

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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<sup>1</sup>I Pobel, <sup>1</sup>A Savry, <sup>1</sup>M Le Grand, <sup>2</sup>V Rey, <sup>3</sup>D Braguer. <sup>1</sup>Assistance publique – Hôpitaux de Marseille, Marseille, France, <sup>2</sup>9112Inserm U – CRO, Marseille, France, <sup>3</sup>9112Inserm U CRO, Marseille, France

**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  $2.3 \pm 0.2$  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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J Megías Vericat, J Ruiz Ramos, J Reig Aguado, C Borrell García, MJ Esteban Mensua, E López Briz, JL Poveda Andrés. Hospital Universitario La Fe, Servicio de Farmacia, Valencia, Spain

**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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J Ruiz, JE Megías, C Borrell, P Marrero, E López, JL Poveda. Hospital Universitario La Fe, Pharmacy, Valencia, Spain