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Evaluating the Use of Plerixafor in Stem Cell Mobilisation – An Economic Analysis of the PHANTASTIC Trial

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Plerixafor is an effective haematopoietic stem cell mobilising agent in candidates for autologous transplantation, including patients with myeloma and lymphoma. Here we compare 98 plerixafor recipients in the PHANTASTIC trial with 151 historic controls mobilised by conventional chemotherapy (each with granulocyte colony-stimulating factor, G-CSF). Seventy (71.4%) plerixafor-mobilised patients achieved the composite primary endpoint of $\geq 4 \times 10^6$ CD34+ cells kg^{-1} in ≤ 2 aphereses and no clinically significant neutropenia, compared to 48 (31.8%) historic controls ($P < 0.001$), and this significant advantage was maintained in scenario analyses testing components of this composite endpoint. A patient-level cost analysis was undertaken for 249 patients, which included the cost of remobilising patients where initial mobilisation had failed. Combined mean treatment cost for plerixafor mobilised patients was £12,679 compared with £11,694 for historical controls. However, plerixafor produces an average saving of £3,828 per lymphoma patient but average cost increase by £5,245 per myeloma patient. The present data demonstrate cost-effectiveness for plerixafor as a first line mobilisation agent, certainly for lymphoma patients, where substantial resource savings and achievement of the primary endpoint are likely. J. Clin. Apheresis 31:434–442, 2016.

Key words: stem cell mobilisation; stem cell transplantation; lymphoma; myeloma; haematology

INTRODUCTION

The outlook for many haematological malignancies has steadily improved over the last couple of decades, due to both newer treatment agents and also better management of their side effects [1–3]. The mainstay of treatment is standard chemotherapy, which is typically given as several cycles lasting 3–6 months. Unfortunately, such first-line chemotherapy is not always curative as a proportion of patients achieve a remission, but subsequently relapse [4]. Many will respond to further chemotherapy often at much higher doses to give the best chance of cure. Life-threatening marrow aplasia associated with this high-dose chemotherapy is mitigated by infusing haematopoietic stem cells shortly after completion of the high-dose chemotherapy. In the case of multiple myeloma and lymphomas [both Hodgkin's disease (HD) and non-Hodgkin lymphoma (NHL)], it is standard practice to use the patient's own stem cells [5–7]. Strictly speaking, the entire procedure is "high-dose chemotherapy with autologous stem cell rescue," but this is usually colloquially termed "autografting" or autologous stem cell transplantation (ASCT).

It is of course essential to collect and cryopreserve sufficient stem cells, prior to commencing the high-dose chemotherapy component of the autograft. Detection of the antigen CD34 is widely used as a marker of early haematopoietic cells, and the CD34+ population contains the stem cells responsible for long-term marrow recovery post autografting. It is generally accepted that 2×10^6 CD34+ cells per kg of recipient weight is the minimum dose for satisfactory engraftment, but doses up to 4×10^6 CD34+ cells kg^{-1} may lead to more rapid engraftment; doses higher than this may not achieve any additional

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clinical advantage [8,9]. Formerly, these CD34+ cells were collected by aspirating several hundred mls of marrow under general anaesthesia, but nowadays most units prefer to mobilise these CD34+ cells into the bloodstream, as haematopoietic stem cells from this source engraft more quickly and also due to practical considerations and patient preference. These cells are collected by harvesting the mononuclear fraction of the blood by standard leukapheresis [10,11].

Several strategies have been used to mobilise CD34+ cells into the bloodstream. Granulocyte colony stimulating factor (G-CSF) alone may be used, especially for patients with myeloma. However, CD34+ yields are improved by giving "mobilising" chemotherapy together with G-CSF, and this strategy is common in Europe [12]. A single dose of cyclophosphamide is widely used as mobilising chemotherapy, especially in myeloma; for lymphoma patients who are responding to salvage (second or subsequent line) chemotherapy, a further course of salvage chemotherapy is often used instead [13,14].

