Institution: University of Leicester

Unit of Assessment: UoA5 Biological Science

Title of case study: Discovery of a Clinical Strategy to Abrogate the Toxicity of Trabectidin, a Novel Useful Anticancer Drug

1. Summary of the impact

This case relates to preclinical research which profoundly aided the successful licensing of trabectidin, a novel anticancer drug. The discovery described here has a beneficial impact on the survival of certain cancer patients and on the income of the major Spanish biotech company Pharmamar SA, which owns and markets trabectidin. Early preclinical and clinical studies of this agent showed that it exerts severe liver toxicity, a side effect which jeopardised its further clinical evaluation. The Leicester group led by Prof **Andreas Gescher** (AG) investigated the mechanisms by which the drug engages this deleterious effect with funds from Pharmamar. The preclinical work showed eventually that pretreatment of rats with the glucocorticoid steroid drug dexamethasone profoundly counteracts trabectidin-mediated hepatotoxicity. Crucially, this combination did not adversely affect the antitumour activity of trabectidin.

Subsequent clinical evaluation of the combination demonstrated dramatically reduced liver toxicity in patients compared to those who received trabectidin alone. Since 2007 trabectidin has been administered routinely in combination with dexamethasone in the treatment of sarcomas and metastatic ovarian cancer. [text removed for publication] Revenues for Pharmamar from the sale of trabectidin in 2011 were ~81M Euros.

2. Underpinning research

Trabectidin (yondelis), a small molecule originally isolated from the Caribbean sea squirt *Ecteinascidia turbinata,* showed striking antitumour activity in a variety of preclinical rodent models of especially sarcomas, but also ovarian and breast cancer. Significantly, dose limiting liver toxicity, as reflected by liver enzyme release into the blood and subclinical bile duct inflammation, was a major problem observed after trabectidin in these preclinical studies and also in early clinical trials.

The Leicester team headed by AG (from 1993 to 2002 group leader at the Leicester MRC Toxicology Unit and honorary professor in the Dept of Biochemistry; from 2002 to 2013 section leader in the Dept of Cancer Studies) set out to characterise the mechanisms by which trabectidin induces this toxicity in the rat biochemically and pathologically (3.1). Pharmamar SA (liaising company scientists: J Jimeno, L Lopez-Lazaro) funded a research assistant to work at Leicester for 3 years plus research consumables. Funding by Pharmamar had come about because of AG's internationally acknowledged expertise in exploring mechanisms of drug toxicity in the liver. The laboratory work, aimed at unravelling the mechanisms by which trabectidin exerts its hepatotoxicity, used biochemical and pathological state-of-the-art analyses and was carried out by the Leicester team comprising **S Donald** (research assistant/PhD student), RD Verschoyle (MRC Toxicology Unit), **D Dinsdale**, **R Edwards**, **P Greaves** (helped with rodent experiments, pathology, image analysis), **DJ Judah**, **R Davies**, **J Riley**, **AG Smith**, **TW Gant** (helped with gene expression analysis). The effect of trabectedin on the liver had never before been elucidated with the insight and depth applied in Leicester. The results suggested that the toxicity is a consequence of biliary rather than hepatocellular damage (3.1). The team went on to hypothesise that trabectidin hepatotoxicity in the rat could be altered by dexamethasone. Dexamethasone was chosen because it can alter the disposition of drugs by the liver. It is also used in combination with certain conventional anticancer drugs to minimise chemotherapy-induced nausea and vomiting. The hypothesis was tested in collaboration with scientists at the Mario Negri Pharmacological Research Institute (Milan, Italy: T Colombo, M Zaffaroni, R Frapolli, M Zucchetti, M D'Incalci, plus D Meco and R Riccardi at the Universita del Sacre Cuore, Rome Italy). In this collaboration the Leicester team conducted the safety evaluation using a series of doses and schedules and measuring toxicity biochemically and by tissue pathology and expression of toxicity-related genes. The Italian

collaborators contributed measurement of the toxicokinetics and antitumour activity of trabectidin when administered in combination with dexamethasone. High-dose dexamethasone administered before trabectidin dramatically abrogated trabectidin hepatotoxicity in rats without confounding its antitumour activity (3.2). The Leicester researchers and their collaborators investigated also other potentially hepatoprotective interventions in the rat (3.3, 3.4), but none protected the liver more potently against the toxicity of trabectidin than dexamethasone.

