Title

Implanted intrathecal drug delivery systems may be associated with improved survival in patients with cancer

Abstract

Background

Intrathecal Drug Delivery Systems (IDDS) are underused in the management of cancer related pain despite evidence of both efficacy and survival benefit. There is currently limited evidence to indicate which patients might benefit most from IDDS.

Aim

The aim of the study was to describe the baseline characteristics and survival outcomes of patients who accepted IDDS, patients who declined IDDS, and patients who wished to go ahead with IDDS but whose condition deteriorated before they could do so.

Design/participants

The survival data for 75 consecutive patients who had been offered intrathecal drug delivery were examined as part of a retrospective cohort study. Survival data was compared between three groups: those who accepted intrathecal drug delivery and went on to receive it (n=41), those who accepted it but whose condition deteriorated before it commenced (n =17), and those who declined this treatment modality (n=17).

Results

Patients who received IDDS survived significantly longer after assessment compared to those who declined IDDS (hazard ratio (HR) for the IDDS group relative to the declined group 0.29 (95% CI 0.16 to 0.53), and 0.23 (95% CI 0.12 to 0.44) after adjustment for gender and baseline functional status. In patients who accepted IDDS but who were unable to commence treatment, survival after assessment was not significantly different from those who declined the IDDS (HR for the deteriorated group relative to the declined group 1.28 (95% CI 0.65 to 2.53), and 0.80 (95% CI 0.65 to 2.53) after adjustment for gender and baseline functional status).

Conclusion

In this retrospective analysis, an improvement in survival may be associated with patients who accept ongoing pain management with an implanted intrathecal drug delivery system compared to those patients who either declined intrathecal drug delivery or deteriorated before it could be commenced.

Key Statements

What is already known about this topic?

- Cancer pain is not well controlled in all patients
- Intrathecal drug delivery systems are under-utilised in the management of cancer related pain.
- Patients receiving analgesia via Intrathecal drug delivery systems can have a survival advantage over those who do not

What this paper adds?

- Our work appears to indicate a survival advantage for cancer patients who receive analgesia via Intrathecal drug delivery systems over patients who either declined the treatment or who deteriorated before receiving it.
- Fitter patients have a survival advantage
- Patients on higher doses of morphine at assessment are less likely to meet IDDS trial goals and proceed to implanted pump

Implications for practice, policy, or theory

- This study indicates that an improvement in survival may be associated with patients who accept ongoing pain management with an implanted intrathecal drug delivery system which has the potential both to inform discussion with patients and inform future research.
- Policymakers should aim for equity of access to services which can offer assessment for and delivery of Intrathecal drug delivery systems where appropriate.
- The establishment of prospective national or international registries of patients referred for cancer pain management would greatly enhance future research in an area where randomised trials are often very challenging.

Introduction

Background

Intrathecal drug delivery systems (IDDS) are an effective treatment for patients with refractory cancer pain. The use of IDDS in appropriately selected patients leads to an improvement in quality of life, pain control, and reduced drug toxicity compared to comprehensive medical management.[1-3] IDDS has been found to be a cost-effective alternative for cancer patients who require pain management for three months or more[4-5.] Smith et al published an RCT in 2002 comparing Comprehensive Medical Management (CMM) with IDDS confirming both a possible survival benefit and pain improvement in patients receiving IDDS[6]. Despite this evidence, IDDS is underutilised,[7] and many patients either do not have access to IDDS or are referred too late to benefit from the intervention. [8-9]

We run an Interventional Cancer Pain Service (ICPS) in the United Kingdom and follow national recommendations.[10] The Interventional Cancer Pain Service is a multidisciplinary team comprising consultants in Palliative Medicine and Pain Management, and specialist nursing, physiotherapy and psychology staff. We offer assessment and where appropriate an intervention including IDDS for patients with refractory cancer pain. Not all patients who are offered IDDS accept this treatment modality, and some who do accept it then become unfit to proceed due to changes in their clinical condition. Patients who decline IDDS do so for a range of reasons, which include reluctance to spend time as an in-patient for the procedure, and a desire to focus primarily on oncology treatments.

We observed an apparent improvement in survival in patients with IDDS and decided to undertake a retrospective cohort study to investigate this further.

Aim

The aim of the study was to describe the baseline characteristics and survival outcomes of patients who accepted IDDS, patients who declined IDDS, and patients who wished to go ahead with IDDS but whose condition deteriorated before they could do so.