The mobilising agent plerixafor competes for C-X-C chemokine receptor type 4 (CXCR4), which is expressed on CD34+ cells. Its ligand, stromal cell derived factor 1 (SDF-1), is expressed on marrow stroma, and this interaction is important for CD34+ cell adherence in the marrow. Several studies have shown that plerixafor with G-CSF can mobilise CD34+ cells in sufficient numbers to support an autograft [15–18] and these include randomised studies showing that plerixafor with G-CSF is superior to G-CSF alone [8,12,19,20]. However, plerixafor has not been compared to conventional chemotherapy (each with G-CSF). Our study of Plerixafor Harvesting And No chemoTherapy for Autologous Stem cell Transplantation In Cancer (acronym = PHANTASTIC) examined CD34+ cell mobilisation in 98 patients with myeloma, HD or NHL, and compared the findings with 151 immediately preceding consecutive historic controls mobilised with conventional chemotherapy. The findings on efficacy and toxicity have recently been reported in Clark et al. [21]. Here we summarise these findings and extend them to include a health economic comparison between plerixafor and conventional chemotherapy using individual patient level data.

METHODS

Clinical Details of PHANTASTIC and Historic Control Group

The full eligibility criteria for entry into PHANTASTIC and the historic control group have recently reported [21]. Briefly, these were; patients with underlying myeloma or lymphoma (either HD or NHL), aged $\geq$18, in whom ASCT was intended as their next course of treatment. Patients were ineligible if they had undergone any prior attempt at harvesting for the current transplant. Entry took place between April 2010 and June 2012. Trial entrants received non-pegylated G-CSF from Day 1 for 5–8 days as needed, and plerixafor daily from Day 4 for 1–4 days as needed; stem cell collection was performed daily beginning on Day 5, until either the target stem cell number ($\geq 4 \times 10^6$ $CD34^+$ cells kg^{-1}) was collected or four leukapheresis procedures had been performed. All drug doses were standardised, as previously reported [21].

The historic control group comprised all 151 immediately preceding consecutive patients in whom stem cell mobilisation was undertaken, and who would have fitted the PHANTASTIC eligibility criteria, back to November 2006. They received non-pegylated G-CSF at the same dose, together with mobilising chemotherapy. The latter was either a single dose of intravenous cyclophosphamide together with MESNA (used to protect the lining of the bladder) or a further course of salvage chemotherapy to which the patient was already known to be responding, in line with standard practice. Unless clinically contraindicated, historical control patients who mobilised $<4 \times 10^6$ CD34+ cells kg^{-1} in their first harvest round underwent a second round of harvesting, and those who thereafter still did not yield the minimum safe level of 2×10^6 CD34+ cells kg^{-1} underwent a third round of harvesting. However, plerixafor became available as a second-line harvesting strategy in 2008 (during the accrual of the 151 historic controls). Therefore, two comparator control groups were defined: the perprotocol group of 140 patients (control Group 1) which omits the 11 patients (6 myeloma, 5 NHL) who received plerixafor as second-line mobilisation, and control Group 2 comprising the entire historical control cohort of 151 patients. Patients in the trial group were retrospectively matched with patients in the control group, this was to reduce confounding and strengthen the evidence produced from the study in the absence of a randomised controlled trial.

The primary study endpoint was a composite of both an optimal stem cell harvest ($\geq 4 \times 10^6$ $CD34^+$ cells kg^{-1} in no >2 aphereses) and a neutrophil count that never fell below 1.0×10^9/Litre in the 3 weeks following initiation of mobilisation. In addition to the previously reported clinical analysis centred on the primary composite outcome, three scenario analyses, stratified for each disease subgroup (myeloma, HD and NHL), were conducted to explore whether the patients failing the composite primary endpoint might have passed its individual elements.

Economic Analysis

The economic analysis compared the outcomes and costs of patients mobilised by plerixafor and G-CSF in the PHANTASTIC trial with the historical control arm who received conventional chemotherapy and G-CSF. Treatment costs and outcomes from any secondary or tertiary mobilisation attempts are included in the analyses, as these are part of normal clinical practice for ASCT. All clinical and economic data were reviewed

and quality checked by at least two research personnel before inclusion into the database.

