Developing thalidomide analogues for cancer treatment

Working with a small start-up company, Professor Angus Dalgleish developed several thalidomide analogues, including lenalinomide and pomalidomide. Both drugs significantly prolong patient survival in myeloma and myelodysplasia and received approval in the UK and United States for these purposes.

Background and research

Following the serendipitous observation of improvement in leprosy in a patient taking Thalidomide in 1965, a number of clinicians reported beneficial effects of this drug on certain steroid-resistant diseases, including graft-versus-host disease following organ transplantation.

Professor Dalgleish and colleagues conducted a clinical trial of thalidomide in HIV positive patients in 1997. Although there was substantial dropout in both treatment and placebo limbs of the 24 week trial, it was evident that there were potentially important immune-modulatory effects of Thalidomide. However, it was clear that its widespread use was likely to be impaired by its association with birth defects, significant neuropathy in some patients, and its tendency to induce drowsiness.

Professor Dalgleish therefore proposed a programme to develop a Thalidomide analogue, on the basis that a related drug that lacked these toxic actions could be developed.

Working with Celgene, a small start-up company, several groups of effective analogues were identified and patented jointly by Professor Dalgleish and Celgene. Amongst these, lenalidomide and pomalidomide were the two analogues that had significant immuno-

modulatory and immune stimulatory functions and anti-angiogenic activity, which led to these analogues going forward into the clinic.

Clinical trials showed that lenalidomide and pomalidomide were immune-stimulatory, in addition to their anti-inflammatory properties. This activity was confirmed in a pre-clinical model, where pre-treatment with these analogues greatly enhanced the effect of vaccines.

Lenalidomide proved 50,000 times more potent than thalidomide in inhibiting tumor necrosis factor-alpha, and has less severe adverse drug reactions. This led to the development of lenalidomide as an oral adjuvant for therapeutic vaccines in HIV and cancer.

A second key insight was that the anti-inflammatory, co-stimulatory and anti-angiogenic activities of lenalidomide made it an ideal agent for combining with other classical therapies, such as Gemcitabine and Docetaxol, leading to clinical studies with these combinations in myeloma.

Impact

Multiple myeloma is a relatively common haematological malignancy accounting for around 2 per cent of all cancer deaths. Several large-scale clinical trials demonstrated the efficacy of lenalidomide in treating myeloma. Prior to the advent of thalidomide analogues the median one- and five-year survival figures for myeloma were 60% and 20% respectively, and treatment required use of toxic chemotherapeutic agents such as melphalan.

With thalidomide or lenalidomide the one- and five-year survival figures increased to 70 per cent and 37 per cent respectively. The use of lenalidomide for this indication in the USA was approved by the Federal Drugs Administration (FDA) in 2005. Its use in the UK was delayed largely by concerns over treatment costs.

However, the National Institute for Clinical Excellence (NICE) developed a novel cost-sharing scheme with the manufacturer Celgene and approved the drug for use in myeloma patients who had received two or more prior therapies in 2010.

Whilst the immediate beneficiaries of lenalidomide have been patients who suffered from myeloma or myelodysplasia, this drug is now being found to be effective in chronic leukaemias and lymphomas. Pomalidomide, the second analogue originally developed by Dalgleish in conjunction with Celgene, has a more potent immune co-stimulatory action than lenalidomide and received approval by the FDA in 2013 for relapsed multiple myeloma. It may also be effective in treating tumours.

The development of lenalidomide has has a major impact on the growth of Celgene. From being a small non-clinical research organisation when the collaboration with Dalgleish started in 1993, it is now a worldwide corporation based in New Jersey, USA, employing over 5,700 employees. Many of these employees are in Europe and the UK in particular, and this has led to the funding of many other research groups and clinical trials throughout the UK.

Lenalidomide sales worldwide generated $3.8 billion USD in 2012.