Methods

Study design

This was a retrospective cohort study comparing baseline characteristics and survival data of patients with poorly controlled cancer pain who were offered IDDS as a treatment modality. A total of 75 patients were included. We compared survival between three groups – those that accepted and received IDDS (n=41), those that declined IDDS (n=17), and patients who accepted but were unable to receive IDDS (n=17), as either their condition deteriorated before they could do so (n=15) or the IT catheter was unable to be inserted due to technical challenges (n=2).

Setting

The study period was 1st April 2015 to 18th October 2021.

The setting for the study was the Interventional Cancer Pain Service (ICPS). All patients in the study had cancer pain that had not responded to usual analgesic measures and had been referred to the ICPS by a Palliative Medicine consultant.

They were subsequently reviewed in the ICPS outpatient clinic assessed by the multi-disciplinary team and offered a trial of intrathecal drug delivery.

Participants/eligibility

Patients were eligible for inclusion in the study if during the study period they had been assessed in the ICPS clinic and offered intrathecal drug delivery as a treatment option and had died by the end of the study period.

Patients referred to the ICPS were assessed by a multidisciplinary team as having potential to benefit from IDDS and were offered an inpatient trial of IDDS. This trial was undertaken to establish the efficacy of the treatment prior to committing the patient to a permanent implantable pump.

Those who agreed to proceed were admitted to the cancer centre for a trial of this mode of analgesia, which was delivered into the intrathecal space via an implanted silicone catheter attached to an external pump. All patients receiving IDDS commenced therapy with a similar dose of intrathecal bupivacaine, while the intrathecal preservative free morphine was calculated based on the MEDD at time of assessment. At the end of the trial period if the pre-agreed goals had not been met, the silicone catheter was removed. These pre agreed trial goals are patient directed functional goals that are patient dependent. For example a patient who cannot sit secondary to pain from recurrent rectal cancer rectal cancer might have a trial goal to sit for 30 minutes with a pain score of no more than 4 to allow them to eat a meal with family. However, if at the end of the trial assessment period, pre-agreed trial goals had been met, patients proceeded to intrathecal pump implantation. After implantation, the patient was discharged to their previous place of care, which was usually home or a specialist palliative care unit. The pump was refilled every 2-4 weeks until death.

Not all patients who were offered IDDS chose to go ahead with the intervention. Patients who declined IDDS did so for a range of reasons which included reluctance to spend time as an in-patient for the procedure, and a desire to focus primarily on oncology treatments.

There was a further group of patients who accepted IDDS but whose condition then deteriorated such that they were no longer suitable to undertake a trial of IDDS. Those who deteriorated or who declined IDDS were discharged back to the care of the local specialist palliative care team and received ongoing comprehensive medical management (CMM) of cancer related pain.

Variables

All patients had identical information collected at assessment, including demographic information, cancer type, pain scores using the short form of the Brief Pain Inventory, functional status using the Karnofsky score, morphine equivalent daily dose in 24 hours, and analgesic adjuvant information. Cancer type was initially collated using the classification from Information Services Division (ISD) Scotland. As the numbers in each cohort were small these groups were merged into four

anatomically linked cancer groups: gastrointestinal, gynaecological/urological, respiratory, and 'other' cancer diagnoses. The Brief Pain Inventory (BPI) has four individual pain intensity and seven individual pain interference scores recorded on a scale of 0-10, which give an overall average score for the two main domains – pain intensity and pain interference. The BPI was developed for use on a cancer pain population.[11] Post assessment follow up data included date of death. This data was collected using the ICPS database and paper records, NHS electronic paper record, hospice electronic record and hospice paper record.

Consent

Patients receiving IDDS gave written consent for their data to be analysed for service evaluation. The Caldicott Guardian approved retrospective data collection and analysis for the groups that turned down IDDS or who deteriorated before it could commence and the project was approved by the local Quality Improvement Committee.

Statistical Methods

Continuous data are summarised using mean and standard deviation; categorical data are summarised as counts and percentages.

Kruskal-Wallis rank sum test and Fisher's exact test were used to assess the statistical significance of differences in patients' characteristics at assessment between the study groups.

Kaplan-Meier curves were used to assess overall survival for each study group post assessment, and the groups were compared by a log-rank test. Univariate and multivariable Cox proportional hazard regression analyses were performed to explore differences in post-assessment survival between the study groups. The proportional hazard assumption was assessed using Schoenfeld residuals. In addition to standard Cox models, time-dependent Cox regression models were used to assess the time-dependent effect of IDDS status on survival, taking into account that a patient's status may change over the period between assessment and end of life as they may discontinue to use IDDS. A multivariable Cox proportional hazard model was used to investigate potential factors associated with stopping IDDS among the groups of patients who proceeded with IDDS.

