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Summary

The drug and the review

Plerixafor was licensed in the UK in August 2009 to be used in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly. The recommended dose of plerixafor is 0.24mg/kg body weight per day (to a maximum of 40mg/day) administered by subcutaneous injection 6 to 11 hours prior to initiation of apheresis following a 4 day pre-treatment with GCSF. In clinical trials plerixafor was most commonly used for 2 to 4 consecutive days (although in some patients it was used for up to 7 days).

Background

Stem cell mobilization is mainly, but not exclusively, performed using G-CSF alone or after cyclophosphamide chemotherapy. There is not a universally agreed target CD34+ cell/kg dose to be collected or agreement on the number of apheresis performed but traditionally a minimum of 2 million CD34+ cells/kg collected from up to 5 apheresis days is used to support one cycle of high-dose therapy in the treatment of multiple myeloma.

About 20% of patients fail initial mobilisation in that they do not reach that target yield and repeat mobilisation using the same agents will still result in about 30% of those patients still not achieving the necessary target cell yield after pooling.

For patients who currently fail mobilisation the treatment options are limited: only a small proportion of patients with Non-Hodgkin’s Lymphoma will receive an allogenic transplant due to the high risk of mortality and lack of suitable donors and allogenic transplants may not be considered for myeloma patients at this stage in their treatment. Bone marrow harvest and subsequent autologous transplantation is the only other remaining transplant option. Of the remaining failed mobilisers, the majority would receive no further treatment until relapse.

Literature searched

Embase and Medline databases were searched freetext for articles containing the word plerixafor in either the title or the abstract. The bibliographies of references identified were used to identify additional relevant material. The websites of NICE, EMEA, NeLM and SMC were also searched for information about the drug. The manufacturers were also asked to comment on the first draft review in terms of accuracy and comprehensiveness which led to the inclusion of some additional reference material.

Efficacy Studies

No randomised controlled studies comparing plerixafor with repeat GCSF/GCSF with cyclophosphamide in patients that failed initial mobilisation were identified.
Summary

A series of open-label assessments of the impact of plerixafor in patients that failed initial stem cell mobilisation were identified. The largest of these studies was a compassionate use protocol involving a total of 115 data-audited poor mobilisers. The patients recruited had either NHL (54.8%), multiple myeloma (30.4%) or Hodgkin’s disease (14.8%). In this cohort the use of plerixafor enabled 75.7% of patients to proceed to transplant.

Another report of the results of an open-label rescue protocol involving 62 patients with non-Hodgkin’s lymphoma that failed initial mobilisation with either plerixafor + GCSF (n=10) or G-CSF alone (n= 52) as part of an RCT assessing first-line use. In this protocol a minimum of 2 million CD34+ cells/kg were required for transplantation although patients with fewer than this could undergo transplantation at the investigators discretion. It is reported that a median 2.9 million CD34+ cells/kg (range 0.16 to 7.3) were collected in a median 3 apheresis days in patients that had previously failed mobilisation with G-CSF. Of the 52 patients who had previously failed treatment with G-CSF, 46 (88%) went on to receive a transplant. Of the 6 who did not, 1 died, 4 failed mobilization and 1 did not go on for unspecified reasons.

These data are replicated in a small number of other reports involving smaller patient cohorts. The efficacy of plerixafor has also been explored in 2 relatively large RCTs that assessed its use as a potential first-line treatment, one in patients with multiple myeloma (n= 302) and one in patients with NHL (n=298). In the study in NHL, patients were randomised to receive up to 4 doses of plerixafor or placebo after mobilisation with up to 8 days of G-CSF. It was shown that 95.3% of patients achieved a target yield of 2x10^6 CD34+ cells/kg within 4 days of apheresis compared with 88.3% that received control treatment (nb this was not a primary end-point) – this equates to a number needed to treat of 14 to achieve one additional patient that meets the target yield. The data for patients going on to receive transplantation are almost identical to this. The study involving patients with lymphoma used an identical methodology and showed that 86.7% of patients treated with plerixafor achieved a target cell yield of at least 2x10^6 CD34+ cells/kg within 4 days of apheresis compared with 39.4% in the control group (NNT = 3) and in this case 90% and 55.4% went on to receive a transplant respectively.

