11 years to 0·35 iu/ml at the age of 14 years. That FIX increased at puberty in these two lyonized female carriers of Haemophila B Leyden supports the mice experimental data that that the mechanism of age-related normalization of *F9* expression is mainly mediated by growth hormone rather than androgens.

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Survival outcomes and treatment costs for patients with double-refractory chronic lymphocytic leukaemia (DR-CLL)

Data on treatment outcomes and costs in chronic lymphocytic leukaemia (CLL) that is refractory to both fludarabine and alemtuzumab (double-refractory disease [DR-CLL]) are limited, and there is no defined standard of care. The only published data are from the MD Anderson centre in the US, where a case series reported use of 20 different salvage regimens in 58 patients from 1998 to 2006 (Tam *et al*, 2007). The mean overall response rate was 20%, with median survival from first salvage therapy after failure of alemtuzumab of 8 months.

The disease burden of DR-CLL in the population is uncertain. A market research study for GlaxoSmithKline in 2009 found that approximately 1·2% of treated patients develop double-refractory disease (unpublished data), equating to an estimated annual incidence rate of DR-CLL of 0·02–0·04 per 100 000. In the UK (population 60 million), this is equivalent to approximately 15–20 patients per year. Understanding the economic burden of refractory CLL is likely to become increasingly important in order to balance the costs of recent advances in managing the disease (Delgado *et al*, 2012; Experts in Chronic Myeloid Leukemia, 2013). Little information is currently available to support this understanding (Redaelli *et al*, 2003; Stephens *et al*, 2005).

Here we report two retrospective chart review studies that aimed to describe survival outcomes and characterize patterns of care and resource utilization in DR-CLL. One was conducted in France, Germany, Spain, Italy and the UK (the EU study) and one in the UK only (the UK study). Study protocols were similar, except that in the EU study follow-up was restricted to 18 months after index DR-CLL diagnosis, after which patients still alive were censored, whereas in the UK study it continued until death, loss to follow-up or the end of the study. Patients were enrolled from comprehensive oncology centres between 2002 and 2009. Appropriate review board approval and patient consent was obtained and patient information was anonymized and de-identified prior to analysis. DR-CLL was defined as refractory to both fludarabine-containing regimens (minimum two cycles) and alemtuzumab (minimum 12 administrations in the case of non-response). Data were collected on demographics, clinical outcomes, medical resource use and CLL-related events (infection, neutropenia, thrombocytopenia). Data were also collected on CLL drug treatment and associated clinical events for the 6 months before index DR-CLL diagnosis.

In an exploratory analysis on the combined dataset, UK unit costs as at 2012 were assigned to the resources used. Subsequently, medication and treatment costs were summed to estimate total treatment cost over patients' follow-up duration, mean cost per patient was calculated and the relationship between monthly cost post-diagnosis and time to death was investigated. As treatment patterns vary by country, this provides illustrative costs only. Survival was analysed by Kaplan-Meier estimation using the combined data sets;

Table I. Baseline characteristics and treatments received prior and post-DR-CLL diagnosis.

