60th American Society of Haematology Annual Meeting (ASH) Research Highlights

OPTIMISING CURRENT TREATMENTS

The number of drugs available as myeloma treatment has grown significantly over the last two decades with discovery and approval of immunomodulatory drugs (thalidomide, lenalidomide (Revlimid®) and pomalidomide (Imnovid®)), proteasome inhibitors (bortezomib (Velcade®), cafilzomib (Kyprolis®) and ixazomib (Ninlaro®)), histone deacetylase inhibitors (panobinostat) and monoclonal antibody drugs (daratumumab (Darzalex®) and elotuzumab (Empliciti®)). However, there are still many questions regarding which treatments and drug combinations will deliver the best response in individual patients.

A few of Simon and Ira's highlights from the research looking at optimising current treatments are outlined below.

Optimising combinations of anti-myeloma drugs

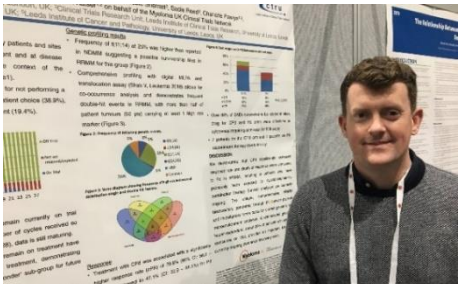
A number of researchers looked at optimising current treatments by combining drugs which work in different ways to kill myeloma cells to improve depth of response and patient outcomes. Due to the different ways trials are set-up, including patient groups and treatments used, it is difficult to compare or conclude definitively which combination delivers better results. However, the combined data suggest that combining drugs which work in different ways improves patient outcomes and that triplet or even quadruplet drug combinations should be considered in the future of myeloma treatment.

Addition of daratumumab to lenalidomide and dexamethasone improves remission time in newly diagnosed myeloma patients – MAIA[1]

Early results from the MAIA clinical trial were presented. The trial assessed the effectiveness of a triplet therapy containing daratumumab, lenalidomide and dexamethasone (DRd) versus a doublet therapy of lenalidomide and dexamethasone (Rd) in newly diagnosed patients. The results indicated that addition of daratumumab to Rd improved remission time, reduced the risk of progression by 45% compared to Rd alone and was well tolerated.

Addition of cyclophosphamide to pomalidomide and dexamethasone improves response rates in relapsed and refractory myeloma patients – MUK *seven* [2,3]

Results from MUK *seven*, funded by Myeloma UK and Celgene, showed that the combination of cyclophosphamide, pomalidomide and dexamethasone (CPd) significantly improved response rates and increased the depth of response in relapsed and refractory patients when compared to pomalidomide and dexamethasone alone (Pd). It is thought the addition of cyclophosphamide enhances the immunomodulatory effects of pomalidomide and dexamethasone.



Dr James Croft from the Royal Marsden presenting results from the MUK *seven* trial

Carfilzomib quadruplet versus triplet induction treatment before high-dose therapy and stem cell transplant – Myeloma XI [4]

Myeloma XI was a UK clinical trial which was also the largest ever conducted in myeloma. The trial looked at the benefits of different combinations and types of treatment in newly diagnosed myeloma patients. The trial compared the effectiveness of a quadruplet combination (carfilzomib,

cyclophosphamide, lenalidomide and dexamethasone (KCRD)) to versus triplet combinations (cyclophosphamide and dexamethasone with lenalidomide or thalidomide (CRD or CTD)) as intensive induction treatments prior to high-dose therapy and stem cell transplant (HDT-SCT) in newly diagnosed myeloma patients. The trial indicates the carfilzomib quadruplet was well tolerated and associated with deep responses both pre- and post-transplant. The quadruplet delivered improved remission time compared to the triplet combination.

Optimising the use of proteasome inhibitors

Maintenance treatment (further treatment given over an extended period of time after the main treatment has finished) is thought to be a key strategy for prolonging the duration of disease control. To date, the majority of research has focused on maintenance treatment using immunomodulatory drugs (thalidomide and lenalidomide) which have delivered significant improvements in remission time in newly diagnosed patients. However, researchers are now exploring the potential of proteasome inhibitors as maintenance treatment and whether they can deliver improved outcomes.

Ixazomib maintenance after high-dose therapy and stem cell transplant increases remission time in newly diagnosed myeloma patients – Tourmaline-MM3[5]

The trial explored the benefit of ixazomib maintenance after HDT-SCT in newly diagnosed patients. This results showed that ixazomib maintenance delivered a deeper response and improved remission time. Ixazomib maintenance was well tolerated with low rates of peripheral neuropathy. The data indicate ixazomib is an option for maintenance therapy in post HDT-SCT patients and should be explored further.