Safety
The most common adverse effects seen with plerixafor are diarrhoea, nausea and injection site reactions. Overall the EMEA estimate that 3.3% of patients exposed to plerixafor experienced an adverse effect that led to the treatment being discontinued, interrupted or modified. They also note that the sample size of patients was considered limited for the detection of uncommon adverse effects but suggest that the following serious adverse effects occur more in plerixafor-treated patients: hypotension, cardiac disorders, deep vein thrombosis, and systemic anaphylactic reactions. As a condition of licensing Genzyme have also undertaken to follow up the patients enrolled in the Phase 3 studies for up to 5 years to assess whether the theoretical risk of tumour cell mobilisation associated with plerixafor leads to an increase in relapse rates or a reduction in progression-free survival compared to patients treated with G-CSF only regimens.

Critical evaluation
The main weakness in the evidence base for this drug is that there are no randomised trials comparing plerixafor with repeat mobilisation using GCSF in patients that fail initial mobilisation. Without these data it is not possible to robustly estimate the incremental benefit of this agent. However the uncontrolled data do seem to support that the fact that the drug is efficacious in this population. The randomised trials assessing the role of plerixafor as a first-line agent (unlicensed indication) are methodologically robust and establish its efficacy in that setting, however it is not possible to extrapolate efficacy data from the first-line setting to its role as a rescue treatment.

Potential benefits over existing technologies
There are indirect data to suggest that addition of plerixafor enables a higher proportion of patients that fail initial mobilisation to proceed to transplant than might otherwise do so if treated with alternative regimens. It is not possible to directly quantify this incremental gain – particularly over some of the more aggressive mobilisation regimens used in some centres. There are also potential benefits in reducing the number of apheresis attempts which should lead to some costs offset in terms of hospitalisation, a reduced number of patients requiring allograft and a reduced requirement for bone marrow harvests.

Potential disadvantages over existing technologies
Plerixafor is a relatively expensive new drug – costing just under £10,000 to treat a patient with 2 doses. There is also some concern about the theoretical risk of tumour cell mobilisation associated with plerixafor leading to an increase in relapse rates or a reduction in progression-free survival compared to patients treated with G-CSF only regimens.
Discussion points/Issues for consideration

- Whilst there is reasonable evidence that the use of plerixafor increases cell yield in poor cell mobilisers and in crossover studies is significantly better than G-CSF - there are no direct data available that enable us to quantify the incremental benefit over repeating a G-CSF cycle in patients who have failed a single mobilisation attempt.

- Is the target cell yield of $2 \times 10^6$ CD34+ cells/kg within 4 apheresis days accepted as reasonable and is it usual practice to abandon mobilisation after 2 days of apheresis if only $0.8 \times 10^6$ CD34+ cells/kg have been collected?

- Does the St Louis experience that around 20% of patients will fail to generate sufficient cells on initial mobilisation and that 30% of those will fail to generate enough cells on repeat mobilisation after pooling samples reflect UK experience?

- Is it reasonable to expect a robust economic analysis for this type of intervention?

- Is this an affordable development?

- Is it possible to define a cohort of patients that are unlikely to achieve an agreed pooled cell harvest target if-retreated with a G-CSF-based regimen?

- Is it possible to quantify the costs offset through a reduction in apheresis days?

- Is there consensus on the role of tandem transplantation and therefore the requirement for more cells to be harvested?

- The EMEA suggest that the common adverse effect profile of plerixafor has been reasonably well established and is acceptable. However there are concerns about the potential for plerixafor to mobilize tumour cells and this concern led to a restricted license and a request for longer term follow up in exposed patients.

Background

Plerixafor was licensed in the UK in August 2009 to be used in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly (1).

High-dose chemotherapy (HDT) with autologous stem cell support (ASCT) remains the treatment associated with the highest complete remission rate and when compared with conventional chemotherapy is associated with improvements in survival in multiple myeloma (2). In one study it was shown that increasing the dose of chemotherapy to a level that required autologous stem cell rescue resulted in a longer median overall survival compared to that seen in patients treated with conventional dose regimens (54.1 months vs 42.3 months) (3).

In 2005 the Guidelines Working Group of the UK Myeloma Forum stated that the use of HDT with ASCT should be part of the primary treatment strategy in newly diagnosed patients up to the age of 65 years with adequate performance status and organ function and recommended that it may also be considered in patients aged over 65 years with good performance status (4).

In a study of patients with relapsed Non-Hodgkin’s Lymphoma (NHL) it was shown that the 5-year overall survival rate in patients that received intensive chemotherapy with ASCT was 53% compared with 32% in patients treated with conventional chemotherapy (5).