All statistical analyses were conducted using R version 4.2.1. A 2-sided significance level of $p < 0.05$ was used throughout.

Results

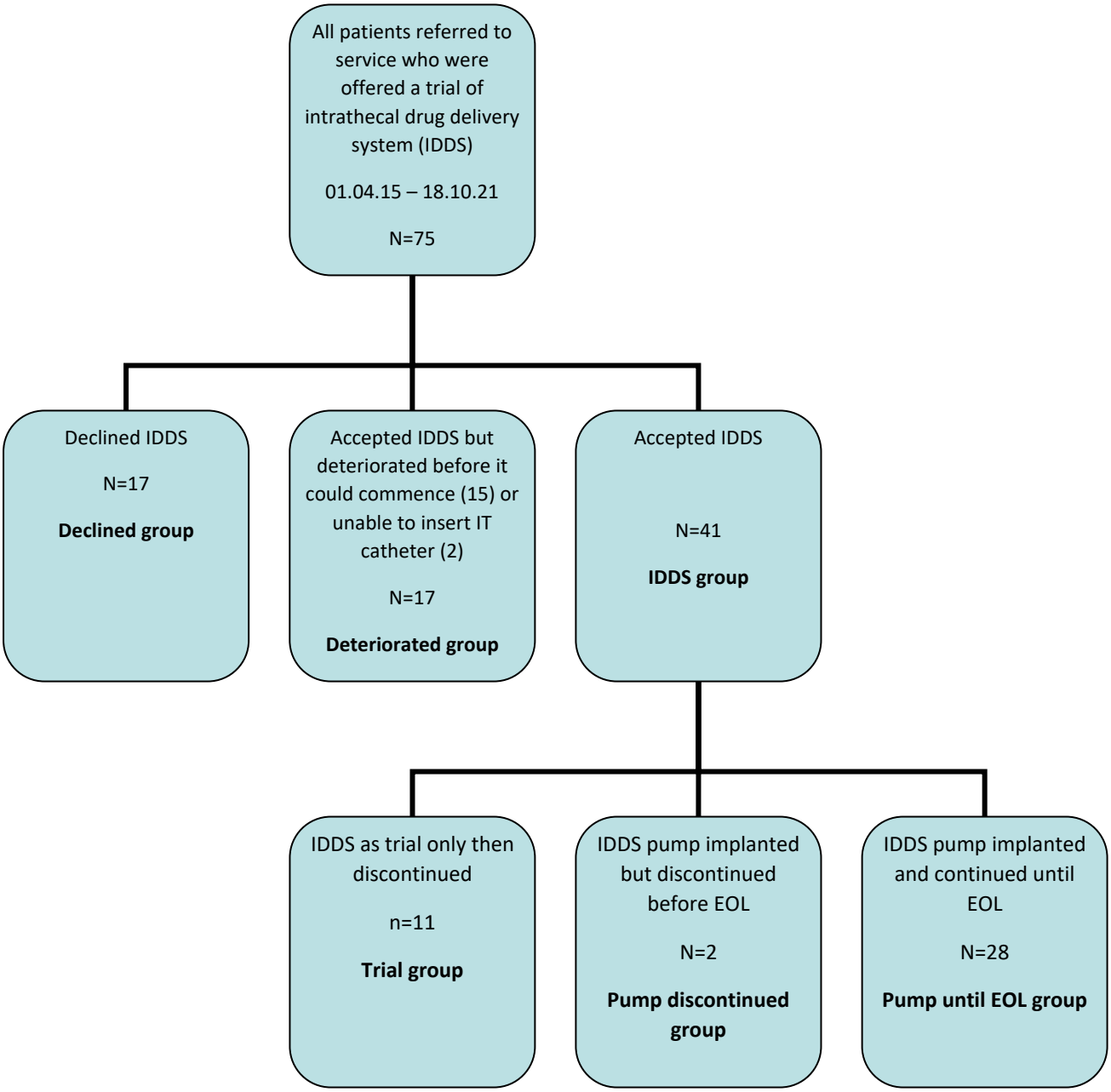
Study population

Between 1st April 2015 and 18th October 2021, 75 patients were offered an IDDS system to help manage cancer related pain. 58 patients (77%) consented to a trial of IDDS with 17 (23%) turning IDDS down and continuing CMM.

