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Case study

The use of isoflurane and desflurane as inhalational agents for glioblastoma surgery. A survival analysis

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ABSTRACT

Background: Several studies have examined the impact of anesthetics on cancer recurrence. Isoflurane but not desflurane has protumoral effects. We hypothesize the use of isoflurane but not desflurane during surgery for primary GBM is an independent predictor of disease progression and mortality.
Methods: 378 adult patients were included in the study. The progression free survival (PFS) and overall survival (OS) rates at 1 and 5 years were compared in patients who had either desflurane or isoflurane alone or in combination with propofol infusion. Multivariate analyses were conducted to test the association between preoperative, intraoperative and postoperative hyperglycemia with PFS and OS.
Results: Kaplan–Meier curves demonstrated similar survival in patients who had either desflurane or isoflurane. The use of a propofol infusion during surgery did not affect survival. Univariate analysis demonstrated that age, body mass index and the adjusted Charlson comorbidity score were associated with reduced survival. The multivariate analysis confirmed that age and BMI but not the type volatile anesthetic use were independent prognostic factors for PFS (HR, 95%CI: 1.07, 0.85–1.37, 9 = 0.531) and OS (HR, 95%CI: 1.13, 0.86–1.48, $p = 0.531$).
Conclusion: The use of isoflurane or desflurane during GBM surgery is not associated with reduced PFS or OS.

1. Introduction

Glioblastoma multiforme (GBM) is the most common type of brain tumor. Despite the combined use of temozolomide and radiation as adjuvant therapies, the survival of patient with GBM remains dismal [1,2]. Recent studies indicate that the postoperative progression and response to treatment of GBM depends not only on patients' demographic characteristics such as age, but also on the genomic characteristics and the molecular profile of the tumors. For instance, *MGMT* (O-6-methylguanine-DNA methyltransferase) hypermethylation and mutations in isocitrate dehydrogenase (*IDH1*) and protein serine 1 (*PRSS1*) are associated with better response to treatment and therefore survival [3,4].

Inhalational general anesthetics are known to modify the gene expression of cancer cells. In neuroblastoma cells, both isoflurane and desflurane cause a time-dependent increase in the expression of genes involved in DNA repair and the cell division cycle [5]. However, the effects of these anesthetics on gene expression are not uniform across different cancer cell lines. For instance, isoflurane increases the mRNA expression of chemokine receptor type (CXCR)-2, vascular endothelial growth factor (VEGF)-A, metalloproteinase (MMP)-11, and transforming growth factor (TGF)-β in ovarian cancer cells. Desflurane does not appear to have such an effect on the same cell type. In GBM stem cells, isoflurane has been shown to increase invasion and growth through a mechanism that might involve VEGF expression [6,7]. But, the effect of desflurane in this cell line is unknown.

The immune system also plays a significant role in the progression of GBM. Experimental and clinical data demonstrates that natural killer (NK) cells actively inhibit the spread of GBM cells [8,9]. Inhalational anesthetics have been shown to modulate the immune system, particularly the function of NK cells. Human studies indicate that isoflurane has suppressive effects on the function of NK cells, while desflurane does not significantly impair their function [10,11].

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Based on these premises, we conducted a retrospective study to investigate the impact of inhalational anesthetics (desflurane vs. isoflurane) on the survival of patients who had surgery for non-recurrent GBMs. We tested the hypothesized that the use of isoflurane during GBM surgery was associated with a shorter progression-free survival (PFS) and/or overall survival (OS) than desflurane.

2. Material and methods

After obtaining institutional review board approval (IRB# PA12-0447), we conducted a retrospective study that included patients with GBM who underwent surgery between January 2006 and July 2015 at The University of Texas M.D. Anderson Cancer Center. Patients were included in the study if they were 18 years or older, had surgery for non-recurrent GBM and had received adjuvant temozolomide and/or radiation. We excluded those patients with recurrent GBM, those who underwent biopsy, and those with benign lesions. Our database contains demographic, perioperative, and survival data; therefore we were able to retrieve information for the following variables: patient age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, age-adjusted Charlson comorbidity index (aCCI), intraoperative dexamethasone use, anesthesia duration, and adjuvant temozolomide and radiation treatment.

2.1. Statistical analysis

The primary clinical endpoints were PFS and OS. PFS was defined as the time between the surgery date and the date of first evidence of progression (radiological) or the date of death, whichever occurred first. Patients were censored at the last known date if neither recurrence nor death occurred. OS was defined as the time from the date of surgery to the date of death or last follow-up. Patients were censored at the last follow-up if death did not occur.

