Inotuzumab Ozogamicin versus FLAG-Ida in the Treatment of Relapsed or Refractory B-cell Acute Lymphoblastic Leukaemia - Real-world Resource Use Data.

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In June 2017, Inotuzumab ozogamicin (IO), a humanised anti-CD22 monoclonal antibody conjugated to a cytotoxic antibiotic agent calicheamicin (Shor et al, 2015), was approved by the European Medicines Agency (EMA) for treating adults with Philadelphia chromosome positive and negative relapsed or refractory CD22-positive B-cell acute lymphoblastic leukaemia (ALL). The pivotal phase 3, randomised controlled INO-VATE 1022 trial (n=326) demonstrated a significantly higher complete remission rate (80.7% versus 29.4%, P<0.001) and longer duration of remission (4.6 months versus 3.1 months, P=0.03) in the IO group compared with the standard therapy group (fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG)-based combination chemotherapy, high dose cytarabine, or cytarabine with mitoxantrone) in treating relapsed and refractory ALL (Kantarjian et al, 2016). IO has recently been recommended by the National Institute for Health and Care Excellent (NICE) for U.K. practice with the real-world data collected having been taken into account in the economic analysis.

In the adoption of novel agents, the cost of the agent and overall survival of the patients are the predominant considerations for reimbursement decisions. However, other advantages for patients and healthcare facilities, such as toxicity reduction, ease of administration, reduction in length of stay and a reduction in supportive care needs can be considerable. Clinical trials exhaustively document adverse events and such pivotal international registration studies provide the critical evaluations by which regulatory agencies make decisions. However, data which predict the overall impact of a novel approach in a particular healthcare system are rarely collected in such trials and are often not available for

consideration at the time of reimbursement decisions. We aimed to determine whether IO conferred advantages for UK patients and the NHS in terms of length of stay and toxicity reduction, compared to salvage chemotherapy. We collected "real-world" data on resource usage in two centres - University College London Hospital and University Hospitals Bristol, which had enrolled patients to the IO compassionate use programme. We analysed data from all consecutive patients who had received IO and compared it with consecutive patients who had received FLAG-Ida, the most commonly used salvage regimen in ALL which, without the Idarubicin, had been the comparator in the pivotal study.

We identified forty patients aged between 14 and 71 years who had received one or more cycles of either IO (one cycle contains 3 doses, given at weekly intervals) or FLAG-Ida chemotherapy for relapsed or primary refractory B precursor ALL between August 2008 and December 2017 in University College London Hospital or University Hospitals Bristol. Patient characteristics, including disease status at the time of treatment, number of previous lines of therapy and number of IO or FLAG-Ida cycles received were recorded. We also extracted data on length of inpatient stays, defined as admissions for one or more nights to a hospital bed. Data on infective complications and blood product usage in the 30 days immediately following the first dose of therapy were also extracted from our electronic records. Statistical analysis was by Chi Squared or Mann-Whitney U test.

Patient characteristics are shown in table 1. The patients were a relatively young but very heavily pre-treated group. The IO and FLAG-Ida groups were reasonably well, but not completely, matched. The only statistically significant difference was that 5 of 17 (29%) IO recipients had received

prior allogeneic stem cell transplant (alloSCT), compared to none of the 23 FLAG-Ida recipients. The IO group had also received more prior lines of therapy than the FLAG-Ida group, with 7 of 17 (41%) being on their third or fourth line of therapy whereas no FLAG-Ida recipient had received more than two prior lines of therapy, but these differences were not statistically significant.

Resource usage was analysed in terms of cycles administered. Thirty-one cycles of IO were analysed; consisting of 14 patients treated with one or two cycles and 3 patients who received three cycles. Twenty-nine FLAG-Ida cycles were analysed; 17 (74%) patients received one cycle of FLAG-Ida and the remaining 6 patients received two cycles each.

The median length of inpatient stay for a cycle of IO was 5 days (range 0-100 days) versus 41 days (range 16-115 days) for FLAG-Ida, and the difference was highly statistically significant, $P < 0.0001$ (Mann-Whitney U test), as shown in table 1. The IO group is heavily skewed to very short stays with 11 of the 31 cycles (35%) administered not requiring any inpatient admission.

Infective complications in both groups, including bacterial, fungal and viral infections, are also shown in Table 1. There were defined by positive cultures in the relevant infection sites. There were 12 complications in 31 IO cycles, and 39 complications in 29 FLAG-Ida cycles. The two sets of data were compared using Chi-square test, indicating that they were significantly different with a p value of <0.0001.