First, a detailed patient-level cost analysis was undertaken for each patient in both groups. The analysis evaluated resource use from the first dose of G-CSF (PHANTASTIC trial patients) or the beginning of the mobilising chemotherapy schedule (historic control patients), up to and including the end of stem cell collection. It was not possible to assess the extent to which plerixafor might have altered clinical outcome or not (e.g., overall or relapse free survival), since patients were not routinely followed beyond 12 months after their transplant. The analysis is therefore a cost-effectiveness study (cost per patient achieving a stem cell yield sufficient to support a subsequent transplant), and contributes to the increasing evidence about the cost-effectiveness of plerixafor in myeloma and lymphoma patients [22–28].

The cost analysis identified the resources used for each of the 249 patients, comprising stem cell apheresis, processing and freezing, pharmaceutical costs of plerixafor, chemotherapy, G-CSF, drugs used to mitigate adverse events, associated plerixafor and chemotherapy administration and their supportive medication costs, blood tests to assess CD34+ numbers, and bone marrow harvesting. The unit costs were collected from a variety of sources, which included the hospital finance department, the British National Formulary and UK National Health Service reference costs. To complete the cost analysis the following assumptions were made:

- The standard dose of plerixafor was 240 μg kg^{-1} recipient weights and each vial contained 24 g of plerixafor. Because of drug accountability issues within clinical trials, plerixafor vial sharing was not permitted within the PHANTASTIC trial patients, and therefore the minimum vial usage per apheresis day was one, and patients over 100 kg required two vials. In normal NHS practice, it may be possible to use residual vial contents for other patients, reducing plerixafor costs. Even if vial sharing is a pragmatic cost-saving solution that may be justified by users, it is legitimately important to note that the official description of the product advises against the practice.
- In the absence of specific data on individual patient G-CSF dosing, historic control patients were assumed to receive 4 days of G-CSF before stem cell harvesting (plus that given during each additional day of stem cell harvest). Patients who required a subsequent round of stem cell mobilisation were assigned an additional 4 days of G-CSF (plus additional days if additional collections). It is possible that these patients received higher than standard (5 μg kg^{-1}) doses of G-CSF and therefore the costs for the historic control group may be underestimated. No G-CSF was assigned if undergoing bone marrow harvesting, but instead the costs of operating theatre access and general anaesthesia, etc., were included.
- For relapsed patients, our policy for the duration of both the historic control group and the PHANTASTIC trial has been to wait for objective evidence that the patient is responding to salvage chemotherapy, before commencing stem cell mobilisation. This was to avoid unnecessarily harvesting patients with refractory disease, who would be unsuitable for subsequent ASCT. The chemotherapy schedule used for stem cell mobilisation in historic control patients was therefore additional to that required for salvage. However, it was not always possible to verify the point at which a decision was made to proceed to stem cell mobilisation. It was therefore assumed that the patient's final chemotherapy cycle was solely to mobilise stem cells; its costs (but not those of earlier salvage chemotherapy cycles) were included in the analysis.
- Every historic control patient receiving mobilising chemotherapy required a hospital stay. It was assumed that the duration of the hospital stay was dependent upon the chemotherapy type received, as the length of individual patient hospital stays was not always for clinical reasons (e.g., patients living distant from our hospital) yet such reasons were not always recorded. Chemotherapy administration costs were incorporated into the overall costs, although the different chemotherapy schedules required varying administration times. The most appropriate cost available from the healthcare resource groups (HRG) was the day case administration cost for "Malignant disorders of Lymphatic/Haematological system (without complications or comorbidities)," which was £362. This cost was considered appropriate for cyclophosphamide mobilised patients as these only require 1 day.
- Several chemotherapy schedules required some additional costs for safe delivery, such as MESNA for cyclophosphamide or ifosfamide, calcium supplementation during apheresis, and intravenous giving sets, for example. As information on these was not always available, associated costs were allocated to each patient depending on treatment.

RESULTS

Patient demographics (sex, age, and BMI) were similar between the PHANTASTIC trial patients and the historic controls, which can be seen in Table I. Clinical outcomes based on a series of scenario analyses are reported below, along with comparative resource use and a cost-effectiveness analysis.