	UK study (n = 19)	EU study (n = 21)	All patients (n = 40)
Baseline characteristics			
Age, years (mean [SD])	62·2 [7·0]	63·3 [8·2]	62·8 [7·6]
Age >65 years	7 (36·8%)	8 (38·0%)	15 (37·5%)
Male	15 (78·9%)	16 (76·2%)	31 (77·5%)
Therapy in 6 months prior to DR-CLL diagnosis (Yes)	14 (73·7%)	9 (42·9%)	23 (57·5%)
Therapies in 6 months prior to DR-CLL diagnosis (mean [SD])	1·5 [1·4]	1·3 [1·8]	1·4 [1·6]
Received MAbs during study period	16 (84·2%)	18 (85·7%)	34 (85·0%)
Received MAbs post DR-CLL diagnosis	16 (84·2%)	13 (61·9%)	29 (72·5%)
Therapies in the 6 months prior to DR-CLL diagnosis			
Alemtuzumab	6 (32%)	2 (10%)	8 (20%)
Cyclophosphamide	2 (11%)	5 (24%)	7 (18%)
Fludarabine	1 (5%)	1 (5%)	2 (5%)
Lenalidomide	1 (5%)	0 (0%)	1 (3%)
Methylprednisolone	2 (11%)	0 (0%)	2 (5%)
Oxaliplatin	1 (5%)	0 (0%)	1 (3%)
Prednisone	1 (5%)	0 (0%)	1 (3%)
Rituximab	0 (0%)	1 (5%)	1 (3%)
None reported	5 (26%)	12 (57%)	17 (43%)
First treatment after DR-CLL diagnosis (all patients)			
Alemtuzumab	7		
Methylprednisolone	4		
Dexamethasone	2		
Other single agents:			
Ofatumumab	1		
Lenalidomide	1		
Oxaliplatin	1		
Cyclophosphamide	1		
Bendamustine	1		
Prednisolone	1		
Prednisone	1		
Rituximab-containing regimens:			
Cyclophosphamide, fludarabine, mitoxantrone, rituximab	1		
Methylprednisolone, rituximab	2		
Rituximab, cyclophosphamide, prednisone, doxorubicin, vincristine	1		
Rituximab, cyclophosphamide, prednisone, doxorubicin, vincristine	1		
Cyclophosphamide, fludarabine, mitoxantrone, rituximab	1		
Cisplatin, methylprednisolone, cytarabine, rituximab	1		
Rituximab, bendamustine	1		
Alemtuzumab, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone	1		
Cyclophosphamide, doxorubicin, prednisolone, vincristine	2		
Not known/none reported	2		
Cisplatin, dexamethasone	1		
Cyclophosphamide, prednisolone, etoposide, other	1		
Other, other, cytarabine, methylprednisolone	1		
Alemtuzumab, fludarabine, cytarabine, bendamustine, prednisone	1		
Cyclophosphamide, doxorubicin, vincristine, prednisone	1		
Alemtuzumab, fludarabine	1		
Other	1		

DR-CLL, double-refractory chronic lymphocytic leukaemia; SD, standard deviation; MAbs, monoclonal antibodies.

combining them was a limitation but was deemed preferable to censoring UK data at 18 months and losing subsequent survival information.

There were 40 evaluable patients: 21 in the EU study and 19 in the UK study. Mean age at diagnosis was 62·8 years. Patients had received a variety of treatments in the 6 months prior to diagnosis (Table I). First treatment after diagnosis also varied widely, with no clear standard of care: the most common were rituximab-containing regimens or rechallenges with alemtuzumab, and patients also received fludarabine-containing regimens (Table I). Median survival was 17·3 months from DR-CLL diagnosis (95% confidence interval: 11·9 to 26·8; Fig 1) and 12·6 months (95% confidence interval: 9·9 to 19·2 months) from first salvage treatment (first treatment after DR-CLL diagnosis).

In the combined dataset, the total cost of treating 40 DR-CLL patients was £1 070 698, or a mean cost per patient of £26 767 (standard deviation [SD] £21 098) for a mean 12·1 (SD 11·7) months of follow-up. The main drivers of cost were inpatient hospitalizations (29%), transfusions (26%) and health care professional visits (15%). Using the UK study only (where most patients were followed from diagnosis until death), mean cost was £30 266 (SD: 21 851), based on 14 patients treated at a total cost of £423 159, for a mean 14·8 (SD 16·9) months of follow-up. Blood transfusions (52%), healthcare professional visits (16%) and diagnostic procedures (6%) were the main drivers of cost, with drugs accounting for 5% of total costs.

To our knowledge, this is the first study to present data on survival outcomes and to collect data on resource use in DR-CLL in a multicentre population, and the first in a European setting. As such, it provides a valuable addition to the data from Tam *et al* (2007) regarding the prognosis of these patients prior to the availability of a licensed treatment (ofatumumab was conditionally approved by the European Medicines Agency in 2010, after data collection in this study). Median survival from first salvage treatment (12·6 months) was broadly comparable with the 8 months reported by Tam *et al* (2007). Median survival from diagnosis of DR-CLL was 17·3 months, confirming the poor prognosis for these patients and the need for effective therapies. The lack of a recognized standard of care was highlighted by the wide range of initial therapies reported after DR-CLL diagnosis.

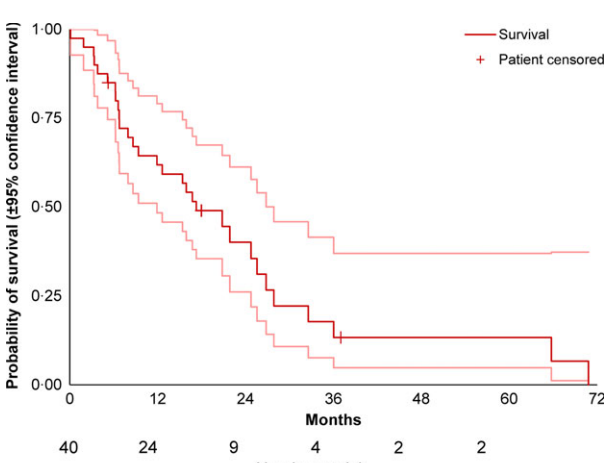

Fig 1. Survival from diagnosis of patients with double-refractory chronic lymphocytic leukaemia, including 95% confidence interval and number at risk (data beyond 18 months are based on UK study only).