In the NICE guideline published in 2003 entitled, “Improving Outcomes in haematological cancers” NICE support the use of HDT with ASCT and state that it should be available for patients who have multiple myeloma or recurrent or treatment-resistant Hodgkin’s lymphoma or aggressive lymphomas and who are fit enough to undergo this form of treatment. However they note that it should only be offered to those with other types of haematological cancer in the context of multi-centre RCTs (6).

Stem cell mobilization is mainly, but not exclusively performed using G-CSF alone or after cyclophosphamide chemotherapy. There is not a universally agreed target CD34+ cell/kg dose to be collected or agreement on the number of apheresis performed but traditionally a minimum of 2 million CD34+ cells/kg collected from up to 5 apheresis is used to support one cycle of high-dose therapy in the treatment of multiple myeloma. However in a recently published consensus guideline it was suggested that a minimum target of 4 million CD34+ cells/kg be collected and if feasible an average 8-10 million CD34+ cells be collected as this would allow most patients to undergo at least two autografts with an optimal CD34 dose during the course of their disease (2).
In a retrospective analysis of 1834 patients who underwent stem cell mobilisation for autologous transplantation between 1995 and 2006 in Washington University in St Louis, the authors assessed data from 1040 patients that met their inclusion criteria and made the following observations (7):

- Overall 81.3% of patients collected ≥2 million CD34+ cells/kg after a maximum of 5 aphereses.
- In 28.7% of patient ≥5 million CD34+ cells/kg were collected from a maximum of 5 aphereses.
- There was no significant difference in the failure rates to achieve 2 million CD34+ cells/kg seen between patients treated with GCSF (18.6%) or GCSF with cyclophosphamide (18.8%) however the latter regimen was associated with higher rates of achieving a target of 5 million CD34+ cells/kg (56.3% vs 26.8%)
- Of the 269 patients that were remobilised in this patient cohort following initial mobilisation failure it is reported that only 23% achieved a target 2 million cells/kg (18.4% of patients treated with G-CSF and 26.5% of patients treated with G-CSF and cyclophosphamide) from the second mobilisation process alone. However when stem cells were pooled from both collections 70.3% of patients achieved the target of 2 million CD34+ cells/kg (GCSF/GMCSF – 71.9%, GCSF/cyclophosphamide – 52.9%)

Plerixafor is being promoted for use in this patient population – ie the 20% of patients that fail initial mobilisation and for which a repeat mobilisation using the same agents will still result in about 30% of that 20% of patients that fail initial mobilisation still not achieving the necessary target after pooling.

For the group of patients who currently fail mobilisation the treatment options are limited: only a small proportion of patients with NHL will receive an allogenic transplant due to the high risk of mortality and lack of suitable donors. Allogenic transplants may not be considered for myeloma patients at this stage in their treatment. Bone marrow harvest and subsequent autologous transplantation is the only other remaining transplant option. Of the remaining failed mobilisers, the majority would receive no further treatment until relapse with the associated worse survival than if they had received an ASCT.

The purpose of this review is to examine the evidence to support the use of plerixafor in this population.

Pharmacology and pharmacokinetics

Dose
The recommended dose of plerixafor is 0.24mg/kg body weight per day (to a maximum of 40mg/day) administered by subcutaneous injection 6 to 11 hours prior to initiation of apheresis following a 4 day pre-treatment with GCSF. In clinical trials plerixafor was most commonly used for 2 to 4 consecutive days (although in some patients it was used for up to 7 days). (1)

Special Populations

The obese
In clinical studies the dose of plerixafor was based on body weight in patients up to 175% of ideal body weight – the treatment of patients that weight more than this have not been investigated, although the maximum dose recommended is 40mg/day. (1)

Renal impairment
Patients with a creatinine clearance of between 20 and 50ml/min should have their plerixafor dose reduced to 0.16mg/kg/day and within the SPC it is stated that there is insufficient data to make dosage recommendations for patients with a creatinine clearance of less than 20ml/ min or in patients on haemodialysis (1)

Pregnancy and breast feeding
Within the SPC for this product it is stated that plerixafor should not be used during pregnancy unless the clinical condition of the woman requires treatment with this drug. Based on pharmacodynamic mechanism of action the drug may cause congenital malformations and studies in animals have shown teratogenicity. Women of childbearing potential should use effective contraception during treatment with plerixafor (1)

