Bone Marrow Transplantation (2017) **52,** 452–454

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LETTER TO THE EDITOR

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

Bone Marrow Transplantation (2017) **52,** 452–454; doi:10.1038/bmt.2016.244; published online 16 January 2017

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 Formulary[5] and other resource values from the Department of Health.[6] 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[a] (range)*
Palliative chemotherapy only	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. [a]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.

Figure 1. Patient follow-up in days.

chemotherapy were associated with the highest number of outpatient visits during the follow-up period (30.0 and 27.9 visits per patient, respectively), longest durations of hospitalisation and number of scans (8.9 and 7.7, respectively). However, fewer day case visits overall were recorded among patients receiving alloSCT compared with those receiving palliative chemotherapy or chemotherapy followed by second ASCT. Finally, BSC and chemotherapy followed by second ASCT were associated with the lowest resource use overall.

AlloSCT was the most costly intervention overall (mean £110 374/patient), followed by palliative chemotherapy. A large proportion of the costs associated with alloSCT were due to the procedure itself: ranging between £34 783–£44 059 depending on the exact protocol (accounting for 31.5–39.9% of the total cost).[6] However, the period over which the costs were accrued differed for each treatment (Figure 1). The mean length of follow-up was substantially greater in the alloSCT group (1253 days) compared with the other treatment groups (palliative chemotherapy: 627 days; BSC: 458 days; second ASCT: 274 days).

Recent studies found the median overall survival following relapse post ASCT to be only 25–32 months,[7,8] and a study of patients with relapsed HL demonstrated 5-year overall survival rates of 42% in 24 patients post ASCT and 1-year overall survival rates of 80% in five patients following allo.[9] Our results compare favourably with these data and the appropriate selection of patients most likely to benefit from alloSCT is likely to have contributed to the high survival rate. Crucially, the demographic data indicate that these patients were younger and had relapsed later than those treated with palliative treatment or BSC; this is important as outcomes are generally considered poor for patients with early relapse (within 6–12 months of ASCT).[4] Although viable alternatives to transplant for recurrent HL are lacking, novel biological and targeted therapies, and immune checkpoint inhibitors, have shown promising results[10] and are welcome additions to the growing number of treatment strategies.[11] However, their place in therapy is still being established.[11]

To our knowledge this is the first report of health-care resource use for patients who relapse post ASCT. In general, palliative chemotherapy and alloSCT were associated with the greatest level of health-care resource use compared with BSC and chemotherapy followed by second ASCT (Table 1). In particular, patients receiving alloSCT tended to have the longest overall duration of hospital stay, around 70% longer than patients receiving palliative chemotherapy. It is not surprising, therefore, that the overall treatment costs were greatest for alloSCT with more than 30% of total costs due to the alloSCT itself. However, patients receiving alloSCT had much greater survival or longer follow-up compared with those receiving other treatments. The high treatment cost of alloSCT must, therefore, be considered in the context of substantially improved survival and a comparatively limited increase in health-care resource use overall.

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.

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REFERENCES

1 Connors JM. Evolving approaches to primary treatment of Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program* 2005; **2005**: 239–244.
2 Mendler JH, Friedberg JW. Salvage therapy in Hodgkin's lymphoma. *Oncologist* 2009; **14**: 425–432.
3 Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M *et al.* Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet* 2002; **359**: 2065–2071.
4 Martinez C, Canals C, Sarina B, Alessandrino EP, Karakasis D, Pulsoni A *et al.* Identification of prognostic factors predicting outcome in Hodgkin's lymphoma patients relapsing after autologous stem cell transplantation. *Ann Oncol* 2013; **24**: 2430–2434.
5 British National Formulary. No 64. https://www.bnf.org/.
6 Department of Health. 2010–2011 NHS reference costs. 2011. https://www.gov.uk/government/publications/2010-11-reference-costs-publication.
7 Moskowitz AJ, Perales MA, Kewalramani T, Yahalom J, Castro-Malaspina H, Zhang Z *et al.* Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. *Br J Haematol* 2009; **146**: 158–163.
8 Kaloyannidis P, Voutiadou G, Baltadakis I, Tsirigotis P, Spyridonidis A, Repousis P *et al.* Outcomes of Hodgkin's lymphoma patients with relapse or progression following autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2012; **18**: 451–457.
9 Ramirez P, Ocqueteau M, Rodriguez A, Garcia MJ, Sarmiento M, Ernst D *et al.* Outcomes in relapsed Hodgkin's lymphoma treated with autologous and allogeneic hematopoietic cell transplantation at the Pontificia Universidad Catolica de Chile. *Rev Bras Hematol Hemoter* 2015; **37**: 184–189.
10 Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ *et al.* Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol* 2012; **30**: 2183–2189.
11 Stathis A, Younes A. The new therapeutical scenario of Hodgkin lymphoma. *Ann Oncol* 2015; **26**: 2026–2033.
12 Collins GP, Parker AN, Pocock C, Kayani I, Sureda A, Illidge T *et al.* Guideline on the management of primary resistant and relapsed classical Hodgkin lymphoma. *Br J Haematol* 2014; **164**: 39–52.