Of the 58 patients who agreed to a trial of IDDS, 15 (26%) deteriorated before it could be commenced and 2 (3.5%) were unable to have a catheter inserted for technical reasons. These two patients were included in the 'Deteriorated group' for the purpose of analysis giving the 'Deteriorated group a total of 17 patients. There were therefore 41 patients in the 'IDDS' cohort, 17 patients in the 'Declined' cohort and 17 patients in the 'Deteriorated' cohort (Figure 1).

The 41 patients in the IDDS cohort included 11 patients who had undergone a trial but did not meet their trial goals and so did not proceed to implanted pump and two patients who had the pump explanted prior to end of life (Figure 1).

Figure 1



Patient characteristics

The characteristics of each study group at assessment are shown in Table 1. Demographic and clinical characteristics of patients were similar between the three study groups.

Table 1. Patient characteristics at assessment

	N	Declined, N = 17	Deteriorated, N = 17	IDDS, N = 41	*P* value[1]
Age, Mean (SD)	75	58.8 (12.7)	57.6 (9.4)	58.7 (9.8)	0.8
Gender, *n (%)*	75				0.4
Female		9 (53%)	6 (35%)	23 (56%)	
Male		8 (47%)	11 (65%)	18 (44%)	
SIMD, *n (%)*	75				0.2
1 – Most deprived		4 (24%)	3 (18%)	17 (41%)	
2		7 (41%)	3 (18%)	4 (9.8%)	
3		1 (5.9%)	3 (18%)	5 (12%)	
4		2 (12%)	5 (29%)	5 (12%)	
5 – Least deprived		3 (18%)	3 (18%)	10 (24%)	
Cancer group, *n (%)*	74				0.2
Other		0 (0%)	2 (12%)	6 (15%)	
Gastrointestinal		6 (35%)	9 (53%)	15 (38%)	
Gynaecological/urology		8 (47%)	3 (18%)	16 (40%)	
Head and Neck		0 (0%)	1 (5.9%)	0 (0%)	
Respiratory		3 (18%)	2 (12%)	3 (7.5%)	
Unknown		0	0	1	
Karnofsky, *n (%)*	75				0.050
40		0 (0%)	2 (12%)	0 (0%)	
50		3 (18%)	7 (41%)	13 (32%)	

Table 1. Patient characteristics at assessment

	N	Declined, N = 17	Deteriorated, N = 17	IDDS, N = 41	*P* value[1]
60		6 (35%)	6 (35%)	11 (27%)	
70		8 (47%)	2 (12%)	11 (27%)	
80		0 (0%)	0 (0%)	6 (15%)	
MEDD, Mean (SD)	75	709.4 (749.2)	390.9 (282.0)	489.2 (490.9)	0.8
Adjuvant count, Mean (SD)	75	3.1 (1.1)	3.5 (1.3)	3.5 (1.6)	0.7

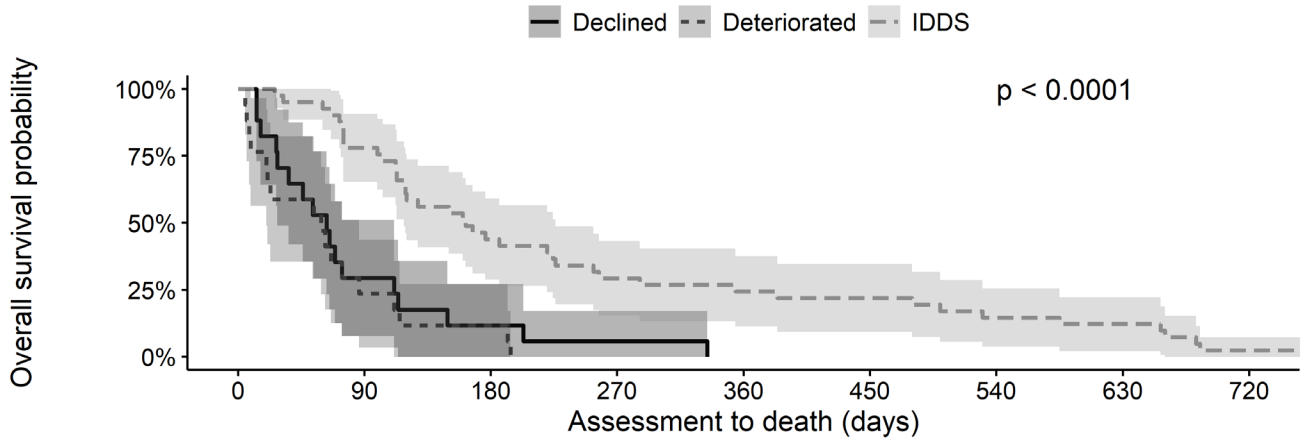
N: number; SD: standard deviation; Declined: patients who turned down option of IDDS; Deteriorated: patients who accepted option of IDDS but they were unable to proceed with IDDS; IDDS: patients who proceeded with IDDS; SIMD: Scottish index of multiple deprivation; MEDD: morphine equivalent daily dose