Recruitment to the studies was difficult, and the small, heterogeneous sample was a limitation that increases the level of uncertainty around the findings. Differences in clinical practice across countries may affect conclusions about resource use and cost estimates based on the combined dataset. A treatment duration of one day was assumed where duration data were missing, with the result that drug costs are likely be underestimated. Total treatment costs are also likely to be underestimated due to missing data, e.g. resource use in primary care. However, the data that are available suggest that patients treated for DR-CLL continue to have considerable on-going healthcare needs, with treatment costs increasing as they approach death.

Patients with a diagnosis of DR-CLL are likely to become rarer in the future, making further research difficult. This study adds to the limited information available on outcomes and costs in this small and difficult-to-treat group.

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Competing interests

Adrian Bloor has received grants and honoraria from GSK in relation to the submitted work; Anthony Hatswell and Jamie Elvidge are employees of BresMed Health Solutions, which received funding from GSK to conduct the original analyses in the submitted manuscript; Anthony Hatswell is a previous employee of GlaxoSmithKline; Amin Haiderali, Ceilidh Stapelkamp and Tsveta Hadjivassileva are current employees of GlaxoSmithKline, which funded this research; Radek Wasiak and Erwin De Cock have a present or past affiliation with United BioSource Corporation, which was commissioned by GSK to execute both chart review studies; Julio Delgado has received honoraria from GSK for contributions to an advisory board meeting in relation to the submitted work.

Author contributions

Adrian Bloor, Julio Delgado, Radek Wasiak, Erwin De Cock and Amin Haiderali designed the research study; Adrian Bloor, Julio Delgado, Radek Wasiak and Erwin De Cock performed the research; Radek Wasiak, Erwin De Cock, Anthony J Hatswell, Jamie Elvidge, Julio Delgado, Adrian

Bloor, Tsveta Hadjivassileva and Ceilidh Stapelkamp contributed to the analysis and interpretation of the data; Adrian Bloor, Anthony J Hatswell, Jamie Elvidge, Radek Wasiak, Erwin De Cock, Amin Haiderali, Tsveta Hadjivassileva, Ceilidh Stapelkamp and Julio Delgado wrote and reviewed the manuscript.

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Long-term outcomes of autologous stem cell transplantation for peripheral T-cell lymphomas across the Thames Valley (1997–2012)

Peripheral T-cell lymphoma (PTCL), a heterogeneous, chemo-resistant group of disorders, often presenting with extranodal features, B symptoms and paraneoplastic phenomena, presents a treatment challenge. In the western world, PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and anaplastic large cell lymphoma (ALCL) together represent approximately 75% of cases (Vose *et al*, 2008).

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy is widely used first-line. With the exception of anaplastic lymphoma kinase (ALK)-positive ALCL, outcomes remain disappointing, with 5-year overall survival (OS) estimated around 50% for ALK-negative ALCL and 30% for PTCL-NOS and AITL (Vose *et al*, 2008). Clinical trials investigating alternative therapies or additions to CHOP have been hampered by the rarity and heterogeneity of PTCL. Many studies are retrospective and difficult to compare.

There has been much debate surrounding the role of etoposide in PTCL. The much-quoted data comes from the German High-Grade NHL Study Group (GHGNHL) retrospective study, where data from a variety of GHGNHL trials was collated to compare six to eight courses of CHOP-14 with CHOP plus etoposide (CHOEP-14 or CHOEP-21) or compared CHOEP to a dose-escalated (Hi-CHOEP) or mega-dose CHOEP (Mega-CHOEP) (Schmitz *et al*, 2010). This analysis involved predominantly (289 of 343) ALK-positive ALCL ($n = 78$), ALK-negative ALCL ($n = 113$), PTCL-NOS ($n = 70$) and AITL ($n = 28$). The data suggested the addition of etoposide in those under 60 years of age improves the 3-year event-free survival (EFS): 75·4% versus 51·0%, ($P = 0{\cdot}003$); however, when ALK-positive ALCL was