Thanks to Myeloma UK for preparing this Q&A (2011-March-25)

Revlimid® treatment and second cancers – is there a link?

Revlimid® (lenalidomide) is one of several novel treatments introduced in the last decade that has changed the course of treatment for myeloma. It is currently licensed for use in combination with the steroid, dexamethasone, to treat myeloma patients who have had at least one previous line of treatment.

Preliminary results from several international clinical studies have suggested that it is effective both as a front-line treatment and as a maintenance treatment for myeloma.

However, data emerging from three separate studies during the American Society of Haematology in December 2010 all indicated that long-term use of Revlimid® for myeloma may be associated with the development of secondary cancers. These observations have since come under intense scrutiny and stimulated debate worldwide.

Q. What did the clinical studies find?

The three Phase III clinical studies in question were each investigating the effect of Revlimid® as a maintenance treatment for myeloma patients.

Two of the studies, the US-led CALGB 100104 study and the French-led IFM 2005-02 study, looked at the effect of Revlimid® maintenance treatment after high-dose therapy and stem cell transplantation, on the length of remission. The third, the international MM-015 study, investigated the effect of Revlimid® maintenance treatment on the length of remission after an initial treatment combination including Revlimid® in older and / or less fit newly diagnosed patients unable to undergo high-dose therapy and stem cell transplantation.

The results from all three studies unanimously showed a significant improvement in the length of the remission period in patients receiving Revlimid® maintenance treatment compared to patients who did not receive Revlimid® maintenance treatment.

In the CALGB 100104 study, the 18 month follow-up results showed that the median remission period was 42 months with Revlimid® maintenance compared to 22 months without. For the IFM 2005-02 study, the researchers found in the four year follow-up, the median remission from the start of randomisation was 42 months in the Revlimid® maintenance group compared to 24 months in the non maintenance group. Similarly, for newly diagnosed older / less fit patients, Revlimid® maintenance significantly prolonged remission from 14 months in the non maintenance group to 31 months in the Revlimid® maintenance group.

So compelled by the data, researchers in the CALGB study gave patients in the non maintenance treatment group the option to 'cross-over' to the Revlimid® maintenance treatment group.

However, none of the studies have yet shown any significant difference in overall survival between the treatment groups. This is because the follow-up period to date has not been long enough to obtain survival data. Of more immediate concern though, has been the observation across all three studies of an apparent increase in the incidence of a second cancer in patients who received Revlimid® maintenance compared to patients who had not received Revlimid® maintenance.

Q. What is a second cancer and why does it occur?

A second cancer is an unrelated cancer which develops in a patient who already has a particular type of cancer. In medical terms, these are called secondary primary cancers.

Second cancers increase in frequency following certain cancer treatments particularly those that work by damaging DNA. Although such cancer treatments are effective against cancer cells they can also damage the DNA of normal cells. While most normal cells are able to repair the damage, occasionally the damage cannot be repaired causing these cells to become cancerous.

Historically, second cancers in myeloma have been rare largely because of the relatively short rate of survival once a diagnosis was made. However, they appear to be slowly on the increase because of the improved treatments - patients are now surviving long enough for them to become an issue. In myeloma, many second cancers are other haematological cancers such as leukaemias and lymphomas.

Q. Is the apparent increased risk of second cancers seen in these clinical studies due to Revlimid®?

No. At the moment there is not enough data to show a statistical difference between the Revlimid® maintenance and non Revlimid® maintenance groups to conclude that Revlimid® is the cause of this observation.

The figures reported in the CALGB study were 18 cases out of 231 patients with second cancers in the Revlimid® maintenance group compared to five cases out of 229 patients in the non Revlimid® maintenance group. In the IFM study, 17 out of 306 patients in the Revlimid® maintenance group developed second cancers compared to three out of 302 patients in the non maintenance group. Most of these occurred in patients who had been on Revlimid® maintenance for over two years. Second cancers were also observed in the MM-015 study with 12 cases in the Revlimid® maintenance group compared to four in the non-Revlimid® treatment group.