The total number of units of red cells transfused was significantly fewer in the IO group (57) than in the FLAG-Ida group (244), P=<0.0001 (Chi-square). The total pools of platelets transfused was also significantly fewer in the IO group (108) than in the FLAG-Ida group (271), P=<0.0001 (Chi-square).

We calculated, using the reference cost data published by the U.K. National Health System (NHS), NHS Blood and Transplant and the British National Formulary, the total cost of inpatient stay, blood and platelet transfusion and the drugs for one cycle of each therapy; this was £36 946 (46 445 USD) for IO and £22 687 (28 526 USD) for FLAG-Ida.

Our real-world data on basic healthcare resource usage between patients who were treated with IO and those who received FLAG-Ida chemotherapy show a highly significant reduction in inpatient stay, blood product usage and infectious complications between the two groups, despite the fact the IO group were a more heavily pre-treated group with over a third having received prior alloSCT. We did not attempt to compare clinical outcomes as the numbers of patients were small and were not comparable in disease status and prior therapy.

Our study is limited by its retrospective nature, and the fact that the periods over which the treatments were administered were not contemporaneous. However, the highly significant differences demonstrated between the two groups, despite their relatively modest size, showed that the high drug costs of IO are very heavily mitigated by highly significant reductions in inpatient stay, blood product cost savings and savings in treatment of infective complications. The NHS-discounted price for IO, which is not publicly available, will also mitigate the cost difference. Blinatumumab, another high-cost, NICE-

approved drug for treating relapsed of refractory precursor B-ALL, is priced at £34 106 (42 853 USD) per cycle and as per Summary of Product Characteristics, mandates a minimum 9-day inpatient stay. The true cost of using the chimeric antigen receptor (CAR) T cell approach, Kymriah, priced at £282 000 (354 876 USD) per patient, should also be calculated to include a significant chance of intensive care unit stay and the use of other high cost agents to control toxicity .The high cost of all of these novel agents in ALL will clearly place increasing cost pressure on health systems around the world. Despite this, the potential economic and psychological advantages to patients with relapsed or refractory ALL and their families in not being obliged to submit to inpatient care to receive these agents are considerable and are generally not taken into account in assessing overall societal benefit.

In conclusion, this study demonstrates the importance of collecting real-world data on resource usage when novel agents are introduced, in order to afford a better evaluation of the true societal cost effectiveness of novel approaches.

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Competing Interests

The authors declare no competing financial interests.

References

1. Shor B, Gerber HP, Sapra P. Preclinical and clinical development of inotuzumab-ozogamicin in hematological malignancies*. Molecular Immunology* 2015; 67:107-16.
2. Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W *et al*. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukaemia. *New England Journal of Medicine* 2016; 375:740-53.
3. Nice.org.uk. (2019). Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia | Guidance and guidelines | NICE. [online] Available at: https://www.nice.org.uk/guidance/TA541/chapter/1-Recommendations.
4. Reference costs 2017/18: highlights, analysis and introduction to the data. (2018). Available at: https://improvement.nhs.uk/documents/1972/1_-_Reference_costs_201718.pdf.
5. NHSBT Pricing Proposals for 2017-18. (2016). Available at: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/2188/16-80.pdf.
6. British National Formulary. Available at: https://bnf.nice.org.uk/
7. EMC Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/

Table 1

		IO	FLAG-Ida	P value
Patient characteristics				
Gender	Male	9	19	
	Female	8	4	
Age (range)	Median	19 (14 - 71)	23 (19 – 50)	
Disease status	Primary	1	6	
	Relapse	16	15	
	Unknown	0	2	
Number prior lines of therapy	None	0	2	
	One	5	18	
	Two	5	3	
	Three	2	0	
	Four	5	0	
Previous alloSCT	Yes	5	0	0.005
	No	12	23	
Outcome data				
Number of cycles		31	29	
Inpatient days/cycle	Mean	11.2	44.1	
	Median(range)	5(0-100)	41(16-115)	*<0.00001
Infections (events in all cycles)	Bacterial	5	25	
	Fungal	0	6	
	Viral	5	3	
	Not specified	2	5	
	Total	12	39	<0.0001
Blood product usage	Red cell units (per cycle)	57 (1.96)	244 (10.4)	<0.0001
	Platelet pools (per cycle)	108(3.48)	271 (9.34)	<0.0001

	Granulocyte transfusion units (per cycle)	24 (0.77)	107 (3.69)	<0.0001

* Mann-Whitney U test, all other P values by Chi squared test