It is not known whether the drug is excreted in breast milk and therefore current advice is that breast-feeding should be discontinued during treatment with plerixafor (1)

Contraindications
The only absolute contraindication to treatment with plerixafor is hypersensitivity to the drug itself or any of the excipients (sodium chloride, hydrochloric acid, sodium hydroxide) (1)

Drug / Food Interactions
No specific interaction studies have been undertaken but in vitro tests suggest that the product does not interact with the Cytochrome P450 enzymes (1)
Efficacy Studies

Efficacy in patients that have failed initial mobilisation
No randomised controlled studies comparing plerixafor with repeat GCSF/ GCSF with cyclophosphamide in patients that failed initial mobilisation were identified. Presented below are a series of open-label assessments of the impact of plerixafor in patients that failed initial stem cell mobilisation.

Micallef et al recently published the results of an open-label rescue protocol involving 62 patients with non-Hodgkin’s lymphoma that failed initial mobilisation with either plerixafor + GCSF (n=10) or G-CSF alone (n= 52). In this trial initial failure was defined as not achieving cumulative yields of 0.8 million CD34+ cells/kg or more after 2 days of apheresis or 2.0 million CD34+ cells/kg or more after 4 days of apheresis (8). These patients were eligible for treatment within the rescue protocol as follows: after a rest period of at least 7 days, patients were given G-CSF (10 microgram/kg/day) for 4 days. On the evening of the fourth day patients were given plerixafor (0.24mg/kg) and on the morning of the 5th day G-CSF was given again followed by apheresis (i.e. approximately 10 to 11 hours after the dose of plerixafor). Patients continued to receive plerixafor followed by G-CSF and apheresis for up to a total of 4 apheresis or until at least 5 million CD34+ cells/kg had been collected. After completion of stem cell collection, patients underwent myeloablative chemotherapy followed by transplantation. A minimum of 2 million CD34+ cells/kg were required for transplantation although patients with fewer than this could undergo transplantation at the investigators discretion. It is reported that a median 2.9 million CD34+ cells/kg (range 0.16 to 7.3) were collected in a median 3 apheresis days in patients that had previously failed mobilisation with G-CSF. Of the 52 patients who had previously failed treatment with G-CSF, 46 (88%) went on to receive a transplant. Of the 6 who did not, 1 died, 4 failed mobilization and 1 did not go on for unspecified reasons. Similarly for the 10 patients that previously failed treatment with plerixafor, 6 went on to receive a transplant, 1 died, 1 refused a transplant and 2 failed mobilization. It is reported that 40 of 44 evaluable patients had a durable graft at 12 months.

In the St Louis cohort discussed above (7) the authors report that of the 18 patients treated with GCSF/ plerixafor, there was a 27.8% failure rate to achieve a target of 2 million CD34+cells/kg but this decreased to 16.7% when the cells were pooled from the previous mobilisation/s. The corresponding figures for patients retreated with GCSF/ GMCSF (n= 217) were 81.6% and 28.1% and for patients treated with GCSF/ cyclophosphamide (n= 34) the failure rates were 73.5% and 47.1%.

Calendra et al have published the results of a compassionate use protocol involving a total of 115 data-audited poor mobilisers (9) Inclusion criteria for this programme included the following: aged between 18 and 70 years (revised to 8 and 78 to allow specific individual cases), have failed prior mobilisation or collection, be able to undergo transplant, WBC count> 3x10^9 per litre, ANC count > 1.5 x10^9 per litre, PLT count > 100x10^9 per litre, serum creatinine <= 1.5mg/dl, LFTs with 2x upper limit of normal and ECOG status of 0 or 1, LEV > 45%, no brain metastases and no hypercalcaemia. Successful mobilisation was defined as collection of a total of >= 2 million CD34+ cells/ kg during mobilisation. The patients recruited had either NHL (54.8%), multiple myeloma (30.4%) or Hodgkin’s disease (14.8%).