[1]Kruskal-Wallis rank sum test; Fisher's exact test

Main results

The overall survival after assessment was significantly higher in patients who commenced IDDS compared with the two groups of patients who did not (log-rank P<0.0001; Figure 2). The 6-month overall survival probabilities were 44% (95% CI, 29%-59%) for the IDDS group but only 12% (95% CI, 0%-27%) for both the Declined and Deteriorated group.

Figure 2. Kaplan-Meier survival curves



Number at risk: n (%)

Declined	17 (100)	5 (29)	2 (12)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Deteriorated	17 (100)	4 (24)	2 (12)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
IDDS	41 (100)	32 (78)	18 (44)	12 (29)	10 (24)	9 (22)	6 (15)	5 (12)	1 (2)

Declined: patients who turned down option of IDDS; Deteriorated: patients who accepted option of IDDS but they were unable to proceed with IDDS; IDDS: patients who proceeded with IDDS

In Cox regression analyses with the study group as a time-fixed covariate, the estimated hazard of death in the IDDS group was 71% lower compared with the Declined group (HR, 0.29; 95% CI, 0.16-0.53 [P<0.001]). In contrast, the estimated hazard of death in the Deteriorated group was 28% higher than the Declined group (HR, 1.28; 95% CI, 0.65-2.53 [P=0.5]). A similar result was found after multivariable adjustment for gender (HR, 1.82; 95% CI, 1.11-2.98 [P=0.017]) and Karnofsky score (HR, 0.66; 95% CI, 0.51-0.85 [P=0.001]) at assessment which were independently associated with patients' survival. Compared with the Declined group, the estimated hazard of death was 77% lower in the IDDS group (HR, 0.23; 95% CI, 0.12-0.44 [P<0.001]) and 20% lower in the Deteriorated group (HR, 0.80; 95% CI, 0.65-2.53 [P=0.5]). However, the estimated hazard ratios between the Deteriorated and the Declined failed to achieve statistical significance in both analyses (Table 2).

Table 2. Univariate and multivariable Cox regression analyses for the association between patient group and post-assessment survival in patients with refractory cancer pain

	Unadjusted		Adjusted[1]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Patient group				
Declined	1[Reference]	—	1[Reference]	—
Deteriorated	1.28 (0.65, 2.53)	0.5	0.80 (0.39, 1.63)	0.5
IDDS	0.29 (0.16, 0.53)	<0.001	0.23 (0.12, 0.44)	<0.001
Gender				
Female			1[Reference]	—
Male			1.82 (1.11, 2.98)	0.017
Karnofsky			0.66 (0.51, 0.85)	0.001

HR: hazard ratio; CI: confidence interval; IDDS*: intrathecal drug delivery system; Declined: patients who turned down option of IDDS; Deteriorated: patients who accepted option of IDDS but they were unable to proceed with IDDS; IDDS: patients who proceeded with IDDS

[1]A multivariable Cox proportional hazard model adjusted for gender and Karnofsky score at assessment

In Cox regression analyses with receiving IDDS as a time-dependent covariate, the hazard of death for those receiving IDDS compared to those who were not, was estimated to be 57% lower (HR, 0.43; 95% CI, 0.26-0.71 [P<0.001]) in unadjusted analysis, and 53% lower after accounting for gender and Karnofsky score at assessment (HR, 0.47; 95% CI, 0.28-0.78 [P=0.004]) (Table 3, Appendix).

