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Oral etoposide as a single agent in childhood and young adult cancer in England: Still a poorly evaluated palliative treatment

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Abstract

Background: Oral etoposide is commonly used in palliative treatment of childhood and young adult cancer without robust evidence. We describe a national, unselected cohort of young people in England treated with oral etoposide using routinely collected, population-level data.

Methods: Patients aged under 25 years at cancer diagnosis (1995–2017) with a treatment record of single-agent oral etoposide in the Systemic AntiCancer Dataset (SACT, 2012–2018) were identified, linked to national cancer registry data using NHS number and followed to 5 January 2019. Overall survival (OS) was estimated for all tumours combined and by tumour group. A Cox model was applied accounting for age, sex, tumour type, prior and subsequent chemotherapy.

Results: Total 115 patients were identified during the study period. Mean age was 11.8 years at cancer diagnosis and 15.5 years at treatment with oral etoposide. Median OS was 5.5 months from the start of etoposide; 13 patients survived beyond 2 years. Survival was shortest in patients with osteosarcoma (median survival 3.6 months) and longest in CNS embryonal tumours (15.5 months). Across the cohort, a median of one cycle (range one to nine) of etoposide was delivered. OS correlated significantly with tumour type and prior chemotherapy, but not with other variables.

Conclusions: This report is the largest series to date of oral etoposide use in childhood and young adult cancer. Most patients treated in this real world setting died quickly. Despite decades of use, there are still no robust data demonstrating a clear benefit of oral etoposide for survival.

KEYWORDS
AYA, cancer, children, etoposide, population, survival

Abbreviations: CNS, central nervous system; CTYA, children, teenagers and young adults; ICCC3, International Classification of Childhood Cancer, 3rd edition; NHS, National Health Service; OS, overall survival; SACT, systemic anti-cancer therapy

1 | INTRODUCTION

Most children with cancer in England are either recruited to clinical trials at diagnosis[1] or treated according to clinical guidelines based on phase III clinical trial evidence.[2] Five-year survival has successively increased for decades and in England is now 84% for all childhood cancers combined.[3] However, at recurrence phase III trial data are scarce and treatment relies on less robust evidence.

Oral etoposide is widely used both as a single agent and as a component of multiagent therapy for childhood and young adult cancers. Given orally as a single agent in the relapse setting, it is most commonly used as a palliative treatment, usually towards the end of life on completion of more intensive, hospital-based regimens. The outcomes of little more than 400 children and young adults treated with this regimen have been reported in the literature, comprised entirely of retrospective series, phase I and phase II studies (Table 1).[4–24] Additional reports have detailed pharmacokinetic data but not patient outcomes.[25–27] There have been no phase III randomised studies demonstrating its superiority over no treatment. The series that have specifically reported imaging or survival outcomes after oral etoposide are small (median $n = 14$, range 1–83). The most common tumours reported are Ewing sarcoma ($n = 81$ from seven reports), ependymoma ($n = 69$ from seven reports), low- and high-grade gliomas ($n = 67$ from six reports) and neuroblastoma ($n = 63$ from five reports). Most reports have documented imaging response rates, but with variation in the time points and assessment criteria used, and etoposide doses and schedules have varied. No large series has reported overall survival (OS). Thus, although oral etoposide is a long-established and widely used treatment for childhood cancer, evidence to support its use is weak.

Since April 2012, information on all systemic anticancer treatments given to individuals with a diagnosis of cancer or registrable benign and borderline intracranial and intraspinal tumours diagnosed and treated in England has been collected by Pubic Health England under legal permissions granted by Section 251 of the National Health Service Act 2006.[28] The dataset has been reported previously[29] and currently includes data from April 2012 to March 2018 inlusive. We report here the outcomes of a national cohort of children and young people aged under 25 years at the date of initial cancer diagnosis who had a record of oral etoposide given as a single agent between April 2012 and March 2018.

2 | METHODS

2.1 | Cohort

All children, teenagers and young adults (CTYA) aged under 25 years at diagnosis with a primary malignant cancer or any registrable non-malignant intracranial/intraspinal tumour diagnosed and resident in England in the calendar years 1995–2017 inclusive were identified using the national cancer registration dataset of the National Cancer Registration and Analysis Service (NCRAS). Patients were included if they had at least one record of etoposide administered via the oral route and as a single agent recorded in the systemic anti-cancer therapy (SACT) dataset, regardless of their age at etoposide prescription or the timing of oral etoposide relative to other SACT regimens.