Clinical Outcomes

Full details of the proportion of patients achieving the primary composite endpoint have been previously

TABLE I. Comparison of Baseline Characteristics Between the Plerixafor Mobilised PHANTASTIC Trial Group and Each of the Historical Control Groups (Group 1 Excludes the 11 Patients Who Received Second Line Plerixafor; Group 2 Includes all 151 Cases)

	PHANTASTIC trial	Historic control group 1	Historic control group 2
Number of cases	98	140	151
Sex (M/F)	60/38	87/53	92/59
Median age (range)	56 (20–68)	54 (19–70)	55 (19–70)
BMI (average)	26.5	27.4	27.2

BMI = body mass index, defined as: [weight in kilograms]/[height in metres]^2.

reported [21], and are summarised in Table II, additionally giving the proportions in each of the historic control groups 1 and 2. The proportion achieving the primary composite endpoint was significantly higher in the plerixafor mobilised PHANTASTIC trial patients than in either historic control group ($P < 0.0001$; z test for proportions; two samples), with more than twice as many PHANTASTIC NHL patients achieving the primary endpoint than in the historical control groups, for example. Moreover, all the PHANTASTIC trial patients required only one stem cell harvest round and required, a lower mean number of apheresis days. Overall, a higher proportion of myeloma patients achieved the primary endpoint than NHL patients ($P < 0.01$). One possible reason for this is that mobilisation in myeloma is usually attempted in first response/remission, unlike lymphomas where this is usually done in second or subsequent response/remission; the latter are therefore more heavily pre-treated [21,24].

Scenario Analyses of the Primary Composite Endpoint Components

Three scenario analyses were undertaken to explore the proportion of patients passing the individual elements of the composite primary outcome [29,30]. These are given in Table II.

The first scenario analysis was designed to test the number of patients achieving a minimum harvest without clinically significant neutropenia. It altered the endpoint to the harvesting of adequate cells to support an ASCT (2×10^6 CD34+ cells kg^{-1} rather than 4×10^6) and the number of apheresis collection days to $\leq$4 days rather than ≤ 2, but still with the same cut-off for neutropenia. As shown in Table III, not surprisingly, the proportion of patients passing this increased (94.9% in PHANTASTIC trial vs. 75.7% in historic control Group 1 and 76.2% in historic control group 2). However, the qualitative relationship between the groups remains similar and a similar effect is seen in each of the disease subgroups.

TABLE II. Proportion of the Plerixafor Mobilized PHANTASTIC Trial Group and Each of the Historical Control Groups who Achieved: The Primary Composite Endpoint

	(a) Primary composite endpoint	(b) Scenario analysis 1	(c) Scenario analysis 2	(d) Scenario analysis 3
PHANTASTIC trial group				
HD (%)	11/14 (79)	13/14 (93)	11/14 (79)	13/14 (93)
NHL (%)	21/39 (54)	36/39 (92)	22/39 (56)	37/39 (95)
Lymphoma (HD + NHL) (%)	32/53 (60)	49/53 (92)	33/53 (62)	50/53 (94)
Myeloma (%)	38/45 (84)	44/45 (98)	38/45 (84)	44/45 (98)
All Patients (%)	**70/98 (71)**	**93/98 (95)**	**71/98 (72)**	**94/98 (96)**
Historic control group 1				
HD (%)	6/21 (29)***	16/21 (76)	15/21 (71)	17/21 (81)
NHL (%)	10/48 (21)***	29/48 (60)	24/48 (50)	34/48 (71)***
Lymphoma (HD + NHL) (%)	16/69 (23)***	45/69 (65)***	39/69 (56)	51/69 (74)***
Myeloma (%)	32/71 (45)***	61/71 (86)**	39/71 (55)**	65/71 (92)
All Patients (%)	**48/140 (34)*****	**106/140 (76)*****	**78/140 (56)*****	**116/140 (83)*****
Historic control group 2				
HD (%)	6/21 (29)***	16/21 (76)	15/21 (71)	17/21 (81)
NHL (%)	10/53 (19)***	32/53 (60)	24/53 (45)	37/53 (70)***
Lymphoma (HD + NHL) (%)	16/74 (22)***	48/74 (65)***	39/74 (53)	54/74 (73)***
Myeloma (%)	32/77 (42)***	67/77 (87)**	39/77 (51)***	71/77 (92)
All patients (%)	**48/151 (32)*****	**115/151 (76)*****	**78/151 (52)*****	**125/151 (83)*****