Factors associated with stopping IDDS

The differences in patient characteristics at assessment between the sub-groups of the cohort are shown in Table 4 (Appendix). On average, patients who had IDDS until their end of life took a significantly lower equivalent daily dose of morphine at assessment compared with the patients who stopped IDDS (mean, 336.1 vs 777.2 vs 1,048.0; P=0.014). A multivariable Cox regression analysis demonstrated that an increase (functionally better) of one point on the Karnofsky score was associated with 6% decrease in the estimated risk of stopping the IDDS (HR, 0.94; 95% CI, 0.89-1.00 [P=0.034]). It also showed that a two-fold increase in MEDD at assessment was associated with 95% increase in the estimated risk of stopping the IDDS (HR, 1.95; 95% CI, 1.15-3.30 [P=0.013]) (Table 5, Appendix).

Table 3. Univariable and multivariable time-dependent Cox regression analyses for the association between receiving IDDS and the post-assessment survival in patients with refractory cancer pain

	Unadjusted		Adjusted[1]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Receiving IDDS				
No	1[Reference]	—	1[Reference]	—
Yes	0.43 (0.26, 0.71)	<0.001	0.47 (0.28, 0.78)	0.004
Gender				
Female			1[Reference]	
Male			1.78 (1.10, 2.85)	0.018
Karnofsky			0.71 (0.56, 0.91)	0.006

HR: hazard ratio; CI: confidence interval; IDDS: intrathecal drug delivery system

[1]A multivariable time-dependent Cox regression model adjusted for gender and Karnofsky score at assessment

Table 4. Characteristics of sub-groups of IDDS group at assessment

	N	Pump to EOL N = 28	Trial only N = 11	Pump stopped N = 2	*P* value[1]
Age, mean (SD)	41	59.8 (9.4)	56.2 (11.9)	57.5 (0.7)	0.6
Gender	41				0.5
Female		14 (50%)	8 (73%)	1 (50%)	
Male		14 (50%)	3 (27%)	1 (50%)	
SIMD, *n (%)*	41				0.4
1 – Most deprived		12 (43%)	5 (45%)	0 (0%)	
2		3 (11%)	0 (0%)	1 (50%)	
3		4 (14%)	1 (9.1%)	0 (0%)	
4		3 (11%)	1 (9.1%)	1 (50%)	
5 – Least deprived		6 (21%)	4 (36%)	0 (0%)	
Cancer group, *n (%)*	40				0.4
Other		3 (11%)	3 (27%)	0 (0%)	
Gastrointestinal		9 (32%)	5 (45%)	1 (100%)	
Gynaecological/urology		13 (46%)	3 (27%)	0 (0%)	
Head and Neck		0 (0%)	0 (0%)	0 (0%)	
Respiratory		3 (11%)	0 (0%)	0 (0%)	
Unknown		0	0	1	
Karnofsky, *n (%)*	41				0.3
50		7 (25%)	6 (55%)	0 (0%)	
60		7 (25%)	3 (27%)	1 (50%)	

Table 4. Characteristics of sub-groups of IDDS group at assessment

	N	Pump to EOL N = 28	Trial only N = 11	Pump stopped N = 2	*P* value[1]
70		8 (29%)	2 (18%)	1 (50%)	
80		6 (21%)	0 (0%)	0 (0%)	
MEDD, Mean (SD)	41	336.1 (222.0)	777.2 (779.2)	1,048.0 (215.0)	0.014
Adjuvant count, Mean (SD)	41	3.5 (1.5)	3.5 (1.8)	4.0 (2.8)	>0.9

N: number; SD: standard deviation; IDDS: intrathecal drug delivery system; SIMD: Scottish index of multiple deprivation; MEDD: morphine equivalent daily dose

[1]Kruskal-Wallis rank sum test; Fisher's exact test

Table 5. A multivariable Cox regression analysis for the factors associated with stopping IDDS among patients who started IDDS

	HR (95% CI)	*P* value[1]
Karnofsky	0.94 (0.89, 1.00)	0.034
MEDD(log2)	1.95 (1.15, 3.30)	0.013

HR: hazard ratio; CI: confidence interval; IDDS: intrathecal drug delivery system; MEDD: morphine equivalent daily dose;

[1]A multivariable Cox proportional hazard model adjusted for MEDD (log2) and Karnofsky score at assessment

Discussion

Key results

This retrospective study has shown an apparent statistically significant difference in survival for patients with cancer related pain who received IDDS compared with the groups that either declined IDDS or accepted but deteriorated before they could commence this treatment. Patients who received IDDS had a 44% probability of being alive at 6 months post assessment compared to 12% of patients who declined IDDS or whose condition deteriorated before they could commence IDDS. The reasons for this difference in survival are not clear, however it is reasonable to consider that an improvement in pain control with IDDS as shown in previous studies[3, 6] may lead to an improvement in performance status if severe pain is a contributing factor to a lower performance status. There is evidence linking higher performance status to an improvement in survival.[14]