Data collection within the SACT dataset was piloted from April 2012 and was mandatory from April 2014. Patients who were only prescribed oral etoposide before April 2012 or after March 2018 were not captured in the cohort. Two patients had more than one tumour recorded; for this study only the first tumour diagnosis was included in the analysis.

2.2 | Data sources and specification

Patient and tumour characteristics were obtained from the national cancer registration dataset[30]: diagnosis date, age at diagnosis, sex, vital status, date of death and cancer type. Variables relating to etoposide treatment were obtained from the SACT dataset. The SACT dataset is described in reference.[31] In summary, a defined dataset of patient details and prescribed treatments obtained from all electronic and paper records are uploaded monthly by one or more registered uploaders at all National Health Service (NHS) hospitals in England to a secure portal maintained by Public Health England. The inclusion of all public hospitals ensures that data are collected from both childhood and TYA 'principal treatment centres' and from other hospitals responsible for delivering oncology care. The following data were extracted from the dataset for this analysis: first prescription date (regimen start date), cycle number, cycle ID, cycle date, route of administration and number of prior lines of chemotherapy. Treatment intent is collected within the dataset, but there are known quality issues with the data and it was not included in the analysis. The percentage completeness for the major data fields for CTYA patients are reported by Bright et al. for the period April 2017 to March 2018. SACT data were linked to national cancer registry data using NHS number, a centrally allocated number unique to each individual. Cases without an NHS number (0.75% of all registrations during the period) were excluded. Dates of death were obtained from NHS Digital. Cases were followed up until 5 January 2019, at which point the few cases still alive were censored. The date used to determine OS was either date of death or, for patients still alive, the date of censoring. There was no evidence that any patients emigrated or were otherwise lost fo follow-up. First prescription date and drug names were also obtained for SACT regimens prescribed subsequent to oral etoposide.

Cancer type was defined according to the International Classification of Childhood Cancer, 3rd edition (ICCC3).[2] Only two patients with carcinomas were recorded to have had oral etoposide, thus it was not felt necessary to follow the expanded classification of carcinomas in the standard grouping of TYA cancers. Cancer subtypes IXd.1 'Ewing tumour and Askin tumour of soft tissue' and IXd.2 'primitive neuroectodermal tumours of soft tissue' from the ICCC3 classification were grouped with VIIIc 'Ewing tumour and related sarcomas of bone' and combined into a single category, 'Ewing sarcoma family of tumours'. Cancer types with a count ≥10 were analysed as distinct categories; the remaining cases were aggregated into a category of 'other tumours'.

TABLE 1 Previous reports of oral etoposide in CTYA patients

Tumour type	*N*	Age range (years)	Dose (mg/m^2/day) schedule	ORR (%)	Timing of response assessment (cycles)	Median (range) response duration (months)	Median OS (months)	Grade ≥3 toxicity	Subsequent myeloid malignancy	Ref
Retrospective										
Ewing sarcoma	58	2–26	40; 3wk on, 1wk off	19	2–3	8 (2–14)	11[a]	Cytopenias, nausea, gastritis, infection	$n = 2$	19
Ependymoma	12	1–11	50; 3wk on, 1wk off	42	2	7 (4–30)	7	Cytopenias	–	20
Ependymoma	25	–	–	28	nd	nd	nd	nd	–	21
Series type not defined										
Neuroblastoma	20	2–11	50; 3wk on, 1wk off	15	1–3	6 (3–15)	nd	None	–	16
Medulloblastoma	7	4–16	50; 3wk on, 1wk off	86	2	nd	nd	Cytopenias, FN, colitis	–	4
Mixed tumours	12	3–19	50; 10 days on, 1wk off	25	2–4	nd	nd	Thrombocytopenia	$n = 1$	22
Phase I										
Mixed tumours	20	1–17	50–70; 3wk on, 1wk off	21	2	nd	nd	Cytopenias, mucositis, diarrhoea, infections	$n = 0$	17
Mixed tumours	17	3–17	60–75; 2wk on, 1wk off	6	Best observed	6 (3–20)	nd	Cytopenias, FN, nausea/vomiting, mucositis, diarrhoea, abdominal pain	$n = 0$	12

(Continues)

TABLE 1 (Continued)

