Treatment pathways and resource use associated with recurrent Hodgkin lymphoma after autologous stem cell transplantation

Although many patients with Hodgkin lymphoma (HL) achieve sustained remission following first-line chemotherapy with or without consolidation radiotherapy, there remain 5–10% who are refractory to first-line therapy and up to 30% of patients relapse.1,2 Second-line treatment with multi-agent salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) provides durable clinical benefit in around 50% of patients or more.2,3 Currently, treatment options for patients with recurrence of HL post ASCT include: further salvage chemotherapy, reduced intensity conditioning allogeneic stem cell transplant (alloSCT) in younger patients, palliative chemotherapy (often gemcitabine based) and/or radiotherapy, trials of new agents and occasionally a second ASCT.2,4 However, there is little information about the use and effectiveness of these strategies and no guidelines or standard of care recommended in the United Kingdom. We undertook a multicentre retrospective observational study to better understand UK treatment pathways and resource use in order to inform future clinical decisions and further research required.

Treatment patterns, National Health Service (NHS) resource use and treatment-associated outcomes were observed.

Five UK NHS hospitals with specialist services providing stem cell transplantation for HL participated in our study. These centres were selected to provide a geographical distribution across the United Kingdom and represent ~20% of all NHS centres with specialist stem cell transplantation services. We identified eligible patients via the hospital transplant database or equivalent, which was reviewed by clinical staff with routine access to the database for clinical care. The study eligibility period was the 5 years to 2009, which allowed treatment of subsequent recurrence of HL to be studied in a recent time frame, but with a sufficient follow-up period available to describe the whole management pathway and outcomes. This period was expected to provide a total of ~60 eligible patients. There was no sampling of patients due to the rarity of the disease and small numbers who have recurrence of post ASCT HL; the whole cohort was included to ensure all treatment pathways were described. All data were obtained by review of medical records by NHS clinical staff and clinicians then provided anonymised, coded study data to external researchers for analysis.

All data were collected retrospectively to the patient’s death or up to the most recent relapse or treatment received. Summary data on patient characteristics and treatment pathways were collected from the time of diagnosis to the time of ASCT. More detailed data on the treatment regimens, number of cycles, courses of radiotherapy, hospital resources and patient outcomes were collected for the post ASCT period. Data were pooled from all the centres for analysis and stratified by centre to check for large differences in treatment patterns between them. However, due to the small size of the available cohort at each centre, no results are presented from these comparisons.

Costs were calculated by multiplying the number of units per resource item by the cost of each item for every patient. Treatment costs were calculated using the resource usage variables described above, drug costs were obtained from the British National Formulary2 and other resource values from the Department of Health.4 There was no cost listed for alemtuzumab; therefore a representative cost was used. Mean costs were estimated by treatment group: second ASCT, allo, chemotherapy alone and best supportive care (BSC) were considered appropriate as they include differences in observation periods and patient profiles for the different treatment options.

All 40 patients who met the eligibility criteria were included in our study (range 5–13 per centre). Baseline characteristics were evenly balanced and our cohort at diagnosis included 10 (25.0%) patients who were Ann Arbor stage I/IIA (early stage), 29 (72.5%) who were Ann Arbor stage IIB/III/IV (advanced stage) and 1 (2.5%) for whom the stage was not recorded. Of the 10 early stage patients, 8 (80.0%) received ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) as their first regimen pre-ASCT, one received radiotherapy only and one received OEPP/COPP (vincristine, epirubicin, procarbazine and prednisone/cyclophosphamide, vincristine, procarbazine and prednisone; two cycles of each). Six (60.0%) of these patients achieved complete remission or ‘complete remission uncertain’. Of the 29 advanced stage patients, 23 (79.3%) received ABVD as their first regimen pre-ASCT with four achieving ‘complete remission uncertain’. Overall, seven (24.1%) advanced stage patients achieved complete remission or ‘complete remission uncertain’ in response to first-line therapy.

Allogeneic transplantation was emerging as the standard goal for consolidation of patients following failure of ASCT during this period. All involved centres considered patients with responsive disease and appropriate organ function to be potential candidates for such consolidation. Lack of an appropriate donor was an uncommon reason for not proceeding, as was patient preference. Recognising some limitations with respect to retrospective studies and ascribing treatment intent in all cases, our study demonstrated that treatment of HL post ASCT was highly variable in terms of intensity, outcome and resource use. In relation to recurrence and treatment pathways, the median time to recurrence of HL post ASCT was 6 months (range 0.23–65 months). Following recurrence post ASCT, 19 (47.5%) patients received palliative chemotherapy only, 15 (37.5%) received chemotherapy followed by alloSCT or a second ASCT and 6 (15.0%) received BSC. The most commonly received first- and second-line chemotherapy regimen following recurrence post ASCT was platinum-based. Of the 34 (85.0%) patients who received chemotherapy (including alloSCT and second ASCT), 12 (35.3%) received a second regimen, 6 (17.6%) a third regimen and 2 (5.9%) a fourth regimen.

