Professor Ray Powles CBE

Head of Haemato-Oncology

Advances in treating Myeloma in the UK in 2016

Multiple myeloma is a form of blood cancer that involves malignant proliferation of immune precursor (Plasma) cells in the marrow, usually manifested by painful bone disease, kidney failure, anaemia and/or infection.

A brief history..

In the 1980's treatment consisted of simply having the chemotherapy agent Melphalan. The UK National Medical Research Council trial of Melphalan at that time showed that average survival was 2.4 years, with progressive disease, with all patients suffering from increasing debility, pain, loss of dignity and hospitalisation. In 1982 there were advances in the US, when it was found that drugs used in acute leukaemia, such as Vincristine and Doxorubicin, when combined could have the effect of making some patients symptom free, albeit, only for a relative short period of time.

In 1983, we started the work on using bone marrow stem cells for transplants. This involved patients having their own stem cells harvested, followed by intensive treatment to destroy their remaining marrow; their stem cells were then returned and allowed to repopulate their marrow with fresh cells. They remained in hospital for around three weeks, and currently with this treatment less than 1% of patient experience serious side effects. We found that for the first time patients could achieve complete remission, in which they were seemingly disease free, i.e. by standard tests no disease could be detected (although we knew that some myeloma cells still lurked hidden in the body). The average survival increased from 2.4 years to 4.7 years, with a 20% plateau of patients surviving between 10 and 20 years. Although this treatment has been standard worldwide for the last 30 years, no patients were cured; many went on to live normal life span and died from other causes.

Biological Treatment

In the United States, remarkably, Thalidomide, which had produced deformities in new born babies, was found to have a biological effect on myeloma; inhibiting the blood supply to myeloma cells in the marrow and boosting the body's natural immune system. This was the start of the era of the so called biological treatments, and since then other biological drugs have been developed, such as Velcade, which interferes with the excretory mechanism in myeloma cells and again produces extraordinary benefit. Analogues of these drugs have become available such as Revlimid, Pomalidomide, and Carfilzomib, all with better activity, and less side effects.

Both Velcade and Carfilzomib are administered by injection, while Ixazomib is an oral variation of Velcade which is at least as effective. It can be taken weekly in 28 day cycles as induction as well as maintenance treatment, and has been shown to be considerably more effective when combined with Lenalidomide and Dexamethasone. Ixazomib received its product licence late in 2015 on the basis that it is not only effective, but easy to administer, with low toxicity.

Breakthrough 2016..... Immunotherapy

In November 2015 a major breakthrough occurred with two new 'antibody' drugs receiving regulatory approval for use in routine treatment clinics that are, to some extent, changing the face of myeloma.

Elotuzumib

Elotuzumib is a humanized antibody produced by the pharmaceutical industry, which uses recombinant technology and when injected activates the patient's own lymphocytes, acting as immunotherapy. Elotuzumab exerts a dual effect by directly activating receptors (SLAMF7 target) on immune lymphocytes directed against myeloma cells, and paradoxically using the same target on myeloma cells to kill them. It was tested in a worldwide study (Google ELOQUENT-2) involving 656 patients in combination with Lenalidomide and Dexamethasone, and compared with Lenalidomide and Dexamethasone alone for patients with the relapsed disease. There was a 33% improvement in progression-free survival which was highly significant and it was based on these findings that it received its license to be used in treating patients. .

Daratumumab

Daratumumab is a monoclonal antibody directed against CD38, and was also approved for the treatment of multiple myeloma in November 2015. It was found to be effective in patients who had received multiple treatments, and were refractory. It was seen to be effective as a single agent in heavily pre-treated patients, including doubly refractory patients. The overall response rate in these patients was 36%, including two patients who had complete response, and two patients who had a very good partial response; two thirds of the patients who had responded were free of progression one year later. The effects of this drug are mediated by the immune system of the patient; i.e. the patient is using their immune system to fight the disease.

Soon after the first study, the results were so promising in this very poor risk group of patients, that a multinational study was undertaken of 498 patients (google CASTOR) in patients at an earlier stage of their disease, and combining the Daratumumab with Velcade. The progression free survival at 12 months was 60%, when compared with 26% in which the drug was not used: a degree of response not previously seen in this group of Myeloma

patients. Similar results were seen when Daratumumab was combined with Revimid (google POLLUX Study), and both combinations received very rapid approval in the US in June of this year, and are now currently available, in selected centers, in the UK.

Studies are now being undertaken that are moving Daratumumab it to the front line of treatment, and it is likely it will end up as an adjunct in all stages of the disease, in conjunction with other drugs. There appears to be no ideal partner, literally all single agents in combination seem to work, and will undoubtedly be effective in combination with standard stem cell transplant; now routinely given.

The question is, does the immunotherapy effect continue after the Daratumumab has ceased to be given? Has the patient's immune system been educated to continue suppressing myeloma cells, which may, of course, be the 'natural' process that happens in patients who never develop active myeloma?

Author: Professor Ray Powles CBE and Linda Little