Tumour type	N	Age range (years)	Dose (mg/m^2/day) schedule	ORR (%)	Timing of response assessment (cycles)	Median (range) response duration (months)	Median OS (months)	Grade ≥3 toxicity	Subsequent myeloid malignancy	Ref
Prospective pilot, feasibility or phase II										
Ependymoma	12	4–16	50; 3wk on, 2wk off	17	–	7 (4–10)	nd	Cytopenias, FN	–	9
Supratentorial malignant glioma	14	4–18	50; 3wk on, 2wk off	21	–	8 (6–10)	nd	Alopecia (57%), weight loss >10% (29%), cytopenias (29%), FN (14%)	–	7
Hypothalamic glioma	14	2–15	50; 3wk on, 2wk off	36	2	8 (6–10)	nd	Alopecia (50%), weight loss >10% (36%), cytopenias (29%)	–	6
Brain stem glioma	12	3–49	50; 3wk on, 2wk off	33	–	8 (4–20)	nd	Thrombocytopenia	–	5
PA (cerebellum)	12	5–15	50; 3wk on, 2wk off	17	1	7 (6–12)	2.5–12[c]	Cytopenias, FN	–	8
Medulloblastoma	8	4–36	50; 3wk on, 2wk off	25	1	6 (4–11)	5.5	Cytopenias, FN	–	24
Mixed tumours	21	3–16	50; 20 days on, 10 days off	14	2	10 (2–87)	nd	None	$n = 1$	14
Ependymoma[b]	12	3–16	50; 3wk on, 1wk off	17	Best observed	nd	nd	Cytopenias, hypokalaeia, hypophosphataeia, stomatitis	–	13
Mixed tumours	83	–	50; 3wk on, 1wk off	7	2	nd	nd	Cytopenias, FN, nausea/vomiting, mucositis, diarrhoea, alopecia	–	10
Mixed tumours	14	5–60	50; 3wk on, 1wk off	0	2	(6–17)	5.5	FN, gastrointestinal	–	15
Mixed tumours	28	2–20	50; 3wk on, 1wk off	18	–	nd	nd	Cytopenias, FN	–	18
Mixed tumours	20	2–19	50; 3wk on, 1wk off	5	2	nd	nd	Cytopenias, FN, nausea/vomiting	–	11
Retinoblastoma	5	2–5	50; 3wk on, 1wk off	0	1	nd	nd	Thrombocytopenia	$n = 1$	23

Abbreviations: FN, febrile neutropenia; nd, not defined; ORR, objective response rate; PA, pilocytic astrocytoma.

[a]Excluding two long-term survivors.

[b]Etoposide randomised against erlotinib.

[c]Rates reported separately for responders and nonresponders.

TABLE 2 Baseline characteristics and cycles of etoposide prescribed

	N	Median age in years (IQR): initial cancer diagnosis	Median age in years (IQR): first etoposide prescription	Median cycles (range)/missing data
Ewing sarcoma	21	14.0 (11.0–20.0)	16.7 (13.1–20.9)	3 (1–9)/19%
Osteosarcoma	18	14.5 (12.2–16.8)	18.2 (15.0–20.3)	1 (1–4)/22%
Embryonal CNS tumour	16	8.0 (2.5–12.2)	12.5 (3.8–19.5)	1 (1–5)/38%
Neuroblastoma	13	3.0 (1.0–5.0)	5.7 (1.9–7.8)	2 (1–6)/31%
Ependymoma	10	7.0 (1.8–8.8)	13.8 (8.1–18.8)	2 (1–2)/40%
Other[a]	37	16.0 (8.0–20.0)	18.5 (11.3–23.9)	1 (1–9)/32%
Total	115	12.0 (5.0–18.0)	16.4 (10.1–20.9)	1 (1–9)/30%

[a]Acute lymphoid leukaemia, acute myeloid leukaemia, unspecified and other leukaemia, Hodgkin lymphoma, astrocytoma, oligodendroglioma, pineal parenchymal tumours and unspecified CNS neoplasms, Wilms tumour, hepatoblastoma, chondrosarcoma, rhabdomyosarcoma, fibroblastic and myofibroblastic tumours, liposarcoma, CNS germ cell tumour, extracranial germ cell tumour, thyroid carcinoma, other carcinoma, unclassified.

Treatment start dates and cycle start dates were available for all patients. However, the number of chemotherapy cycles prescribed is known to have low data quality, particularly for orally administered SACT as multiple cycles can be prescribed at one time to be taken by a patient at home.[32] Therefore, the number of oral etoposide cycles prescribed per patient was derived by comparing three independent data items: the number of distinct cycles recorded, the number of distinct cycle start dates recorded and the highest recorded cycle number. Where there was agreement between all three data items, the number of cycles was retained, in all other cases it was recorded as missing.