In relation to 3-year survival we found that it was highest among patients who received alloSCT. Following relapse post ASCT the proportions of patients surviving to 3 years were 71.5% in the alloSCT group, 5.9% in the palliative chemotherapy group and 0% in the BSC group. Furthermore, a separate analysis of time from relapse to death or last follow-up also indicated a substantial advantage of alloSCT over other treatment pathways.

Overall resource use and mean total costs per patient post ASCT recurrence is summarised in Table 1. AlloSCT and palliative
Table 1. Resource use and costs of treatment pathways for relapse after ASCT

| Post-ASCT relapse          | Time from relapse to data of death or last follow-up, years | No. patients (n=40) | Outpatient visits, mean/patient (range) | Day case visits, mean/patient (range) | Inpatient stays, mean/patient (range) | Length of stay, mean/patient (range) | Scans, mean/patient (range) | Cost of resources and treatments, mean cost/patient* (range) |
|----------------------------|-------------------------------------------------------------|---------------------|----------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|-----------------------------|------------------------------------------------------------|
| Palliative chemotherapy    | 1.72                                                        | 19 (47.5%)          | 27.89 (1–99)                           | 6.18 (0–35)                          | 4 (0–17)                            | 29.28 (0–146)                        | 7.74 (0–20)                  | £32 264 (£2 686–£119 820)                                      |
| Chemotherapy followed by allogeneic transplant | 3.44                                                        | 14 (35.0%)          | 30 (4–95)                              | 3.07 (0–16)                          | 3.29 (0–14)                         | 48 (0–195)                          | 8.93 (2–32)                 | £110 374 (£69 289–£191 670)                                     |
| BSC only (no HL-directed therapy) | 1.25                                                        | 6 (15.0%)           | 10.67 (2–20)                           | 0.33 (0–2)                           | 1.67 (1–4)                          | 14.5 (1–27)                         | 2 (1–5)                     | £13 288 (£8 485–£23 295)                                       |
| Chemotherapy followed by second ASCT | 0.75                                                        | 1–2.50%             | 13 (13–13)                             | 6 (6–6)                              | 2 (2–2)                             | 24 (24–24)                          | 3 (3–3)                     | £21 612 (£21 612–£21 612)                                      |

Abbreviations: ASCT = autologous stem cell transplantation; BSC = best supportive care; HL = Hodgkin lymphoma.
*Cost of resources and treatments is calculated from date of relapse after ASCT to date of death or to most recent follow-up within the study period.
Limitations of this study were typical of any study reliant on retrospective data, including the availability and completeness of health records, which subsequently limited the completeness of treatment details reported in our results. Our study suggests that optimal disease management requires a choice of appropriate treatment aimed at achieving a balance between efficacy and toxicity in circumstances where what may be suitable for one patient may not be appropriate for another. We found that treatment approaches, survival and resource use in patients with recurrent HL post ASCT is diverse. Management of such patients requires further evaluation, including greater understanding of treatment planning and decision-making at post ASCT relapse, particularly given the emergence of newer therapeutic agents with activity in such patients. Larger patient numbers treated according to evolving standards of care and with longer follow-up are necessary to improve the current understanding of the implications of HL management on health-care budgets and patient outcomes.12

CONFLICT OF INTEREST
FP is employed by pH Associates Ltd, who were under a commercial contract with the study sponsor to support the design and management of the study and analysis and reporting of the data. The remaining authors declare no conflict of interest.

ACKNOWLEDGEMENTS
The study was sponsored by Takeda Pharmaceuticals International, GmbH. PHMR, London, provided the cost calculations and editorial support during preparation of the manuscript.

J Radford1, P McKay2, R Malladi3, R Johnson4, A Bloor5, F Percival6, A Sureda7 and KS Peggs8
1The University of Manchester and the Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK; 2The Beatson West of Scotland Cancer Centre, Glasgow, Scotland; 3Queen Elizabeth Hospital, Birmingham, UK; 4The Christie NHS Foundation Trust, Manchester, UK; 5pH Associates, Marlow, UK; 6Addenbrooke’s Hospital, Cambridge, UK and 8University College London Hospitals NHS Foundation Trust, University College London Cancer Institute, London, UK
E-mail: k.peggs@cancer.ucl.ac.uk

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