$P < 0.01$ = *** $P < 0.05$ = ** $P < 0.10$ = * (z test for two population proportions).
Scenario Analysis 1: a cell yield $\geq 2 \times 10^6$ CD34+ cells kg^{-1} in $\leq$4 or fewer days (but the same neutropenia criterion as the primary composite endpoint). This tests the number of patients achieving a minimum harvest without clinically significant neutropenia.
Scenario Analysis 2: a cell yield of 4×10^6 CD34+ cells kg^{-1} in $\leq$2 days (i.e., the same as the primary composite endpoint) but with no stipulation about neutropenia. This tests the proportion who would have passed the primary composite endpoint were it not for the emergence of neutropenia.
Scenario Analysis 3: a yield of 2×10^6 CD34+ cells kg^{-1} irrespective of the number of aphereses or evidence of neutropenia. This tests solely the number of patients achieving a minimum harvest to support a subsequent ASCT.

TABLE III. Incremental Cost (ΔC) and Incremental Effectiveness (ΔE) of the PHANTASTIC Trial Patients Compared to Historic Control Groups 1 and 2

	Average costs by group			Incremental costs (ΔC)		Incremental effects (ΔE)		Incremental cost effectiveness ratio ($\Delta C/\Delta E$)	
Groups	PHANT-ASTIC trial	Historic control group 1	Historic control group 2	Trial vs. historic control 1	Trial vs. historic control 2	Trial vs. historic control 1	Trial vs. historic control 2	Trial vs. historic control 1	Trial vs. historic control 2
HD	£11,377	£19,241***	£19,241 ***	***–£7864***	***–£7864***	50.0%	50.0%	***Dominant (–£15,729)***	***Dominant(–£15,729)***
NHL	£15,425	£17,360 ***	£17,763 ***	***–£1936***	*–£2338*	33.0%	35.0%	***Dominant*** (–£5871)	***Dominant*** (–£6680)
Lymphoma	£14,355	£17,933 **	£18,183 **	***–£3577***	*–£3828*	37.2%	38.8%	***Dominant*** (–£9617)	***Dominant*** (–£9866)
Myeloma	£10,705	£4622 ***	£5460 ***	£6083	£5245	39.4%	41.6%	£15,450	£12,608
All patients	£12,679	£11,182 ***	£11,694 ***	£1497	£985	37.1%	39.6%	£4030	£2487

$P < 0.01$ = *** $P < 0.05$ = ** (Mann–Whitney U-value).
Italicised bold figures denote where plerixafor-based mobilisation is more cost effective than conventional chemotherapy.

The second scenario analysis in Table II tested the proportion of patients who would have passed the primary composite endpoint were it is not for the emergence of neutropenia. It utilised the same stem cell mobilisation and number of apheresis days thresholds as the primary composite endpoint, but with no stipulation concerning neutropenia. In the PHANTASTIC trial patients, there was only one patient who failed to achieve the primary composite endpoint solely due to neutropenia (and this was likely to be disease-related rather than plerixafor-induced), whereas in the historic controls (control 1 and control 2) 30 more patients (mostly lymphoma) would have achieved the composite primary outcome if neutropenia had not been a component.

The third scenario analysis was designed to test solely the number of patients achieving a minimum harvest (2×106 CD34+ cells kg^{-1}) to support a subsequent ASCT; it removed any criteria for apheresis days or neutropenia. The proportion of patients achieving this less rigorous outcome is now higher, but there was still a significant advantage ($P < 0.01$) for PHANTASTIC trial patients over both historic control groups 1 and 2 (95.9% vs. 82.9% and 82.8%) and this difference was again seen in each disease subgroup.

Comparative Resource Use

Table III compares the mean costs for the PHANTASTIC trial patients with the mean costs in the historic control groups 1 and 2. The mean costs for all PHANTASTIC patients were £12,679, compared to £11,182 and £11,694 ($P < 0.01$) in historic control groups 1 and 2, respectively. For PHANTASTIC trial patients, since no overnight inpatient stay or supportive medication for chemotherapy is required, their dominant cost was that of plerixafor itself. Their overall costs are therefore highly sensitive to the actual cost of plerixafor; the most costly subgroup was in NHL (mean cost £15,425 per patient of which the mean plerixafor component was £12,144). Myeloma patients in the PHANTASTIC trial group had the least expensive average patient cost of £10,705 of all the mobilising schedules, which requires the shortest hospital stay and supportive medication regime. In the historic control groups 1 and control 2, HD patients were the most costly subgroup to treat at £19,241 (primarily due to the inpatient hospital stay resulting from their mobilising chemotherapy), while myeloma patients were the least costly. Moreover, between the PHANTASTIC trial and both historic control groups, the resource use costs were found to be significantly higher for lymphoma patients over myeloma patients ($P < 0.01$).