2.3 | Statistical analysis

Descriptive statistics were calculated for the cohort as a whole (all tumour types) and by tumour type. Survival in days was calculated from the date of first prescription of oral etoposide, recorded in the SACT dataset as 'regimen start date'.

OS analysis was performed using Kaplan–Meier plots and Cox proportional hazards regression. Kaplan–Meier plots were computed for all tumour types combined and by tumour type. Log rank tests were used to establish whether there was heterogeneity in observed differences between tumour types.

Univariable Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals for death for the variables age (as a continuous variable), tumour type and sex, and a multivariable model adjusting for all variables included in the model. Wald tests were carried out to determine which associations were statistically significant.

All analyses were performed in R v.3.5.3.[33]

3 | RESULTS

In total, there were 145,657 tumours diagnosed in children and young people during the study period, of which 133,385 were not associated with a record in the SACT database, and 12,155 had SACT records that did not include etoposide given as a single agent and administered orally. Two second primary tumours were excluded. Therefore, 115 children and young people received orally administered etoposide as a single agent during the study period for a first primary tumour and were included in the study population. Ten patients were still alive at the date of censoring. Cancer diagnoses included Ewing sarcoma ($n = 21$), osteosarcoma ($n = 18$), embryonal central nervous system (CNS) tumours ($n = 16$), neuroblastoma ($n = 13$), ependymoma ($n = 10$) and other tumours ($n = 37$). Baseline characteristics are shown in Table 2. The 'other' tumour group included cases from every main group in the ICCC3 except retinoblastoma (Table 2). Mean patient age at initial cancer diagnosis was 11.8 years (±SD 7.2 years) and mean age at first cycle of oral etoposide was 15.5 years (±8.4 years). Year of initial cancer diagnosis was as follows: 1995–2004 (10 cases); 2005–2009 (16 cases), 2010–2014 (62 cases), 2015–2017 (27 cases). Median time between initial cancer diagnosis and treatment with oral etoposide was 2.3 years (IQR 1.4–4.2 years) (Figure 1). A total of 93 cases (80%) had received one or more lines of chemotherapy prior to oral etoposide.

Median OS from date of first prescription of etoposide for the whole cohort was 5.5 months (Figure 2A). One- and 2-year survivals were 26.4% (95% CI 19.4–36.0%) and 13.7% (8.5–22.1%), respectively. In total, 13 patients (11%) survived beyond 2 years from the date of the first etoposide prescription, of whom five were still alive at the censor date. No second malignancies were observed after treatment with oral etoposide. Differences in OS were apparent between tumour types (Figure 2B). Patients with osteosarcoma and Ewing sarcoma had the worst survival (median 3.6 and 4.0 months, respectively, Table 3). No patient with Ewing sarcoma was observed to survive beyond 1 year from the start of treatment. A single patient with osteosarcoma survived beyond 1 year. In contrast, individuals with ependymomas and CNS embryonal tumours had the longest median survival (9.2 and 15.5 months, respectively) and included a single 5-year survivor with ependymoma.

The number of prescribed cycles could be confidently derived in 81/115 cases (70%) (Table 2). For these cases, the number of prescribed cycles was small: a median of one cycle of etoposide was prescribed to patients with osteosarcoma, embryonal CNS tumours and 'other

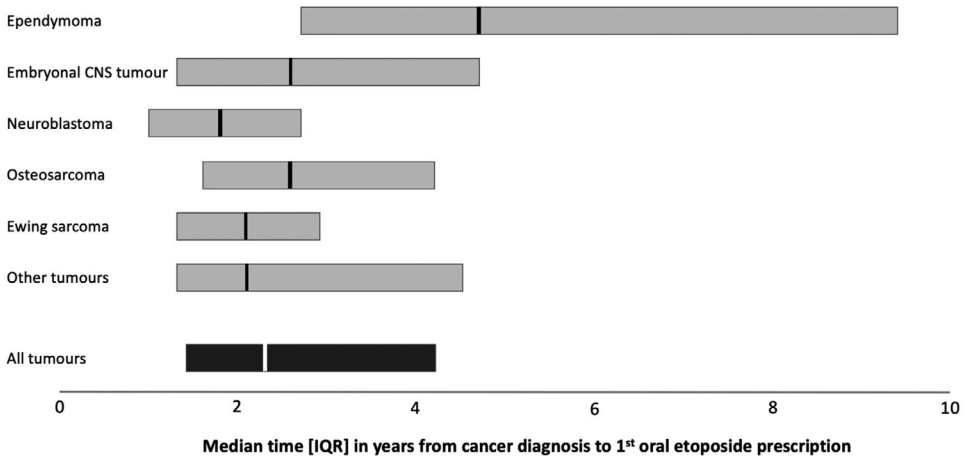

FIGURE 1 Time interval between initial cancer diagnosis and first recorded prescription of oral etoposide