Summary statistics included mean, standard deviation (SD), median, and range. Frequency counts and percentages were calculated for categorical variables. Fisher's exact test or Chi-square test was used to evaluate the association between two categorical variables. Wilcoxon rank sum test was used to evaluate the difference in a continuous variable between patient groups. Only patients with complete covariate data were included in our analysis. This left us with 381 patients in our data set. Three additional patients were excluded due to lack of follow-up, leaving us with 378 patients for analysis.

Estimating a median PFS times for the isoflurane and desflurane groups of 7.4 and 12 months (1-year PFS rate: 0.325 vs. 0.50) respectively, a sample size of 138 patients in each group would be needed to have at least 80% power to detect this difference in median PFS time assuming a two-sided type I error rate of 0.05. The PFS time was estimated from data a similar group of patients [12].

The Kaplan–Meier method was used for time-to-event analysis including PFS and OS. Median time to event in months with 95% confidence interval was calculated. The log-rank test was used to evaluate the difference in time-to-event endpoints between patient groups. Univariate Cox proportional hazards models were fitted to evaluate the effects of continuous variables on time-to-event outcomes. Multivariable Cox proportional hazards models were used for multivariate analysis to include important and significant covariates. Statistical software SAS 9.1.3 (SAS, Cary, NC) and S-Plus 8.0 (TIBCO Software Inc., Palo Alto, CA) were used for the analyses.

3. Results

3.1. Overall population

Three-hundred and seventy-eight patients were included in the study. The mean (SD) age and BMI of the group was 56.63 years (13) and 28.1 (5), respectively (Table 1). There were more male (65.6%) than females (34.4%) and more than two-thirds of the patients had an ASA physical status of 3 or 4 (Table 1). Nearly half (45%) of the patients received only inhalational anesthetics for the maintenance of general anesthesia while the rest of the group was treated with a combination of a volatile anesthetic (desflurane or isoflurane) and a propofol infusion. In regards to adjuvant therapy, most patients (96.9%) were treated with radiation postoperatively. As shown in Table 3, the median (95%CI) PFS and OS times for the overall group of patients were 8.84 (7.92–10.28) and 19 (17.31–22.93) months, respectively. At 5 years, the progression and overall mortality rate were 93% and 85%.

Table 1
Demographic and perioperative variables by choice of inhalational agent.

Variable	Levels	All patients (n = 378)	Desflurane (n = 261)	Isoflurane (n = 117)	p-value
Age, mean (SD)		56.63(13)	57.4(12.6)	54.91(13.4)	0.175
BMI, mean (SD)		28.1(5)	28.71(4.9)	27.95(5.2)	0.684
Gender	Female	130(34.4%)	88(33.7%)	42(35.9%)	0.679
	Male	248(65.6%)	173(66.3%)	75(64.1%)	
ASA	1–2	61(16.1%)	36(13.8%)	25(21.4%)	0.064
Physical status	3–4	317(83.9%)	225(86.2%)	92(78.6%)	
aCCI	1–2	186(49.21%)	124(47.5%)	62(53%)	0.324
	3–9	192(50.79%)	137(52.5%)	55(47%)	
Dexamethasone	No	6(1.6%)	6(2.3%)	0(0.%)	0.182
	Yes	370(98.4%)	253(97.7%)	117(100%)	
Anesthesia	Inhalational only	170(45%)	157(60.2%)	13(11%)	<0.0001
Technique	Combined	208(55%)	104(39.8%)	104(89%)	
Anesthesia duration (min)		431.13 (143.57)	378.52 (116.05)	548 (129.15)	<0.002
Adjuvant	No	12 (3.1%)	6(2.3%)	6(5%)	0.146
Radiation	Yes	366(96.9%)	255(97.7%)	111(95%)	
Recurrence	No	49(13%)	32(12.3%)	17(14.5%)	*
Status	Yes	329(874%)	229(87.7%)	100(85.5%)	
Alive status	Alive	112(29.6%)	73(28%)	39(33.3%)	*
	Death	266(70.4%)	188(72%)	78(66.7%)	

* Those endpoints are analyzed as time-to-event endpoints. SD: standard deviation. BMI: body mass index. ASA: American Society of Anesthesiologists. aCCI: adjusted Charlson comorbidity index. Min: minutes.