Although not currently recommended according to the official product description of plerixafor, vial sharing is considered feasible by some clinicians provided that the vial is stored in sterile conditions of aseptic pharmacies. If we assumed that vial sharing would be possible without

TABLE IV. Description of the Methodology for Conducting Cost-effectiveness Analysis

Costing items in PHANTASTIC patient group (PG)	e.g., Plerixafor, GCSF, apheresis, supportive care
Costing items in historical control groups 1 & 2 (CG)	e.g., GCSF, chemotherapy, hospital stay for chemotherapy, apheresis, supportive care
Average cost for each group	$\frac{Total\ costs}{Number\ of\ patients}$
Successful Collection rate for each group	$\frac{Number\ of\ successful\ collections}{Number\ of\ patients}$
ICER	$\frac{Average\ cost\ (PG) - Average\ cost\ (CG)}{Collection\ rate\ (PG) - Collection\ rate\ (CG)}$
Discount rate	Not applicable (less than 1-year time horizon)

waste, in HD and NHL patients, mean resource use would reduce to £9317 and £12,779, while in myeloma patients, mean resource use would reduce to £9209. Therefore, the average cost of PHANTASTIC trial patients would decrease to £10,783 which represents a significant cost-saving ($P < 0.01$) when compared to both historical controls. Less than perfect vial sharing may still result in absolute cost savings, but not of the same magnitude.

Incremental Cost-effectiveness Ratios

The incremental cost-effectiveness ratio (ICER) involves a comparison of separate treatments which is defined as the ratio between the difference in costs and the difference in effects of two interventions or strategies. The ratio is used to highlight the cost-effectiveness of a health care intervention and is used as a decision rule in resource allocation. Table III compares both the incremental costs and incremental effects between the PHANTASTIC trial and the historic control groups (see Table IV for description of methodology) [31].

The incremental effects refer to the average proportion of patients who achieve the primary composite endpoint. Lymphoma patients in the PHANTASTIC trial were more successful than historic controls in achieving the primary endpoint and this was achieved at a lower cost. This effect was seen for both the HD and NHL patients. In contrast, myeloma patients in the PHANTASTIC trial had an incremental cost of £15,450 and £12,608 vs. historic control groups 1 and 2, respectively per additional successful stem cell collection (see Table III) [23]. Similarly, when comparing lymphoma patients in the PHANTASTIC trial with historic control Group 1 and 2, the trial group dominated as they were both cheaper and more patients achieved the primary endpoint. Total patients in the PHANTASTIC trial had an incremental cost of £4,030 and £2,487 vs. historical controls 1 and 2, respectively per additional successful stem cell collection. As discussed, if vial sharing was permitted and enabled the most efficient usage of the drug, the treated group as a whole would likely demonstrate cost-savings and therefore dominate the control groups.

DISCUSSION

The PHANTASTIC study and its comparison to historic controls was undertaken to compare first line plerixafor with conventional chemotherapy for stem cell mobilisation. The clinical data [21] reinforced earlier reports that plerixafor is highly effective and with low toxicity. However, the treatment cost is sometimes higher than in the alternative treatment strategies due to the price of plerixafor. The treatment decision in some European countries is therefore not only based on the clinical results, but on economic considerations as well. The present economic analysis was therefore undertaken to explore patient level resource use in the same PHANTASTIC trial and historic control patients.