TABLE 3 Survival estimates from start of oral etoposide by cancer type and for all tumours combined

	Osteosarcoma	Ewing sarcoma	Other tumours	Neuroblastoma	Ependymoma	CNS embryonal tumours	All tumours combined
A. Survival point estimates and 95% confidence intervals at 1-year intervals							
1 year	11.1 (3.0–41.0)	–	24.3 (13.8–42.9)	23.1 (8.6–62.3)	50.0 (26.9–92.9)	62.5 (42.8–91.4)	**26.4 (19.4–36.0)**
2 years	5.6 (0.1–37.3)	–	4.5 (2.7–24.0)	7.7 (1.2–50.6)	37.5 (16.2–86.8)	41.7 (22.9–75.8)	**13.7 (8.5–22.1)**
3 years	5.6 (0.1–37.3)	–	4.1 (0.1–23.6)	–	12.5 (2.1–76.2)	27.8 (12.2–63.3)	**7.4 (3.7–14.8)**
4 years	–	–	–	–	12.5 (2.1–76.2)	20.8 (7.7–56.6)	**4.2 (1.4–12.7)**
5 years	–	–	–	–	12.5 (2.1–76.2)		**4.2 (1.4–12.7)**
B. Median survival[a] and interquartile range in months by cancer type							
	3.6 (1.9–4.8)	4.0 (2.4–7.8)	4.1 (1.4–11.7)	6.5 (4.2–11.4)	9.2 (7.2–24.6)	15.5 (4.8–35.5)	**5.5 (2.4–11.3)**

[a]Including patients alive at end of follow-up.

tumours', two cycles for neuroblastoma and ependymoma and three for Ewing sarcoma. The maximum prescribed to any patient was nine cycles.

The relationships between age, sex, tumour type, number of prior lines of treatment and survival were investigated with a Cox regression model (Table 4). Tumour type was significantly associated with survival in both univariable and multivariable models. Survival of patients with ependymomas and CNS embryonal tumours was significantly better than with osteosarcoma in the univariable model. In the multivariable model, patients with CNS embryonal tumours remained significantly better; adjusted HR 0.34 (0.14–0.81). Number of prior lines of treatment was also significantly associated with survival in both univariable and multivariable models. In the multivariable model, patients with three or more previous regimens had significantly worse survival than those for whom oral etoposide was the first recorded regimen; HR 2.19 (1.10–4.36). No relationship was observed between age or sex and survival.

Because oral etoposide is usually given in the palliative setting and frequently when other more intensive or hospital-based regimens are deemed inappropriate, we examined the proportion for whom oral etoposide was the final regimen prescribed prior to death. In total, 27 patients (23%) were prescribed a subsequent SACT regimen. In 11 cases, a different regimen was given within approximately 2 months of the first prescription of oral etoposide (cisplatin or carboplatin and etoposide $n = 3$, temozolomide +/− irinotecan $n = 2$, liposomal doxorubicin $n = 2$, cytarabine +/− idarubicin $n = 2$, denosumab $n = 1$ and dasatinib $n = 1$). Fourteen additional cases had 11 other subsequent regimens at 85–563 days from the start of oral etoposide, and two patients were treated with a second course of oral etoposide 175 and 417 days after the first course. There was a nonsignificant trend towards better survival in patients who received additional chemotherapy subsequent to oral etoposide: adjusted HR for death in those who had subsequent chemotherapy was 0.62 (0.36–1.09) compared to those for whom oral etoposide was the final SACT regimen. When patients who received subsequent chemotherapy were removed from the dataset, median OS was 4.7 months (IQR 2.0–10.1). In this subset of patients age, tumour type and number of lines of chemotherapy all correlated with survival on univariable analysis, with better survival in younger patients, those with ependymomas and CNS embryonal tumours and those for whom oral etoposide was the first recorded regimen (Table 4) but no variables