As a direct consequence of the preclinical results obtained in the Leicester laboratory, the chief Mario Negri collaborator (M D'Incalci) of the Leicester group instigated a clinical study at the Istituto Nazionale Tumori Milan, Italy (3.5). This trial showed that pre-medication of patients with dexamethasone from the day before commencement of trabectidin treatment dramatically reduces the risk of liver toxicity, just as the rodent study had predicted. The validity of the preclinical finding described here for the clinical scenario was buttressed by an epidemiological paper published in 2008 by researchers unrelated to the Leicester/Milan groups, which describes pharmacodynamic/pharmacokinetic modelling using data from 771 cancer patients enrolled in several clinical trials of trabectidin. This study concluded that dexamethasone pretreatment reduces trabectidin-associated liver damage, as reflected by liver enzyme release, by as much as 63%, compared to no pretreatment.

3. References to the research

3.1. **Donald S**, Verschoyle RD, **Edwards R**, **Judah DJ**, **Davies R, Riley J**, **Dinsdale D**, Lopez-Lazaro L, **Smith AG**, **Gant TW**, **Greaves P**, **Gescher AJ** (2002). Hepatobiliary damage and changes in hepatic gene expression caused by the antitumor drug ecteinascidin-743 (ET-743) in the female rat. Cancer Res 62:4256-4262 (Cancer Res 2012 impact factor: 8.65)

3.2. **Donald S**, Verschoyle RD, **Greaves P**, **Gant TW**, Colombo T, Zaffaroni M, Frapolli R, Zucchetti M, D'Incalci M, Meco D, Riccardi R, Lopez-Lazaro L, Jimeno J, **Gescher AJ** (2003). Complete protection by high-dose dexamethasone against the hepatotoxicity of the novel antitumor drug yondelis (ET-743) in the rat. Cancer Res 63:5902-5908 (Cancer Res 2012 impact factor: 8.65)

3.3. **Donald S**, Verschoyle RD, **Greaves P**, Colombo T, Zucchetti M, Falcini C, Zaffaroni M, D'Incalci M, Manson MM, Jimeno J, **Steward WP**, **Gescher AJ** (2004). The chemopreventive agent indole-3-carbinol protects female rats against the hepatotoxicity of the antitumor drug yondelis (ET-743). without compromising efficacy in a rat mammary carcinoma. Int J Cancer, 111: 961-967 (Int J Cancer 2012 impact factor: 6.20)

3.4. **Donald S**, Verschoyle RD, **Greaves P**, **Orr S**, Jimeno J, **Gescher AJ** (2004). Comparison of four modulators of drug metabolism as protectants against the hepatotoxicity of the novel anticancer drug yondelis (ET-743) in the female rat and in hepatocytes in vitro. Cancer Chemother Pharmacol 53: 305-312 (Cancer Chemother Pharmacol 2012 impact factor: 2.80).

3.5. Grosso F, Dileo P, Sanfilippo R, Stacchiotti S, Bertulli R, Piovesan C, Jimeno J, D'Incalci M, **Gescher A**, Casali PG (2006) Steroid premedication markedly reduces liver and bone marrow toxicity of trabectidin in advanced sarcoma. Eur J Cancer 42:1484-1490 (Eur J Cancer 2012 impact factor: 5.10)

4. Details of the impact

During the quinquennium 2008-2013 the study described here has had - and continues to have - a beneficial impact at two levels, *i.* on cancer patients in terms of improved survival, and *ii.* on finances pertinent to Pharmamar SA, the company which developed trabectedin.

Clinical impact: Currently trabectidin is mainly used to treat certain soft tissue sarcomas. These are cancers in tissues connecting/surrounding limbs or trunk, breast, stomach, skin and uterus, which account for ~1% of all malignant tumours. The incidence in England is ~2,500 individuals annually. About 35% of cases occur in economically active people (aged 50 or below). Whilst in the UK treatment with trabectedin is largely confined to oncology centres which specialise in sarcoma

therapy, the drug is more widely used in mainland Europe. [text removed for publication]

The preclinical findings by the Leicester team showed for the first time that dexamethasone pretreatment can protect rodents from the liver toxicity exerted by trabectidin. These results pointed to a potential clinical antidote strategy, the viability of which was borne out by the Italian clinical study alluded to above (5.1). The findings by the Leicester Group and their collaborators constituted a significant advance, in that they suggested for the first time that dexamethasone co-treatment can alleviate the very serious liver toxicity which trabectidin exerts. This information was disseminated among the oncology community in the early 2000s. Premedication with dexamethasone to ameliorate trabectidin toxicity in patients was made mandatory in the USA in 2003 and implemented world-wide in 2005/6. Since 2007 it has become standard practice.