We report that the mean treatment costs in the PHANTASTIC trial group were £12,679 compared with £11,182 in historic control Group 1 (which excludes recipients of plerixafor). However, plerixafor is licensed for second line and also for "pre-emptive" use, in patients who are not mobilising well to their primary mobilisation strategy. None of the present controls received pre-emptive plerixafor, but 11 cases received it second line. When these cases are also included in the historic control cohort (Group 2), which is more reflective of present day practice, their treatment cost becomes £11,694, i.e., marginally lower than that for first line plerixafor. Compared with conventional chemotherapy mobilisation, first line plerixafor enabled a higher proportion of patients to achieve the primary composite outcome in all three disease subgroups, with cost savings in lymphoma patients but an incremental cost in myeloma patients of £6,083 (and £5,245 when the 11 second line plerixafor cases are included in the historic control group).

In terms of cost-effectiveness, lymphoma patients who received plerixafor were dominant as more patients achieved the primary composite endpoint (or any of the scenario analyses) and at a lower cost. The key cost driver between lymphoma and myeloma patients was duration of hospital stay when stem cell mobilisation was undertaken. The assumption of 4 days of G-CSF before stem cell harvesting in the control group does not appear to be a big cost driver overall. These findings support the

adoption of plerixafor as a first line stem cell mobilisation strategy, certainly for lymphoma patients where substantial savings are likely. It may be possible that the savings made for lymphoma can patients can offset the increased expenditure for myeloma patients; this is however sensitive to the relative proportions of lymphoma to myeloma patients in individual transplant teams, with the proportion of myeloma patients in the cohort higher than we would expect on average (NICE, 2010). An additional reason for favouring first line plerixafor, which is difficult to formally evaluate clinically or economically, is that the decreased number and better "predictability" of the apheresis days needed for an individual patient can help with day to day practical planning for the clinical, apheresis, and cryopreservation teams and may increase throughput [32–34].

The present study uses historic controls. During the overall period of the present study (Nov 2006 to June 2012), we have not detected any trends in patient selection for ASCT (data in Clark et al.) [21] or any changes in stem cell mobilisation/harvesting techniques other than those compared in this report. Nevertheless, we acknowledge that it would be preferable to have data from a prospective randomised trial. However, it is unlikely that such a trial would recruit well, given the compelling clinical data on plerixafor efficacy and excellent side effect profile, and there has been little enthusiasm for such a study within the UK. The inclusion of 11 patients who received plerixafor into control group 2 means that the costs of the control group increase predominantly due to the cost of plerixafor itself. This results in a smaller incremental cost between treatment and control group 2. These 11 patients may be similar to other patients historically who failed to mobilise but were treated at a time when plerixafor was available. The change in practice during the period of retrospective data collection highlights the disadvantages of such a comparator group.

Some health economic analyses have been conducted previously to establish the cost effectiveness of plerixafor [22,24,26]. However, many of these studies have been based in the US setting and as health care systems vary between countries, the results cannot be directly generalized [34]. This analysis provides additional evidence in support of the pre-emptive use of plerixafor as a cost-effective method for successful mobilisation and preventing the need for remobilisation. Our results show that plerixafor tends to dominate in terms of cost and efficacy in lymphoma patients. For myeloma patients, successful mobilisation is more likely to be achieved at a higher cost. However the additional spend required is a cost-effective use of NHS resources is difficult to determine without a benchmark of value for successful stem-cell mobilisation. However, although reaffirmed by other studies, due to the relatively small sample size of HD patients, caution is required in the interpretation of some results [36].

Almost all (93%) patients mobilised by plerixafor yielded enough cells to support a subsequent ASCT (Scenario analysis 3, Table II) after a single round, and this compares well with the 83% achieving this in the historic control group, some of whom required additional harvesting rounds. However, the present cost-effectiveness evaluation is confined to the period from initiation of stem cell mobilisation until its completion. It cannot therefore comment on whether the higher "success rate" of stem cell mobilisation with plerixafor translates into superior long term relapse free and overall survival and improved quality of life, nor whether plerixafor is cost effective in all patients. For example it is plausible that with first line plerixafor, additional patients may reach ASCT and more quickly, resulting in improved outcome, but that this is offset by the substantial cost of the additional ASCT procedures. Conversely, a useful by-product of conventional chemotherapy mobilisation is an anti-tumour effect, which is absent with plerixafor mobilisation. Moreover, further studies are required to determine the long term outcome and additional resource use of patients beyond completion of stem cell harvest.

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