TABLE 4 Cox regression models

	All patients				Patients for whom oral etoposide was the final SACT regimen			
Variable	Unadjusted HR (95% CI)	*p*-Value[a]	Adjusted HR[b] (95% CI)	*p*-Value[a]	Unadjusted HR (95% CI)	*p*-Value[a]	Adjusted HR[b] (95% CI)	*p*-Value[a]
Age	1.02 (0.99–1.04)	.19	1.01 (0.97–1.04)	.67	1.04 (1.01–1.07)	.02	1.03 (0.99–1.07)	.15
Sex								
Male	Reference		Reference		Reference		Reference	
Female	1.07 (0.72–1.59)	.75	1.25 (0.80–1.96)	.32	1.26 (0.79–1.99)	.33	1.60 (0.92–2.79)	.09
Cancer type								
Osteosarcomas	Reference		Reference		Reference		Reference	
Ewing sarcoma family	0.94 (0.48–1.82)	.85	0.81 (0.38–1.71)	.58	0.72 (0.33–1.57)	.41	0.63 (0.26–1.52)	.30
Neuroblastoma	0.63 (0.30–1.30)	.21	0.73 (0.32–1.68)	.46	0.60 (0.26–1.37)	.22	0.65 (0.26–1.62)	.36
Ependymomas	0.33 (0.14–0.78)	.01	0.44 (0.16–1.18)	.10	0.30 (0.12–0.72)	.01	0.40 (0.14–1.12)	.08
CNS embryonal tumours	0.30 (0.14–0.62)	.001	0.34 (0.14–0.81)	.02	0.31 (0.13–0.73)	.01	0.38 (0.14–1.02)	.06
Other tumours	0.71 (0.39–1.27)	.25	0.78 (0.41–1.47)	.45	0.78 (0.40–1.51)	.46	0.77 (0.38–1.55)	.46
Number of previous chemotherapy regimens								
0	Reference		Reference		Reference		Reference	
1	1.73 (0.93–3.22)	.08	1.49 (0.77–2.89)	.24	1.90 (0.93–3.89)	.08	1.94 (0.91–4.14)	.09
2	2.62 (1.45–4.75)	.002	1.77 (0.91–3.44)	.09	2.47 (1.26–4.83)	.008	1.55 (0.74–3.27)	.25
3+	3.17 (1.70–5.88)	<.001	2.19 (1.10–4.36)	.03	2.40 (1.20–4.83)	.01	1.68 (0.79–3.60)	.18
Subsequent chemotherapy recorded								
No	Reference		Reference					
Yes	0.69 (0.43–1.10)	.12	0.62 (0.36–1.09)	.10				

[a]Based on the Wald test.
[b]Adjusted for other variables in the model.

