

## **Background**

Myeloma is a malignant disorder of plasma cells, which is characterised by an excess of abnormal plasma cells, lytic bone lesions and a paraprotein in the serum and urine. It is frequently associated with painful bone lesions, fractures, myelosuppression and renal failure. It is a relatively common disease with an increasing incidence with age, the majority of cases occurring over the age of sixty. Cases occurring in the childbearing age group are rare. It is an incurable condition, which, in the absence of treatment, has a very poor prognosis. With modern treatments, the median survival is approximately 4 – 5 years. A number of staging systems/prognostic factors have been developed and the  $\beta_2m$  has proved to be the most useful, however, it is a surrogate marker not based on the biology of the tumour. More biologically relevant prognostic factors include the recurrent cytogenetic changes 13q-, t(11;14) and t(4;14).

The evaluation of treatment strategies in myeloma approaches to treatment have developed over the last 30 years. In early studies from the MRC, the equivalence of cyclophosphamide and melphalan was identified, however, oral treatment with Melphalan became the world standard treatment. In the 1980s, the value of combination chemotherapy was investigated and in the MRC Myeloma V trial, Melphalan alone was compared with ABCM (Adriamycin, BCNU, cyclophosphamide and melphalan). In this study there were significant differences in the achievement of plateau (61% v 49%) and in median overall survival (32 months v 24 months), indicating that ABCM was more effective than melphalan. Despite this overviews of published trials and of individual patient data from trials did not show a significant advantage for other combinations (VMCP, VBAP, VCAP), in comparison with the global standard of melphalan plus prednisolone (MP). However, relatively few of the combinations included the use of an anthracycline as in the ABCM regime. Thus, Melphalan remained the world standard against which developments were compared.

Alternative combinations, dose schedules and modes of administration of active chemotherapeutic agents were also explored in order to improve outcomes. High response rates were reported with VAD in which vincristine and adriamycin were given by 4-day

infusion with High-Dose Dexamethasone. Contemporaneously with this, Dexamethasone was recognised as a key component in VAD, and that good response rates could be obtained using this agent alone. (It is worth noting however, that these are not maintained long-term in the absence of consolidation with High Dose Melphalan (HDM)). Melphalan, the basis of standard treatment, was investigated in dose escalation studies and doses of  $140\text{mg}/\text{m}^2$  were found to achieve high response rates - 'complete responses' (CR) being reported in about 30% of patients compared to only 5% maximum in melphalan. The development of autologous stem cell rescue allowed safe escalation of the dose of melphalan to  $200\text{mg}/\text{m}^2$  and resulted in even higher remission rates, with CR being reported in approximately 50% of patients. In these early studies it also became apparent that melphalan should not be given prior to transplant as it impaired stem cell mobilisation and so standard became induction with VAD followed by stem cell mobilisation, followed by HDM, at a dose of  $200\text{ mg}/\text{m}^2$  with stem cell resource. These newer approaches to treatment were demonstrably associated with improved response (CRs 30% vs 5%) and it became important to investigate whether these improved response rates also translated into improved PFS and OS.

The first randomised trial to compare standard chemotherapy with HDT was carried out by the Intergroupe Français du Myelome (IFM). In an intention-to-treat analysis there was a significant advantage for patients in the intensive arm both in terms of response rate, response duration and survival, with median overall survival (OS) 56 months compared with 44 months in the standard arm. The MRC Myeloma VII trial randomised 400 patients, addressing the same question, comparing ABCM with a more intensive regimen, C-VAMP, followed by HDM. Response rates and response durations were improved in the HDT arm and there was a significant improvement in OS, median of 54 months compared with 42 months. In both of these studies and in studies from the RMH, the achievement of a CR correlated with improved survivals.