Maintenance with carfilzomib following carfilzomib, cyclophosphamide and dexamethasone in relapsed or refractory myeloma patients – MUK *five* [6]

The MUK *five* trial, funded by Myeloma UK and Amgen, compared effectiveness of carfilzomib maintenance vs observation only in patients refractory to initial treatment or patients at first relapse after treatment with carfilzomib, cyclophosphamide and dexamethasone KCd for a fixed duration. The results showed that carfilzomib maintenance deepened the response to treatment and increased remission time compared to observation. This indicates that carfilzomib maintenance could be a useful treatment option and should be studied further.

Prof. Kwee Yong from University College London presenting the MUK *five* results

OPTIMISING PATIENT STRATIFICATION

Myeloma can differ significantly between individuals. Having a better understanding of what is driving the differences between patients, such as age, fitness or the genetics of myeloma cells, or immune factors, can help tailor treatments for individual patients to deliver better patient outcomes.

Reduced remission time following HDT-SCT is a feature of high-risk myeloma – Myeloma XI[7]

Myeloma XI, the largest trial ever conducted in myeloma, looked at the benefits of different combinations and types of treatment in newly diagnosed myeloma patients focusing on the impact that this had on remission times and overall survival. A number of the participants in the trial had a short remission (less than 12 months). The research found patients with short remission times were more likely to be high-risk myeloma patients, with 64% having at least one

high-risk genetic abnormality. This finding highlights the need for studies to better understand high-risk patients and to develop treatments that can improve their outcomes.

Comparison of carfilzomib and bortezomib combinations in high-risk myeloma patients – MUK *five* [8]

The MUK *five* trial also compared the effectiveness of carfilzomib or bortezomib in combination with cyclophosphamide and dexamethasone (KCd and VCd, respectively) in relapsed or refractory patients. The data showed that patients treated with KCd achieved deeper responses and higher response rates than those treated with VCd. This data indicates that cafilzomib may be a better treatment option versus botezomib for the treatment of high-risk myeloma patients. Large scale trials in high-risk myeloma patients are needed to further support this result.

DEVELOPMENT OF NEW TREATMENTS

There were a number of talks and posters regarding the development of novel anti-myeloma treatments. Researchers are continually looking at ways to improve response rates and reduce side effects by developing treatments which are more effective and more targeted to myeloma cells.

Myeloma cells are different from healthy cells as they multiply uncontrollably. Myeloma cells do this due to changes in their biology which alter how cell growth and cell death are controlled and balanced. Understanding and exploiting these biological differences helps researchers to discover novel treatments to improve patient outcomes in myeloma.

It is encouraging to see so many novel treatments being developed which work in so many different ways to target and kill myeloma cells. Some of these novel drugs are detailed below.

Selinexor is known as a selective inhibitor of nuclear export (SINE). It works by blocking the action of a protein (XPO1) which is responsible for moving other proteins out of the central part of a cell (nucleus). Myeloma cells use XPO1 to move proteins which activate normal cell death (tumour suppression proteins) out of the nucleus, thereby deactivating them and stopping cell death. By blocking XPO1, selinexor stops myeloma cells from moving tumour suppression proteins out of the nucleus and leads to controlled death of the myeloma cells.

Venetoclax (Venclyxto®) is known as a pro-survival inhibitor. It works by accelerating myeloma cell death. Venetoclax targets a protein called BCL-2, which prevents apoptosis (programmed cell death) of some cells. Myeloma cells exploit the BCL-2 protein to promote their survival, allowing them to keep growing and multiplying. Venetoclax inhibits the action of BCL-2, which then causes myeloma cells to die.

BITEs (bispecific T-cell engager) – BITEs are immunotherapy drugs. They work by using the body's own immune system to kill myeloma cells. BITEs work by helping immune cells (T-cells) recognise myeloma cells as harmful by attaching to the surface of myeloma cells.

CAR-T cells (chimeric antigen receptor (CAR) T cells) are T cells that have been modified to express a receptor that will recognise one or more specific proteins found on the surface of myeloma cells. This means they can find and kill myeloma cells.

Melflufen (Ygalo®) is an adaption of the chemotherapy drug melphalan. It is made of melphalan and a peptide (small protein). Melflufen targets myeloma cells exploiting peptidases (enzymes which breakdown peptides) which are often over expressed in myeloma cells. The peptidases in the myeloma cells breakdown melflufen releasing melphalan in the cell. It is hoped that this adaption will make melflufen more targeted to myeloma cells and help reduce side effects.

GSK2857916 is an antibody drug conjugate. It consists of chemotherapy drug attached to an antibody. The antibody attaches to a specific protein found on the surface of myeloma cells (B cell maturation antigen (BCMA)) and the chemotherapy drug is released, killing the myeloma cell.

Isatuximab is a next generation monoclonal antibody which attaches to a specific protein (CD38) that is present on the surface of myeloma cells. It has been shown to kill myeloma cells directly and to help the immune system to better target and kill myeloma cells.

This research is very promising and shows how much work is going on around the world to find better treatments and, ultimately, a cure for myeloma. However, much of this research is at an early stage so we would stress cautious optimism at present. Larger, longer-term trials are still required in many cases.

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