The results for the patient subgroups are outlined in Table 1

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Mean total CD34+ cell yield x10^6 cells/kg</th>
<th>Median days of apheresis (min and max)</th>
<th>% patients collecting &gt;= 2x10^6 CD34+ cells/kg</th>
<th>% patients that proceeded to transplant only using cells from plerixafor mobilisation</th>
<th>% patients that proceeded to transplant using either cells from this mobilisation or a pooled sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL patients</td>
<td>2.97</td>
<td>3 (0.7)</td>
<td>60.3%</td>
<td>33.3%</td>
<td>71.4%</td>
</tr>
<tr>
<td>MM patients</td>
<td>4.44</td>
<td>4 (1.7)</td>
<td>71.4%</td>
<td>54.3%</td>
<td>77.1%</td>
</tr>
<tr>
<td>HD</td>
<td>4.54</td>
<td>3 (1.5)</td>
<td>76.5%</td>
<td>58.2%</td>
<td>88.2%</td>
</tr>
<tr>
<td>Overall</td>
<td>3.51</td>
<td>3 (0.7)</td>
<td>66.1%</td>
<td>43.5%</td>
<td>75.7%</td>
</tr>
</tbody>
</table>
It can be seen from these results that use of plerixafor enabled 75.7% of patients to proceed to transplant but unfortunately it is not possible to assess how many of these patients might have been able to proceed using a repeat mobilisation with G-CSF (+/- cyclophosphamide) and pooling the resultant cell yield.

Fowler et al have also reported on their experience of using plerixafor in their institution in 20 patients who had failed previous mobilisation attempts (15 G-CSF alone and 5 G-CSF plus chemotherapy) (10). Patients had received a median of 2 (range 0 to 8) previous treatment regimens. They report that the use of plerixafor enabled 16 of the 20 patients to proceed to ASCT, 2 other patients had sufficient yield to proceed but elected not to. The authors report a median cell yield of 4.0 million CD34+ cells/kg in 2 (range 1-3) days in patients treated previously with G-CSF and chemotherapy and a median yield of 3.7 million CD34+ cells/kg in a median 2 (range 2 to 3) days in patients treated only with G-CSF. (10)

In a randomised study in patients with multiple myeloma that assessed plerixafor as a first-line treatment (11- discussed in detail below) – 7 patients failed initial treatment with G-CSF alone (n= 151) (10 microgram/kg/day given for up to 8 days) in that they failed to collect at least 0.8 million CD34+ cells/kg after 2 days of apheresis or at least 2 million CD34+ cells/kg (or 4 million cells/kg if planned for tandem transplantation) after 4 days of apheresis. These patients were enrolled into a rescue procedure. After a minimum 7-day rest period, the patients received a course of G-CSF and plerixafor (as described in the cohort study above) and it is reported that all 7 patients collected at least 2 million cells/kg in 4 days of apheresis and all underwent transplantation (4 of the 7 underwent tandem transplantation).

**Efficacy as a first-line mobilisation agent (unlicensed indication)**

Two Phase III placebo-controlled randomised controlled trials assessing the efficacy of plerixafor as a first-line agent were identified – one in patients with multiple myeloma (11) and one in patients with NHL (12)

In the trial in patients with multiple myeloma (11), 302 patients were randomised to receive either plerixafor or matching placebo after mobilization with G-CSF (10 microgram/kg/day given for up to 8 days). Plerixafor at a dose of 0.24mg/kg day given by subcutaneous injection (or matching placebo) was started on the evening of day 4 and continued for up to 4 days or until 6 million CD34+cells/kg were collected by daily apheresis carried out each morning from Day 5 onwards.

The primary end-point was the proportion of patients collecting more than or equal to 6 million CD34+ cells/kg in 2 or fewer apheresis days. Secondary end-points included the proportion of patients collecting more than 2 million CD34+ cells/kg in 4 or fewer apheresis days, the proportion of patients collecting more than 6 million CD34+ cells/kg in 4 or fewer apheresis days, the number of days to platelet and neutrophil engraftment, the proportion of patients maintaining a durable graft at 100 days, 6 months and 12 months after transplantation.

The trial methodology was robust in that both physicians and patients were blinded to allocated treatment, there was no loss to follow up, randomisation produced two well-balanced groups at baseline and the results were analysed using intention to treat principles.

In this trial it is reported that 53 of 154 (34.4%) of patients randomised to placebo and 106 of 148 (71.6%) of patients randomised to plerixafor achieved the primary endpoint of collecting more than 6 million CD34+ cells/kg in two or fewer days of apheresis. This equates to an absolute difference of 37.2% (95% CI: 26.8% to 47.6%) which means that for every 3 (95% CI: 3 to 4) patients that receive plerixafor as part of their initial mobilisation regimen one additional patient will achieve this level of cell target within 2 days of apheresis. The additional secondary end-points are outlined in the table below.