### **New agents and the development of combination treatment for myeloma**

Recently a number of new effective treatment modalities for myeloma have been developed and introduced into the clinic. Thalidomide was introduced as a sedative in the late 1950s

and withdrawn because of its teratogenicity, but was subsequently found to have immunomodulatory properties. In-vitro studies suggest thalidomide not only causes apoptosis of myeloma cells, but also has an anti-angiogenic effect and enhances tumour cell immunosurveillance. In initial clinical trials on groups of heavily pre-treated patients at relapse, a group unlikely to respond to conventional chemotherapy, response rates of 30-40% were seen. Side effects (somnolence, fatigue, tingling/numbness, tremors and headache), are mild and often restricted to doses greater than 200mg daily. A major side effect, which can impair the ability to deliver Thalidomide, is neurotoxicity seen in 30% of cases. There have been concerns about the occurrence of thromboembolic events and the incidence of DVT with single agent thalidomide appears to be low at approximately 10-20%, and this can be reduced by a number of approaches including aspirin, warfarin or low molecular weight heparin. In-vitro, the combination of Dexamethasone with thalidomide potentiates the anti-myeloma effect of thalidomide and in vivo, the combination seems to be particularly effective, increasing the number of responses. Combinations of Thalidomide and Dexamethasone in the presenting setting have been explored and have been shown to be effective and not to impair stem cell mobilisation. In presenting patients responses are greater, occur more rapidly and are associated with fewer infections than with VAD and it is now widely accepted that the VAD regimen will no longer be the main induction regimen for patients going for transplantation. It seems likely that the use of VAD will be replaced by a thalidomide-containing regimen. In the UK this will be Cyclophosphamide, Thalidomide and Dexamethasone, CTD, a regimen investigated in the Myeloma IX Study which is highly effective and well tolerated.

As oral Melphalan was considered the standard treatment for older less fit patients it was natural that it should be combined with thalidomide. MPT is associated with both increased responses (15% vs <3% CR) and survival in at least two large randomised studies. Thus, MPT, it is likely to be taken up widely as the standard approach for patients not destined for transplantation. This regimen is relatively toxic and difficult to deliver and in the UK where we have extensive experience with CTD, which seems to be equally effective but is better tolerated if it is the natural standard against which newer combinations will be assessed in this group of older less fit patients.

Revlimid is a thalidomide derivative, also available as an oral preparation, which is more potent in in-vitro assays with fewer adverse results than Thalidomide. It has been shown to be highly effective in the treatment of myeloma at relapse and two large phase III studies in Europe and the US using the same protocol (Rev/Dex vs Dex) showed identical results confirming the superiority of the combination Revlimid/Dexamethasone compared to Dexamethasone alone, both in terms of response (CR15% vs 4%) and survival. A major potential benefit of Revlimid is the absence of associated neurotoxicity or sedation, making it more tolerable, however, there is a significant rate of myelosuppression (20%) seen with this drug, which is not seen with Thalidomide. We have piloted the combination of Cyclophosphamide, Revlimid and Dexamethasone (CRD) and shown it to be flexible and highly effective and may be better tolerated than the combination MDT.

A further new therapeutic agent, the subject of this evaluation, available for the treatment of myeloma is Bortezomib (Velcade™). This drug reversibly inhibits the proteasome, an intracellular organelle that is central to the breakdown of ubiquitinated proteins. It is administered intravenously in the outpatient setting on days 1, 4, 8 and 11 of a 21-day cycle. Phase II clinical trials demonstrate it is effective for the treatment of relapsed refractory myeloma, with overall response rates (CR, PR, and MR) of approximately 35%, with 10% CR or near CR. These response rates can be increased to 50% with the addition of Dexamethasone. Response is independent of the number of previous lines of treatment, and type of previous treatment, confirming in-vitro data that bortezomib works via a different mechanism from standard treatments and overcomes intrinsic and acquired drug resistance. A randomised phase III trial, carried out at relapse, comparing bortezomib to Dexamethasone showed superiority in progression free and overall survival. The response rate (CR+PR) was 38% in the bortezomib arm compared to 18% in the Dexamethasone arm, which translated into a 22% difference in overall survival at 12 months. I would expect the combination Velcade + Dexamethasone to give better response than this and to accentuate the outcome benefits. In the first line setting, encouraging response rates have been seen when used in combination with Dexamethasone (Vel/Dex), or Adriamycin and PAD, with no impairment of the capacity to harvest stem cells.

Velcade has also been combined with Melphalan and Prednisone (MPV) for patients not destined to receive high dose treatment. The MPV regimen is tolerable and gives CR rates of up to 30%. Consequently, there is good evidence that the addition of Velcade to chemotherapy and to other new agents can increase the effectiveness of the regimen and is safe. We have piloted the combination of Cyclophosphamide, Velcade and Dexamethasone, CVD, and shown it to be effective and well tolerated.

