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Editorial Comment

Editorial comment on "*In vitro* toxicity of ET-743 and Aplidine, two marine-derived antineoplastics, on human bone marrow haematopoietic progenitors: comparison with the clinical results" by Albella and colleagues

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In this issue of the *European Journal of Cancer* Albella and colleagues show that both ET-743 and Aplidine are toxic to human bone marrow cells, particularly megakaryocytic progenitors. For ET-743 the concentrations found to be toxic to megacaryocytic cells and neutrophils appear to be close to those achieved in the plasma of patients receiving the maximum tolerated dose (MTD). In contrast, Aplidine showed growth inhibition of haematopoietic cells at concentrations more than 20-fold higher than the maximal drug concentrations found in the plasma of patients given the MTD.

Clinical toxicological data obtained in phase I and II studies have shown that haematopoietic toxicity is the dose-limiting toxicity (DLT) for ET-743, whereas myalgia is the DLT for Aplidine. Therefore, it appears that for the two drugs the *in vitro* assay was predictive of the bone marrow toxicity when extrapolations are made with consideration of the pharmacokinetic data.

The results shown in this study, as well as data reported in the literature for other anticancer drugs, suggest that the use of these assays can provide valuable information for a safe conduction of phase I clinical trials. These assays might also help to predict the bone marrow toxicity caused by combining the new drug with other myelotoxic compounds. In addition, *in vitro* growing human bone marrow cells could be a useful experimental system to investigate the mechanisms of toxicity and possibly to find methods to reduce the toxicity of myelotoxic drugs. Furthermore, this type of study should be performed in parallel with similar experiments in cancer cells in order to examine any selectivity of the anticancer agent or combination of compounds that are to be evaluated in the clinic.

After emphasising the potential utility of these *in vitro* assays, I must stress that these systems require validation so that the data obtained can be applied to the clinical setting with an acceptable degree of confidence.

As Albella and colleagues point out in their paper, the methods currently used are only partially predictive. This is exemplified by the fact that according to the *in vitro* results thrombocytopenia should have been the major haematological toxicity of ET-743, whereas clinical data suggest that neutropenia is much more frequent and represents the DLT.

We should consider that for a new drug there is often incomplete information on its metabolism and on the toxicological properties of each metabolite. Although it might be possible to add the enzymes responsible for the drug's metabolism to the *in vitro* systems, it is still difficult to reproduce metabolic reactions *in vitro* in a way that is representative of the *in vivo* metabolism, both qualitatively and quantitatively. In addition, some toxicities may be mediated by host cells that are not present in the *in vitro* assay. For example, some xenobiotics can induce the production of cytokines by the immune system which can modify the pharmacological properties and toxicity of the drug.

Thus, I believe that the results of the *in vitro* assays, together with pharmacokinetic information, can greatly help to provide data that is useful when undertaking phase I–II clinical trials of new anticancer agents, but, at present, these assays cannot replace the toxicological tests performed *in vivo* in different animal species.

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