<table>
<thead>
<tr>
<th>End-point</th>
<th>Placebo group</th>
<th>Plerixafor</th>
<th>Difference/NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>6x10^6 CD34+ cells/kg within 4 days of apheresis</td>
<td>51.3%</td>
<td>75.7%</td>
<td>24.4% (NNT= 5)</td>
</tr>
<tr>
<td>2x10^6 CD34+ cells/kg within 4 days of apheresis</td>
<td>88.3%</td>
<td>95.3%</td>
<td>7% (NNT= 14)</td>
</tr>
<tr>
<td>% patients that underwent transplant following initial mobilisation regimen</td>
<td>88.3%*</td>
<td>95.9%</td>
<td>7.2% (NNT=14)</td>
</tr>
<tr>
<td>% alive at 12 months</td>
<td>96.1%</td>
<td>95.3%</td>
<td>-0.8%</td>
</tr>
</tbody>
</table>

* this figure does not include the 7 patients that entered the rescue procedure with plerixafor and did subsequently undergo successful transplantation. The results indicate that plerixafor is associated with higher proportions of patients with multiple myeloma achieving target cell harvests more quickly but the data are not yet available to judge whether this leads to improved clinical outcomes.
A trial of identical methodology has been carried out in 298 patients with NHL in which the primary end-point was the proportion of patients able to mobilize at least 5 million CD34+ cells/kg in 4 or less apheresis days. Again a rescue procedure using plerixafor was available for patients that failed to mobilize sufficient cells and the results of this procedure have already been described in detail above (8). Again it is a methodologically robust trial with adequate blinding in place, low rates of loss to follow up (3 patients in the plerixafor arm), randomisation producing two well-balanced groups at baseline and results analysed using intention to treat principles. In this trial it is reported that 59.3% of the plerixafor group achieved the primary end-point of collecting at least 5 million CD34+ cells/kg in 4 or less apheresis days compared to 19.6% in the placebo group. This equates to a difference of 39.7% - which means that for every 3 patients with MM that receive plerixafor one additional patient will achieve the target cell collection. The results of selected secondary end-point assessments are outlined below:

<table>
<thead>
<tr>
<th>End-point</th>
<th>Placebo group</th>
<th>Plerixafor</th>
<th>Difference/ NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 2x10^6 CD34+ cells/kg within 4 days of apheresis</td>
<td>47.3%</td>
<td>86.7%</td>
<td>39.4% (NNT = 3)</td>
</tr>
<tr>
<td>% patients that underwent transplant following initial mobilisation regimen</td>
<td>55.4%</td>
<td>90%</td>
<td>34.6% (NNT= 3)</td>
</tr>
<tr>
<td>% alive at 12 months</td>
<td>87.2%</td>
<td>88%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

Again these results indicate that whilst plerixafor is associated with increased yields of target cells, the data are not yet available to assess whether this leads to improvements in clinical outcomes.

The results of a small cross-over study are reported in the European Public Assessment Report (EPAR) for plerixafor (13). In this study 25 patients (15 with NHL and 10 with MM) were randomly assigned to receive either G-CSF and plerixafor or G-CSF alone as initial mobilising regimen, followed by a 2-week washout and remobilisation with the alternate regimen. Several protocol changes were introduced during this study but the basic results are outlined below

<table>
<thead>
<tr>
<th>End-point</th>
<th>G-CSF + plerixafor (n=298)</th>
<th>G-CSF + placebo (n=295)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 2x10^6 CD34+ cells per kg in 4 or less days of apheresis</td>
<td>10 (100%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Patients with at least 5x10^6 CD34+ cells per kg in 4 or less days of apheresis</td>
<td>10 (100%)</td>
<td>5 (50%)</td>
</tr>
</tbody>
</table>

**Efficacy as a mobilisation agent in patients with Hodgkin’s disease**

Brief details of a small open-label study of plerixafor in patients with Hodgkin’s disease are outlined in the EPAR (13). It is reported that of 22 patients treated with plerixafor (plus G-CSF) 20 (90%) achieved a target of at least 2 million CD34+ cells per kg within 4 apheresis days and 15 (68%) a target of 5 million CD34+ cells within the same timeframe.