There was an association across all 3 groups between a higher level of function at assessment and survival. It is already known both that IDDS is an effective cost effective treatment for cancer patients who require pain management for more than 3 months,[4,5] and that there are multiple barriers to early referral of cancer patients for an intervention.[17] This work further evidences that referral of fitter more active patients for assessment can lead to improved outcomes. It is not unexpected that fitter patients did better across the three groups although the deteriorated group had a marginally smaller proportion of patients with lower Karnofsky scores (poorer function) which was an unexpected finding and it would be interesting to see if this was consistent with a bigger patient population.

We also found an independent association of gender on survival, with male patients having shorter survival times that female patients. Again this finding was unexpected and would benefit from further investigation with a larger sample size.

The sub group analysis compared patient characteristics between those who commenced treatment with IDDS to those who commenced treatment but either stopped it after a trial of IDDS or had an implanted pump removed. This analysis showed that patients on higher mean equivalent daily doses (MEDD) of morphine at assessment were less likely to meet their trial goals and therefore less likely to go on to receive an implanted intrathecal pump. The sub group analysis also demonstrated a relationship between a higher Karnofsky score (better function) at assessment and the likelihood of a patient going on to receive an implanted pump. Both these findings provide further evidence that patients with cancer pain who are functionally fitter with lower MEDD are more likely to demonstrate benefit from a trial of IDDS and go onto receive an implanted intrathecal pump. It can be inferred that earlier referral of patients with difficult to control cancer pain for assessment for IDDS may lead to better trial outcomes, with patients more likely to achieve their trial goals and go onto receive an implanted intrathecal pump.

Limitations

This was a small, non-randomised observational study. As an observational study, comparing three select groups of patients, we cannot infer that the observed differences between groups in survival is entirely causal. Previous randomised trials[1] have shown an association with increased survival in patients receiving IDDS and our data support these findings.

There was a lack of consistent data both for the reasons patients declined IDDS and for the reasons they did not meet trial goals and go onto pump implantation. Collection and detailed analysis of this data going forward will address this information gap.

Interpretation

This study adds to the evidence that patients with cancer who receive IDDS may have a survival advantage over those who do not.[1] It also gives an indication that better function and lower MEDD at assessment are more likely to lead to a successful trial of IDDS and implantation of an intrathecal pump.

Generalisability

This study adds to the existing evidence base that patients with cancer related pain may have a survival benefit from IDDS.

It is a small retrospective study and future studies should be prospective, include health economics analysis, more detailed follow-up of patients with cancer pain who do not receive IDDS and follow up of the group of patients who did not benefit from a trial of IDDS. Investments are required to establish largescale, national or international registries of cancer patients undergoing pain management to collect data on implanted devices, patient's baseline characteristics and procedures/implant complications.

References

1. Smith TJ, Coyne PJ, Staats PS, Deer T, Stearns LJ, Rauck RL*, et al*. An implantable drug delivery system (IDDS) for refractory cancer pain provides sustained pain control, less drug-related toxicity, and possibly better survival compared with comprehensive medical management (CMM). *Ann Oncol*. 2005 May; 16(5):825-33. doi: 10.1093/annonc/mdi156. Epub 2005 Apr 7. PMID: 15817596.