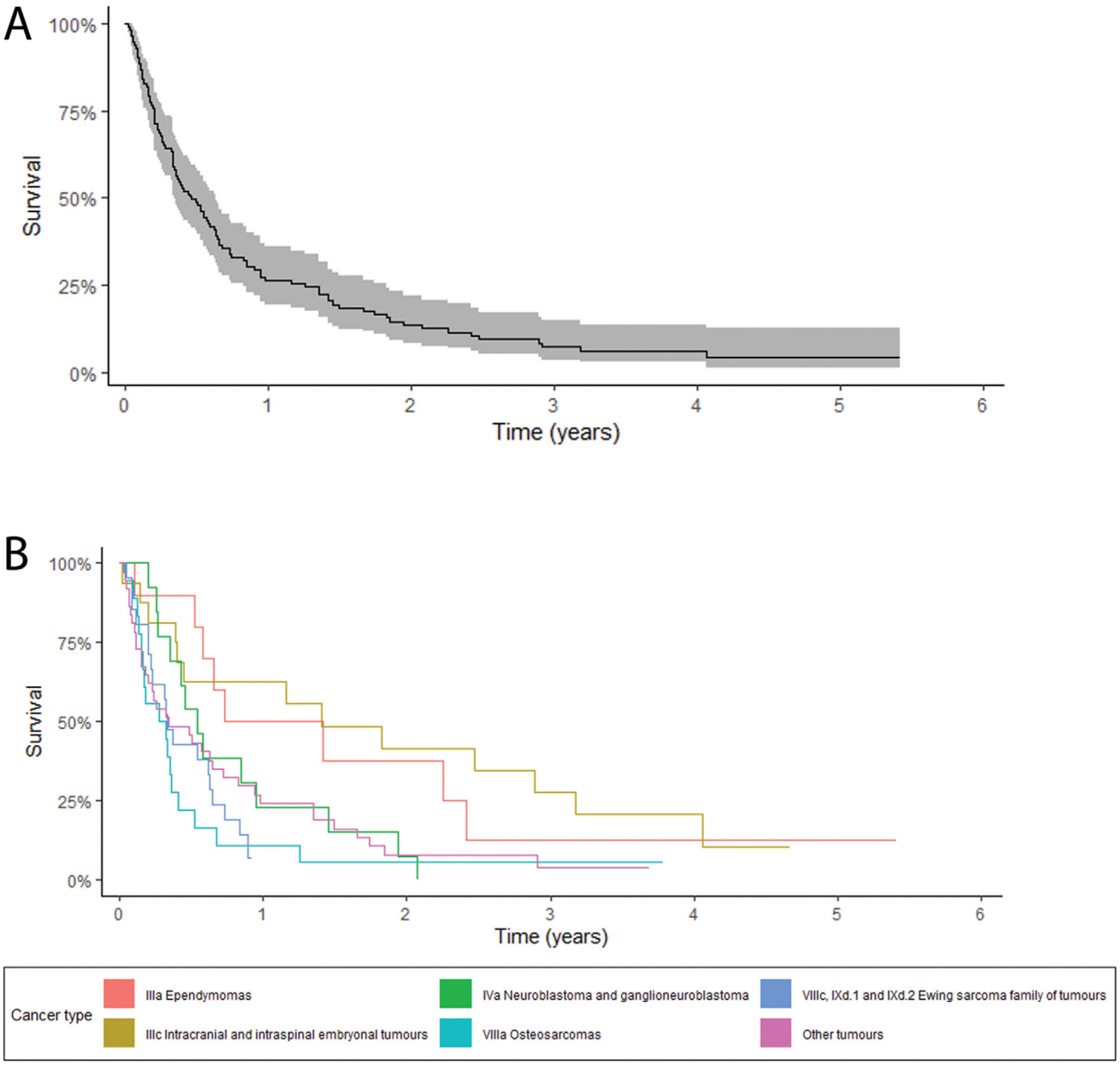

FIGURE 2 Kaplan–Meier overall survival curves of (A) all patients in the final cohort (grey shading indicates 95% confidence intervals), and (B) individual tumour classes

remained significant at a significance *p*-value of .05 in the multivariable model.

4 | DISCUSSION

We report here the largest series to date of children and young adults treated with oral etoposide as a single agent, the largest to report OS, and the first to use routinely collected population-level data. Median survival in our series across the entire cohort of 115 children and young people was 5.5 months, and 4.7 months in the 88 patients for whom oral etoposide was the final chemotherapy regimen.

There are no other directly comparable survival data reported. The series of mixed childhood brain tumours ($n = 14$),[15] childhood recurrent ependymomas ($n = 12$)[20] and locally recurrent medulloblastomas ($n = 8$)[24] that reported survival data are too small to make meaningful comparisons with our series. Podda and colleagues reported the survival outcomes of 58 children and young people with Ewing sarcoma treated at a single centre, the Istituto Tumori, Milan.[19] This is the largest series of a single tumour type in the literature with survival outcomes. The median survival of 11 months was longer than the 4-month median survival of 21 children and young people with recurrent Ewing sarcoma in our national series. Some patients in the Milan series had concomitant or subsequent radiotherapy and/or surgery, and/or

subsequent chemotherapy. A total of 27 patients in our national series had additional chemotherapy but it was not possible to identify how many received radiotherapy or surgery from the SACT database, and the small number of cases in both series precludes any robust comparison.

A key feature of our report is its 'real world' setting: oral etoposide was not given according to a standardised dose, schedule or specified number of cycles, or at a predefined point in the treatment pathway, and compliance with prescribed treatment was not monitored. It is a regimen that is frequently, though not exclusively, used 'when all else has failed'. Given the number of SACT regimens used across the whole spectrum of CTYA cancer and the variable nomenclature applied by individual hospitals to chemotherapy regimens within the SACT database, an analysis of the place of oral etoposide within the overall patient pathway would have been highly complex. However, one can assume given the short median survival, and in the majority no evidence of further chemotherapy, that in most cases it was used as a palliative regimen. It is important to recognise, therefore, that in our national series more than half of cases had only a single cycle of treatment, and more than half with bone sarcomas and 'other tumours' died within 6 months of starting treatment. This finding is in keeping with response durations in the literature, which are typically short-lived. The handful of cases with prolonged survival in our series and other reported series,[14,20] are intriguing and demonstrate that in a small minority of cases, oral etoposide may have useful activity. However, we also found that survival varies between cancer types, and prolonged survival in some cases may reflect natural history rather than etoposide activity. The SACT dataset was not collected throughout the whole study period so we could not identify the patients in our series who definitively did not receive oral etoposide. Therefore, it was not possible to examine whether treatment with oral etoposide correlated with survival. In our series, oral etoposide was the final chemotherapy regimen in over 75% cases. In the minority who did receive further chemotherapy, approximately one-third initiated a different regimen within 2 months of starting oral etoposide, implying that etoposide had limited or no benefit. The remaining cases started alternative treatment up to 14 months after the start of etoposide.