**Safety**

The adverse effects which occurred in at least 5% of participants in the Phase 3 studies and occurred more frequently in the plerixafor group than the control group are listed below (13):

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>G-CSF + plerixafor (n=298)</th>
<th>G-CSF + placebo (n=295)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse effect</td>
<td>97.7%</td>
<td>96.6%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>10.1%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>39.9%</td>
<td>19.3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>38.9%</td>
<td>26.1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14.4%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>6.7%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.4%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28.9%</td>
<td>26.1%</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>26.2%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>15.1%</td>
<td>10.2%</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>5.7%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>13.1%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Headache</td>
<td>22.5%</td>
<td>21.4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10.4%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.1%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.7%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Rash</td>
<td>5.7%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>
As can be seen the most common adverse effects seen are diarrhoea, nausea and injection site reactions. Overall the EMEA estimate that 3.3% of patients exposed to plerixafor experienced an adverse effect that led to the treatment being discontinued, interrupted or modified (13). They also note that the sample size of patients was considered limited for the detection of uncommon adverse effects but suggest that the following serious adverse effects occur more in plerixafor-treated patients: hypotension, cardiac disorders, deep vein thrombosis, and systemic anaphylactic reactions. As a condition of licensing Genzyme have also undertaken to follow up the patients enrolled in the Phase 3 studies for up to 5 years to assess whether the theoretical risk of tumour cell mobilisation associated with plerixafor leads to an increase in relapse rates or a reduction in progression-free survival compared to patients treated with G-CSF only regimens. From the EPAR this theoretical risk appears to be the main reason that the EMEA did not approve the use of plerixafor as a first-line agent.

Health Economics

The Scottish Medicines Consortium have reviewed and approved plerixafor for use in NHS Scotland within its licensed indications (14).

The manufacturer presented a cost-utility analysis of the use of plerixafor for mobilisation in multiple myeloma and non-Hodgkin’s lymphoma patients who had failed at least one previous mobilisation attempt. The comparator mobilisation treatments were G-CSF and GCSF in combination with cyclophosphamide.

Rates of successful mobilisation were drawn from a range of sources, data from the compassionate use programme being used for plerixafor while a retrospective analysis was used for G-CSF and G-CSF + cyclophosphamide. Successful mobilisation was followed by autologous transplantation, while those not mobilising were largely assumed to undergo chemotherapy. The effectiveness, survival estimates and utility estimates for these were taken from the literature. Adverse events during mobilisation were not considered.

The key results in multiple myeloma patients were as follows:

- The cost per successful mobilisation gained was £12,768 compared to G-CSF
- The cost per successful mobilisation gained was £11,074 compared to G-CSF + cyclophosphamide
- A gain of 0.47 QALYs at a cost of £18,832 compared to G-CSF, to yield a cost per QALY of £39,649
- A gain of 0.41 QALYs at a cost of £15,561 compared to G-CSF + cyclophosphamide, to yield a cost per QALY of £38,278

The key results in non-Hodgkin’s lymphoma patients were as follows:

- The cost per successful mobilisation gained was the same as among multiple myeloma patients
- A gain of 1.22 QALYs at a cost of £23,950 compared to G-CSF, to yield a cost per QALY of £19,586
- A gain of 1.06 QALYs at a cost of £20,054 compared to G-CSF + cyclophosphamide, to yield a cost per QALY of £18,874 compared to G-CSF + cyclophosphamide

The economic case was considered demonstrated in the NHL indication. In the MM indication, the cost-effectiveness ratios were comparatively high, but the economic case was considered demonstrated when viewed in light of SMC orphan drug modifiers, particularly the ability of the treatment to allow patients to bridge to an effective treatment (autologous bone marrow transplant).

The All Wales Medicine Strategy Group is also reviewing plerixafor, with final guidance anticipated in early March 2010 (personal communication).

The North England Cancer Drug Approvals Group (NECDAG) have also appraised plerixafor, approving its use in September 2009. NECDAG estimated cost per life year gained ranging from £13,021 to £29,298 and cost QALY estimates ranging from £15,319 to £34,468 (personal communication).

Estimated cost per 100,000 population

Plerixafor costs £4,883 per dose and therefore it costs £9,776 (excluding VAT) to treat a patient with 2 doses of plerixafor and £19,532 to treat with 4 doses. As plerixafor is used in addition to G-CSF the costs associated with its use are additional to the G-CSF costs that are incurred anyway. There may however be some costs offset through a reduced requirement for apheresis days.