2. Smith TJ and Coyne PJ. Implantable drug delivery systems (IDDS) after failure of comprehensive medical management (CMM) can palliate symptoms in the most refractory cancer pain patients. *J Palliat Med* 2005; 8(4): 736–742. DOI: 10.1089/jpm.2005.8.736
3. Mitchell A, McGhie J, Owen M, McGinn G. Audit of intrathecal drug delivery for patients with difficult-to-control cancer pain shows a sustained reduction in pain severity scores over a 6-month period. Palliative Medicine. 2015; 29(6):554-563. doi:10.1177/0269216315570514
4. Hassenbusch SJ, Paice JA, Patt RB, Bedder MD, Bell GK. Clinical realities and economic considerations: economics of intrathecal therapy. *J Pain Symptom Manage* 1997; 14(3 Suppl): S36-48. DOI: 10.1016/s0885-3924(97)00169-3
5. Mueller-Schwefe G, Hassenbusch SJ, Reig E. Cost effectiveness of intrathecal therapy for pain. Neuromodulation 1999; 2(2):77-87. https://doi.org/10.1046/j.1525-1403.1999.00077.x
6. Thomas J. Smith, Peter S. Staats, Timothy Deer, Lisa J. Stearns, Richard L. Rauck, Richard L. Boortz-Marx, Eric Buchser, Elena Català, David A. Bryce, Patrick J. Coyne, and George E. Pool. Randomized Clinical Trial of an Implantable Drug Delivery System Compared with Comprehensive Medical Management for Refractory Cancer Pain: Impact on Pain, Drug-Related Toxicity, and Survival Journal of Clinical Oncology 2002 20:19, 4040-4049
7. Duarte RV, Sale A et al The Unmet Need for Intrathecal Drug Delivery Pumps for the Treatment of Cancer Pain in England: An Assessment of the Hospital Episode Statistics Database Neuromodulation Volume 23, Issue 7, October 2020, Pages 1029-1033
8. Cope DK, Zhao Z. Interventional management for cancer pain. Curr Pain Headache Rep 2011; 15:237–243.
9. Joshi M, Chambers WA. Pain relief in palliative care: a focus on interventional pain management. Expert Rev Neurother 2010; 10:747–756

10. Intrathecal drug delivery for the management of pain and spasticity in adults; recommendations for best clinical practice. British Pain Society December 2015
11. Cleeland CS, Ryan KM. Pain Assessment: Global Use of the Brief Pain Inventory. Annals, Academy of Medicine, Singapore 1994 23(2), 129-138
12. Altilio T, Otis-Green S, Oxford Textbook of Palliative Medicine Oxford University Press 1993. 109.
13. Scottish Index of Multiple Deprivation 2020. Health and Social Care. Scottish Government.
14. Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, Mercadante S, Pasternak G, Ventafridda V; Expert Working Group of the European Association of Palliative Care Network. Strategies to manage the adverse effects of oral morphine: an evidence-based report. J Clin Oncol. 2001 May 1;19(9):2542-54. doi: 10.1200/JCO.2001.19.9.254
15. .O'Brien T, Kane CM. Pain services and palliative medicine - an integrated approach to pain management in the cancer patient. Br J Pain. 2014 Nov;8(4):163-71. doi: 10.1177/2049463714548768. PMID: 26516550; PMCID: PMC4616727.

Declarations

Authorship and roles

Dr Alison Mitchell
(i) Made a substantial contribution to the concept or design of the work, acquisition, analysis, and interpretation of data,
(ii) Drafted the article or revised it critically for important intellectual content,
(iii) Approved the version to be published,
(iv) Has participated sufficiently in the work to take public responsibility for appropriate portions of the content

Ms Lesley Somerville

(i) Made a substantial contribution to the concept and design of the work, and acquisition, of data,

(ii) Revised the article critically for important intellectual content,

(iii) Approved the version to be published,

(iv) Has participated sufficiently in the work to take public responsibility for appropriate portions of the content

Dr Nicola Williams

(i) Made a substantial contribution to the acquisition of data.

(ii) Revised the article critically for important intellectual content,

(iii) Approved the version to be published,

(iv) Has participated sufficiently in the work to take public responsibility for appropriate portions of the content

Dr Jonathan McGhie

(i) Made a substantial contribution to the concept and design of the work,

(Ii) Revised the article critically for important intellectual content,

(iii) Approved the version to be published,

(iv) has participated sufficiently in the work to take public responsibility for appropriate portions of the content

Professor Alex McConnachie

(i) Made a substantial contribution to the analysis and interpretation of data,

(ii) Revised the article critically for important intellectual content,

(iii) Approved the version to be published,

(iv) Has participated sufficiently in the work to take public responsibility for appropriate portions of the content**.**

Dr Gordon McGinn

i) Made a substantial contribution to the concept and design of the work,

(ii) Revised the article critically for important intellectual content,

(iii) Approved the version to be published,

(iv) Has participated sufficiently in the work to take public responsibility for appropriate portions of the content

Ms Jiyoung Lee

(i) Made a substantial contribution to the analysis and interpretation of data,
(ii) Revised the article critically for important intellectual content,
(iii) Approved the version to be published,
(iv) Has participated sufficiently in the work to take public responsibility for appropriate portions of the content**.**

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Data sharing
Anonymised statistical data files are available within the Health Board website

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