Toxicities of at least grade 3 in other reported series include myelosuppression, infections, mucositis, diarrhoea, nausea, vomiting and alopecia and a minority developed therapy-induced malignancies, principally AML.[14,19] Although severe toxicities are infrequent, they are not trivial for the patients who experience them, and toxicities should be considered in the context that most patients have only a single cycle of treatment and die within a year. Quality of life has not been reported in any study to date and only three have attempted to record symptomatic response or performance status: 'useful palliation' of unknown duration was reported in one of 15 children with mixed cancers[11]; two children with recurrent ependymoma had no change in neurological findings or performance status[9]; and two children with recurrent medulloblastoma had improved neurological symptoms but no improvement in performance status.[24] Taking the published childhood data and our findings together, there remains significant uncertainty whether oral etoposide prolongs survival or improves quality of life compared to no treatment despite over two decades of its use in children and young people treated near the end of life. It undoubtedly causes toxicity. There have been no randomised studies against placebo or no treatment. Given the combination of typically short-lived responses reported in the literature, short median survival in this and previous studies, and significant toxicity in a minority of patients, more robust data are needed in this disease setting to determine whether oral etoposide contributes usefully to patient care. Ideally, a randomised, placebo-controlled trial should be undertaken, but as a minimum well-designed, prospective study that collects accurate data on symptom improvement and quality of life would be welcome.

We acknowledge some limitations of our study, which include lack of data on the prescribed dose and schedule of etoposide and incomplete data on the number of cycles prescribed. Ascertainment for the SACT dataset is recognised to be worse for CTYA cancers than for those in older adults, due in part to delayed introduction of routine electronic prescribing for children compared to adults, and worse for oral chemotherapy than for SACT delivered by other routes. Toxicity is not recorded in the SACT dataset and could therefore not be analysed here, and we did not have data on treatment modalities other than SACT that took place subsequent to oral etoposide. We are aware that the SACT database during the period was incomplete[29] and that the collection of SACT data relied on the availability of electronic prescribing, which was not universal in paediatric cancer centres throughout the study period. Moreover, some patients included in our dataset may have started oral etoposide prior to the start of the SACT dataset and others who were diagnosed after 1995 and treated with oral etoposide before the start of SACT data collection could not be identified. Theoretically, the noninclusion of cases treated prior to the SACT dataset who had short survival may have led to relative overestimation of survival in those cases who survived long enough to be included. However, the likelihood of significant bias is small, as most patients had only one or two cycles of treatment, irrespective of cancer type. Although our data were unselected and included all children and young people for whom there were data in the SACT database, missing data from some centres may have introduced additional systematic biases.

Nevertheless, by combining routinely collected, population-level diagnostic treatment and outcome data, we describe here the first report of oral etoposide use in a national, unselected cohort of children and young people. We present data on OS in children and young people prescribed oral etoposide for the treatment of cancer. We have identified differences in survival between cancers of different histologies. Whether these differences are due to differential activity of etoposide or variable natural histories of the cancers concerned is unclear; there is no evidence in our data that patients with CNS embryonal tumours or ependymomas, despite living longer, received more cycles of etoposide than patients with other cancers. Our analysis identifies weaknesses in the literature on rare cancer treatments that are typical of the clinical scenario of relapsed cancer in children and young people: a concentration on imaging response as the primary measure of activity, lack of data on survival, lack of randomised evidence to drive

treatment, little data on whether symptoms are effectively palliated, but nevertheless the incorporation of therapy into routine patient care. This study represents an exemplar of our ability to describe the effectiveness of treatment for rare cancers where clinical trial data are lacking. We have identified the need for a well-designed clinical trial to determine whether a longstanding and widespread palliative childhood cancer treatment is of benefit to the patients who receive it.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Public Health England's National Cancer Registration and Analysis Service. However, restrictions apply to the availability of these data.

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