Each year about 2 autologous transplants are carried out per 100,000 population (Genzyme – personal communication). Assuming that an additional 20% would be carried out if initial mobilisation was successful – this equates to an 2.4 initial mobilisation attempts per 100,000 population per year. If plerixafor is used in the 20% that fail initial mobilisation (ie 0.48 cases per 100,000 population) and an average 3.8 vials (13) are given then the introduction of this drug could increase drug budgets by around £8906 per 100,000 population (excluding VAT). However clinicians feel that the majority of patients will respond to 2 doses of plerixafor and the average 3.8 doses used in the compassionate use programme reflects the fact that the company supplied 5 vials for each patient registered. If the treatment is restricted to a maximum of 2 vials then the treatment cost would decrease to £4688 (excluding VAT).
It is possible that the introduction of plerixafor instead of remobilisation with GCSF/ cyclophosphamide could lead to reductions in other transplant associated costs including those arising from a decrease in apheresis days, reduced use of bone marrow transplants and reduced use of allografts. It is however difficult to quantify the potential costs offset.

**Issues for consideration discussed at LCNDG**

Whilst there is reasonable evidence that the use of plerixafor increases cell yield in poor cell mobilisers and in crossover studies is significantly better than G-CSF - there are no direct data available that enable us to quantify the incremental benefit over repeating a G-CSF cycle in patients who have failed a single mobilisation attempt.

The group felt that the data described are an accurate reflection of clinical experience with plerixafor and this also reflected the feedback from all the major transplant centres in London. Its use enables the vast majority of patients that fail initial mobilisation to proceed to transplant. The data do not exist to quantify the benefit over repeating a G-CSF cycle but the group felt that there are considerable service costs associated with this latter approach which should also be taken into account in such a comparison. However it was noted and accepted that some centres support the use of alternative second-line regimens (e.g. etoposide plus G-CSF) in appropriate patients before considering use of plerixafor.

Is the target cell yield of \(2 \times 10^6\) CD34+ cells/kg within 4 apheresis days accepted as reasonable and is it usual practice to abandon mobilisation after 2 days of apheresis if only \(0.8 \times 10^6\) CD34+ cells/kg have been collected?

A target of \(2 \times 10^6\) CD34+ cells/kg is accepted as reasonable but there is no agreed guidance on when mobilisation should be abandoned in light of poor cell yields during the course of apheresis. However it was accepted that it would be unusual to apherese a patient more than 2-3 times for any single mobilisation attempt as the peak is quite narrow (1-2 days). If a patient has not mobilised adequately they are unlikely to reach a threshold of \(2 \times 10^6\) in that time.

Does the St Louis experience that around 20% of patients will fail to generate sufficient cells on initial mobilisation and that 30% of those will fail to generate enough cells on repeat mobilisation after pooling samples reflect UK experience?

Yes

Is it reasonable to expect a robust economic analysis for this type of intervention?

The SMC analysis (and subsequent approval) was felt to be robust enough to reassure the group that plerixafor was a reasonably cost effective intervention. As this analysis was based on an average use of 1.9 vials and clinical experience suggests that the majority of patients only require two doses the group felt that they would also support this limit.

Is this an affordable development

Whilst the group are unable to assess local affordability it was felt that an estimated cost of less than £5000 per 100,000 population (excluding VAT) is not prohibitive. It was also noted that there may be costs offset which could be negotiated locally.

Is it possible to define a cohort of patients that are unlikely to achieve an agreed pooled cell harvest target if-retreated with a G-CSF-based regimen?

There is research going on into this in various centres but at this time it is not felt to be possible.

Is it possible to quantify the costs offset through a reduction in apheresis days?

The manufacturer has supplied data to the group to suggest that the UK cost of a repeated apheresis procedure have been estimated to be £756 per day in 2003.

Is there consensus on the role of tandem transplantation and therefore the requirement for more cells to be harvested?
Issues for consideration discussed at LCNDG

There is little use of tandem transplantation in the UK at present and therefore the target of $2 \times 10^6$ CD34+ cells/kg is felt to be reasonable for most patients. Although for some myeloma patients it may be reasonable to collect enough stem cells to carry out two transplants.

The EMEA suggest that the common adverse effect profile of plerixafor has been reasonably well established and is acceptable. However there are concerns about the potential for plerixafor to mobilize tumour cells and this concern led to a restricted license and a request for longer term follow up in exposed patients.

Accepted that this is a theoretical risk that is present with all forms of mobilisation treatment – so this concern is not unique to plerixafor. However at present it was felt that in light of this it would be inappropriate to support the use of plerixafor outside licence as a potential first-line agent.

The document reflects the views of LCNDG and may not reflect those of the reviewers.

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