In-vitro studies have shown evidence of synergy of Velcade with Revlimid, Thalidomide and Dexamethasone. The major side effect of Velcade is peripheral neuropathy and concerns about exacerbating peripheral neuropathy when used in combination with Thalidomide are important. The combination of Revlimid rather than Thalidomide with Velcade and Dexamethasone, RVD, would lessen these concerns. Investigators at the DFCI have investigated this regimen and found it to be effective and non-toxic.

While the response rates and impact on outcome of the combination regimens using Thalidomide, Revlimid and Velcade is well described there is little information to guide the sequence in which these combinations are used. As patients with myeloma live longer, with the use of effective treatment cassettes, this will become an increasingly important question, which will allow clinicians to make decisions about when to use a specific combination. In particular, it is important to know if the use of a therapy selects for resistance to a subsequent treatment and whether using upfront treatments leads to the development of resistance at relapse.

### **Response rates with differing treatment strategies**

Achieving a complete response/near-complete response is a prerequisite for the long-term survival and cure of myeloma patients. To date, studies that have given better response rates have translated into better OS and PFS.

Revlimid and Velcade as single agents and in combination have improved both response rates and outcomes. It is now important to understand if when used in combination and

sequentially they can improve the responses seen when in the context of standard treatment regimens.

### **Defining high risk disease**

Understanding and predicting response based on an understanding of the biology of the tumour, with the aim of adjusting treatment based upon this information is an important goal. A number of studies have presented the impact of cytogenetic subgroup on clinical outcome. The t(4;14), (15% of the total), has been shown to respond to induction and autologous transplantation analogous to other subgroups of myeloma; despite this the OS and PFS is short. If similar or better outcomes could be achieved by using novel agents alone, then the short-term impairment of QoL associated with transplantation, could be avoided. The other important high risk group in which this question can be addressed is 13q- detected by cytogenetics. This group constitute 20% of the total, has a very poor prognosis, and should be distinguished from 13q- detected by FISH, which contains the above group but has an intermediate prognosis.

### **Maintenance treatment**

In a recent French study maintenance thalidomide improved both the PFS and OS of patients receiving it – we anticipate similar results in the MRC IX study. A study from Arkansas suggested that using induction and maintenance thalidomide had the potential to generate resistant clones at relapse, however, the treatment approach used by that group differs so markedly from the approach used in the UK, that we do not believe the results are relevant to our practice. Few people tolerate full dose thalidomide long term and improving compliance may improve results; Revlimid has a better toxicity profile and could achieve this. A more in depth analysis of the French data suggests that the therapeutic benefit was driven by cases who failed to achieve a VGPR or CR with the transplant. Thus rather than continuous maintenance treatment, other approaches to post transplant treatment may be more appropriate such as a post transplant block of consolidation chemotherapy. A block containing Velcade, Revlimid and Dexamethasone, RVD, would allow us to understand if this 'cassette' of treatment could improve response and outcome. As a consequence of it side

effect profile and the necessity to give intravenous infusion, Velcade is unlikely to be used continuously as maintenance.

### **Treatment of relapse**

There is no standard of care for relapse but a number of lessons have been learnt from the study of patients relapsing from the early MRC studies (M Drayson personal communication). The duration of the first pfs interval <1, 1-2, 3-4 years correlates directly with outcome following treatment at first relapse. The impact of which standard treatment is used (ABCM, C weekly, Cyclophosphamide, Melphalan and VAD alone) does not seem to effect survival from the time of first relapse. A repeat autologous transplant at first relapse can be useful, even if the patient has had a transplant at presentation. For it to be clinically worthwhile, however, the duration of first pfs should be  $>^{18}/_{12}$ .

The choice of Dexamethasone, as a single agent, as the comparator arm for the Velcade studies was largely pragmatic based on choosing to use of a widely applicable effective agent that was applicable in used both in Europe and America. This choice was not ideal but having taken it, the evidence base now available for the use of Velcade in the relapse setting, is very good and can legitimately considered to be the standard of care, if size of the study is the criteria for defining 'standard'.

What was also learnt in these studies was that Velcade works by a totally different mode of action to standard chemotherapy and can give responses even when myeloma is refractory to other agents or is high risk (abnormal cytogenetics). Obvious clinical settings therefore would be primary refractory disease and possibly in settings where transplantation gives less than optimal results (t(4;14); 13q-). We are currently exploring the use of Velcade/Dex following relapse in the MRC Myeloma IX study, which should allow us to understand with larger numbers the impact of prior therapies and cytogenetics on the efficacy of Velcade.