Overall, the figures equate to an approximate 7% risk of developing a second cancer compared to an approximate 2% risk with other treatments. Until more patients are analysed, the current numbers are not considered enough to be of statistical significance.

Q. What do the experts think?

The issue has been debated amongst the myeloma experts from around the world and the consensus is that they do not think the current data justify a change in the way Revlimid® is being used to treat myeloma patients.

The leading researchers from the CALGB and MM-015 studies have announced their decision to continue with Revlimid® maintenance dosing in their patients. They considered that the benefits of Revlimid® maintenance treatment far outweighed the risks of second cancers. They understood that the incidence of second cancers they observed were within the normal range and that there was not enough evidence to conclusively show that Revlimid® is associated with an unacceptable increase in the incidence of secondary cancers. However, they acknowledged that further research was required.

The researchers leading the IFM study announced their decision to stop Revlimid® dosing in patients still on maintenance treatment - these patients had already received Revlimid® maintenance treatment for more than two

years. Since the study had achieved its primary goal of investigating the effects of Revlimid® maintenance for 24 months, the researchers did not see any further benefit for continuing treatment in these patients.

What makes things difficult to interpret is that the studies cannot be directly compared as several aspects of each study were different. For example: induction treatments were very different in the each of the studies; there was a Revlimid® consolidation treatment period post-transplant in the IFM study; the follow-up period was much longer in the IFM study, and patients in the non maintenance treatment group of the CALGB study were given the option of crossing over to Revlimid® maintenance treatment.

Most agree that some duration of Revlimid® maintenance should be made routine. Some of the experts believe that the incidence of second cancers may be down to what initial treatment the patient had, with those receiving melphalan previously at greatest risk.

More investigations are certainly needed before any decisions on Revlimid® maintenance treatment can be made. A group of the leading European Myeloma experts on behalf of the European Myeloma Network has issued a consensus statement on the current position of the use of Revlimid® in the treatment of myeloma.
This is available to view on the Myeloma UK & MYELOMA EURONET websites: www.myeloma.org.uk & www.myeloma-euronet.org

Q. Are any other actions being taken?

In light of the observed increase in the incidence of second cancers in the clinical studies, the regulatory body, the European Medicines Agency (EMA), is conducting a full review to reassess the benefits and risks of Revlimid® for relapsed / refractory myeloma.

The manufacturer of Revlimid® is conducting all necessary analyses from the data that has been collected from the 170,000 patients who have received Revlimid® in clinical studies or as part of standard treatment. They are working closely with the EMA to provide the required data for the review.

The review process will take approximately six months. Until any recommendations are made by the EMA, Revlimid® will continue to be prescribed and used for myeloma patients.

Q. Is it safe to continue with Revlimid® treatment?

Yes it is. It is important to remember that the concerns are only being raised in patients who received Revlimid® as a maintenance treatment after high-dose therapy and stem cell transplantation, and in newly diagnosed older / less fit patients who are taking Revlimid® in combination with melphalan. These are only available within a clinical study.
Most patients on Revlimid® are treated for relapsed myeloma and there is no evidence that treatment under these circumstances increases the risk of secondary cancer.

Some patients in the UK may also receive Revlimid® treatment upfront as part of a clinical study. There are currently no plans to stop or change these studies, in particular the Myeloma XI study.

This is a large-scale UK study comparing thalidomide, Revlimid® and Velcade® combinations in newly diagnosed myeloma patients of all ages. Some of the patients are randomised to receive Revlimid® maintenance after high-dose therapy and stem cell transplantation. If you are on or are planning to take part in this study and are concerned, speak to your doctor.

Q. What are the future prospects for Revlimid® continuing as a treatment for myeloma?

Overall, Revlimid® is proving to be highly effective in combination with current and new treatments both for relapsed and newly diagnosed myeloma patients and in general, it is well tolerated with manageable side-effects. Under these settings, the benefits of Revlimid® arguably far outweigh the risks and it is likely that Revlimid® will eventually become a standard front-line treatment in myeloma.

If you have any questions, please contact Maggie by emailing Maggie@myeloma.org.uk or by calling +44 (0) 131 557 3332.