In 2007 the European Medicine Evaluation Agency (EMEA) approved trabectidin for the treatment of soft tissue sarcomas. By early 2013 the drug has been approved in 73 countries, 30 of these within Europe, for the treatment of sarcomas and/or metastatic ovarian cancer. According to guidance provided by the UK National Institute for Clinical Excellence (NICE) in February 2010 and confirmed in March 2013, trabectedin is accepted as “second line” therapy for soft tissue sarcomas, after doxorubicin and ifosfamide, or “third line” after consecutive single agent therapy (5.2). Importantly, such NICE guidance takes not only therapeutic and pharmacological facts but also economic issues into consideration. Trabectidin is currently also in phase II-III evaluation as treatment against solid tumours of the prostate, breast or pancreas and mesothelioma, based on promising preclinical results. The “European Public Assessment Report” on trabectidin (written by the European Medicines Agency in 2009) says: “...to protect the liver, patients *must* receive an infusion of corticosteroids such as dexamethasone before treatment...” (5.3). Supportive care measures for patients receiving trabectidine described in articles for oncologists include advice such as “...dexamethasone pretreatment ... used to limit hepatic toxicity and to prevent nausea and emesis. The recommended dose of dexamethasone for adults is 20mg 30 minutes prior to the start of trabectedin infusion...” (5.4).

Various trabectedin regimens have been shown to be clinically efficacious in patients with advanced/metastatic soft tissue sarcoma after failure of treatment with conventional cytotoxic drugs (5.4). In these trials trabectedin therapy achieved overall survival rates of >10 months, significantly superior to the ~6 months obtained with previous standard therapy. This means that patients who receive, and respond to, trabectidin live ~4 months longer than those receiving standard therapy. It is pertinent to stress that in cancer chemotherapy such a seemingly moderate gain in life span constitutes an extremely successful drug treatment outcome. The following summary of a leading UK sarcoma specialist underlines the “significance” of the case presented here: “...In a significant proportion of sarcoma patients trabectidin is efficacious, and the lack of cumulative toxicity against specific organs and generally good tolerability means that treatment can be continued indefinitely in many patients with ongoing response...” (5.5).

Economic impact: Within the last 3 years sales of trabectidin have constituted the predominant part of Pharmamar’s drug-related income (5.6). Information on gross revenues is available for 2011, during which the sale of trabectidin generated 80.6 million Euros for Pharmamar. The extensive use of trabectidin is only possible because pre-medication with dexamethasone obviates its potentially dose-limiting liver toxicity. Pharmamar might have attempted to market this drug without the research described here, but its severe liver toxicity when given without dexamethasone would have undoubtedly strongly curtailed the oncologists’ enthusiasm for administering the drug. Consistent with this notion the current UK national guidance by NICE on how trabectidin should be administered says “...intravenous dexamethasone (20 mg) must be administered to all patients 30 minutes before trabectedin treatment, dexamethasone may also have hepatoprotective effects…” (5.2). Recommendations from many other new drug-approving bodies outside the UK reflect the opinion expressed by NICE, as exemplified by a statement from “Health Canada” in 2010: “...All patients *must* be premedicated with... dexamethasone 20 mg iv, 30 min before trabectidin infusion... because it appears to provide hepatoprotective effects...” (5.7). The number of individuals to receive trabectidin is likely to increase, when the results of ongoing clinical trials become available.

The scientific result obtained in Leicester that trabectidin toxicity can be dramatically ameliorated by dexamethasone pretreatment has rendered routine treatment using this useful anticancer drug possible.

5. Sources to corroborate the impact

5.1 Information on number of patients who receive trabectidin worldwide obtained from Pharmamar SRL, Milan (Pharmamar SA's Italian subsidiary)

5.2 Guidance by NICE as to the use of trabectidin: http://publications.nice.org.uk/trabectedin-for-the-treatment-of-advanced-soft-tissue-sarcoma-ta185

5.3 European Public Assessment Report on the clinical usage of trabectidin by the European Medicines Agency (2009): http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000773/WC500045833.pdf

5.4 Example of advice for oncologists as to the use of trabectidin: Gajdos C, Elias A (2011) Trabectedin: Safety and efficacy in the treatment of advanced sarcoma. Clin Med Insights Oncol 5:35–43

5.5 Statement pertaining to the significance of the case by Head of the Sarcoma Unit at Royal Marsden Hospital, London, past Chairman of the NCRI Sarcoma Clinical Studies Group, the EORTC Soft Tissue and Bone Sarcoma Group and past President of the Connective Tissue Oncology Society

5.6 Revenues generated by trabectidin for Pharmamar in 2011 reported on 10.4.2013 in “The Pharma Letter”, a publication which provides business information on the worldwide pharmaceutical, generic and biotechnology industries

5.7 Statement from “Health Canada”, the Canadian new drug-approving body, as to the use of trabectidin: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2010_yondelis_124729-eng.php