## **Clinical Setting**

Until now, myeloma has been a 'cheap' disease to treat which has been reflected in the poor treatment outcomes and the general nihilistic views of the haematologists treating it. The advent of autologous transplantation and the new drugs above have changed this situation. There is now a degree of optimism about improving both the survival of myeloma patients and their quality of life. This has resulted in a change of clinical practice, and where stable disease was acceptable in the past, now the therapeutic aim is maximum response and stable disease.

This approach of maximum responses is applicable to each relapse. In the past, it was possible to generalise and say that there was a specific presentation and relapse treatment but subsequent to this, the approach was mainly palliative. With the increased understanding of the use of the new drugs it is possible to treat each relapse more effectively and, it is obvious clinically, that if a good response is obtained, patients have long disease free intervals with good quality of life. If response is not obtained, the QoL is poor and death follows rapidly. Based on these discussions therefore, it is not surprising that there was no standard of care for relapsed myeloma and the best evidence base for the treatment of relapse, comes from studies utilising new agents. In saying that however, data held by the MRC offer some insight into the way such previous treatments were used. Consequently, for a relapsing remitting disease the myeloma, restricting Velcade to any particular clinical setting i.e. 1<sup>st</sup> relapse/2<sup>nd</sup> relapse, does not make a lot of clinical sense, as during the course of their illness, it seems likely that most myeloma patients will receive all of the available therapies and that by so doing, responses will be achieved and patients will gain better pfs and os. What is becoming more important is an understanding of the order in which novel treatments should be used.

## **Guidance**

There is a clinical guideline both drawn up by UK Haematologists and with the Nordic Group of Haematologists, which helps to define the standard approach to the treatment of multiple myeloma.



### **Practical aspects of using Velcade**

One of the disadvantages of Velcade relates to its infusion over 10 to 20 minutes on days 1, 4, 8, and 11 of a 21-day cycle. This ties patients to Outpatients and consequently can affect their QoL. There are also a number of side effects of Velcade, including peripheral neuropathy and minor GI distortions. These side effects are all manageable but require some experience, but it is safe to say that Velcade is easily managed clinically.

It is clear that the addition of Dexamethasone increases the responses of Velcade, and in the majority of instances if responses are not seen within 3 to 4 cycles, there will not be clinically meaningful responses beyond this time point. Thus, the use of the combination Velcade and Dexamethasone at presentation means that the 50% to 60% of patients who are going to respond to Velcade can be identified early on, and if no response is seen, Velcade can be discontinued improving its clinical utility.

A major problem around the use of Velcade is the attendance at Outpatient Departments because the administration schedule has to be strictly adhered to. Consequently, treatment is either given on a Monday/Thursday or Tuesday/Friday of any week, and the Outpatient/Day Care facility has to be geared around the delivery of the drug. There are experimental approaches taking the dosing to weekly intervals, which may improve this. It would also be better if there were either an oral agent, or some way of delivering the drug closer to the patients' home.

Due to the issue of peripheral neuropathy, it is important that there is close monitoring of the patients. If neuropathy develops the dose needs to be reduced and/or stopped, but can be reinstated as the symptoms resolve. It is very important that patients who have acute painful peripheral neuropathy do not continue at full dose as it can result in permanent damage.

### **Use of Velcade in combinations**

The natural way to use Velcade is in combination, currently there are trials looking at the combination with Melphalan and Prednisone for elderly patients who are likely to respond to

this combination. Such a combination may well prove to be extremely useful in the presenting setting in older patients unsuitable for transplant. Similarly, for younger patients, defining the use of Velcade in relation to the gold standard treatment of transplantation is important. In this setting Velcade is unlikely to replace transplant but will be used to improve the results i.e. it will be used within the transplant setting to maximise clinical responses.

### **Sources of evidence**

There are no additional sources of evidence as far as I am aware, other than the wealth of clinical experience with the drug now showing that it is effective in relapsed disease, and greater responses are obtained earlier in the disease process.

### **IFM studies**

Data on the use of standard outcome collected over many years is available from the MRC myeloma trials database