients had to reduce the dose due to severe skin toxicity. The OS was calculated in all patients [hypomagnesaemia: 9.5 (95CI:4.9–14.0) vs. normomagnesaemia 8.2 (95CI:4.2–12.3) months (p:0.703)] and in the ENT tumours subgroup [hypomagnesaemia: 13 (95CI:9.3–16.7) vs. normomagnesaemia 4.8 (95CI:2.9–6.8) months (p:0.127)].

Conclusions Despite the low magnesium determinations we observed a trend to greater OS in hypomagnesaemic patients. Further studies are needed to confirm this trend.

Abstract DGI-041 Table 1

	n	Dead/alive	OS (95CI)	p
All patients	72	38/34	17.0(13.2–20.7)	
CRC	64	34/30	17.0(13.1–20.9)	0.952
ENT	8	4/4	9.3(5.2–13.3)	

No conflict of interest.

DGI-042 HYPOMAGNESEMIA AS A POSSIBLE MARKER OF EFFICACY IN PATIENTS WITH HEAD AND NECK CARCINOMA IN FIRST-LINE TREATMENT WITH CETUXIMAB

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