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ORIGINAL ARTICLE

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Lower all-cause mortality rates in patients harboring pituitary carcinoma following the introduction of temozolomide

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Abstract

Objective To evaluate the impact of temozolomide (TMZ) introduction on the survival of patients with pituitary carcinoma (PC) compared to aggressive pituitary adenoma (APA).

Methods Retrospective analysis of the Surveillance Epidemiology and End-Results database (SEER), including patients diagnosed with PC or APA between 1973 and 2015. Age-adjusted Kaplan–Meier analyses were performed, comparing all-cause mortality (ACM) rates before the year 2006, the time of TMZ introduction ("period 1"), and afterwards ("period 2"), in patients harboring PC and APA.

Results Among 107 patients, 18 (16.8%) harbored PC. The prevalence of PC and APA was comparable between genders, ethnicities and age strata. Patients harboring any pituitary tumor (PC or APA) had comparable risk for ACM and disease-specific mortality between the two time periods. However, among patients harboring PC, the risk for ACM was significantly lower in period 2 vs. period 1 ($p = 0.021$), becoming comparable to the risk of ACM in patients diagnosed with APA ($p = 0.48$).

Conclusions In this large cancer-database-based analysis we observed improved overall survival in patients harboring PC in the years following the introduction of TMZ.

Keywords Pituitary carcinoma · Pituitary adenoma · Mortality · Temozolomide

Introduction

Pituitary carcinomas (PC) are rare tumors, defined based on craniospinal or systemic metastases [1, 2] and account for approximately 0.12% of all pituitary tumors. PC usually evolve from macroadenomas, defined by diameter ≥1 cm, and most commonly emerge from neoplasms of the corticotroph and lactotroph, with nonfunctioning tumors being the minority of cases [3, 4]. Patients typically present with PC in the fourth to sixth decades of life, with inconclusive data regarding gender predominance [5–8].

The prognosis of patients with PC is poor, with an estimated mean overall survival of 1–3 years [9]. In a case series of 15 patients with PC, 12/15 (80%) patients died of metastatic disease 7 days to 8 years after the diagnosis with PC; of these, eight (66%) died within 1 year following diagnosis, whereas only 20% were alive at last follow-up, 9–18 months after the diagnosis [4]. Recently, it was suggested that aggressive pituitary tumors defined as invasive tumors with rapid growth, multiple recurrences, and resistance to standard therapies are histologically and clinically similar to PC [10].

Until the introduction of temozolomide (TMZ), the standard of care for PC included surgery, radiation, chemotherapy, and dopamine agonists for prolactin producing PC [4]. TMZ, an alkylating agent chemotherapy was approved by the Food and Drug Administration (FDA) in

This is a retrospective analysis, based on the Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute- an open access database.

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1999, initially indicated for the treatment of anaplastic astrocytoma and glioblastoma. However, it was used "off-label" for patients with PC. The first report of TMZ long-term efficacy in a patient with PC was published in 2006 [11], and opened the way for additional reports of positive response to TMZ, with the outcome ranging from stable disease to complete response [11, 12]. A recent report on the treatment and follow-up of patients with aggressive pituitary tumors showed an improved survival among TMZ responders [13, 14]. Currently, TMZ is regarded as the first line chemotherapy for aggressive pituitary tumors according to the European Society of Endocrinology [6].

In the current analysis we aimed to evaluate the impact of TMZ introduction on the survival of patients with PC and aggressive pituitary adenomas (APA), based on a large database population study.

Materials and methods

This is a retrospective analysis, based on the Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute. The SEER database collects and publishes cancer incidence and survival data from population-based cancer registries in the US. These registries routinely collect data on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and follow-up for vital status (survival) [15]. The 18th update of the SEER (November 2017) was used, including all patients diagnosed between 1973 and 2015. Data were incorporated and sorted using the SEER*Stat software version 8.3.5. Inclusion criteria were primary pituitary tumors (ICD-O-3 code C75.1, and ICD-0-3/WHO 2008 code III (e.1)), classified as malignant, based on histology (8270, 8271, 8272, and 8280), and with a documented age at diagnosis. From these patients, only tumors with documented metastases and known histology of pituitary tumor were classified as having PC, whereas patients with pituitary tumors, either localized or with regional extension without distant metastasis were classified as APA. The histological diagnosis for 25 patients was missing at the original database. However, in the absence of distant metastasis, we defined them as APA and not PC (Fig. 1).

Patients were divided by their age at diagnosis into three equal tertiaries: ≤49 years, 50–64 years and ≥65 years, based on the age 5-years strata reported in the SEER database. Patients were sub-grouped into Caucasians, African-American and other ethnic groups or unknown ethnicities. Tumor extent was defined according to the SEER classification (localized, regional, and distant metastases).

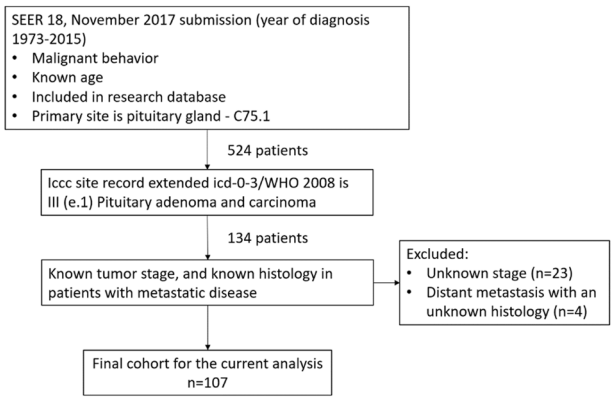

Fig. 1 Flow chart of cohort construction based on the Surveillance Epidemiology and End-Results (SEER) database

Statistical analysis

Continuous variables were compared using Student's *t*-test, and categorical variables were compared by chi-square test. Non-parametric tests were used as appropriate. Age tertiaries-adjusted survival analyses were performed, using the Kaplan Meier method for comparing all-cause mortality (ACM) by the log-rank test. The main comparison was performed between patients harboring APA vs. PC, and by the period of diagnosis: before year 2006 (period 1) vs. at/after year 2006 (period 2). The statistical analysis was performed on SPSS version 22 (IBM). Statistical significance was defined as two-tailed p-value < 0.05.

Results

Patient characteristics

One hundred and seven patients were included in the current analysis, of them 49 (46%) women. The prevalence of PC and APA was comparable between genders [9/18 (50%) women harboring PC vs. 40/89 (45%) women harboring APA, $p = 0.8$]. Seventy-two (72/107, 67%) patients were Caucasians, 27 (25%) African-American and eight (7%) of other ethnic groups or of unknown ethnicity. The minimal age strata at diagnosis was 1–4 years and the maximal age strata was ≥85 years. The prevalence of PC and APA was comparable between the three age tertiaries. All patients diagnosed with PC had histologic confirmation, by definition, as well as 64/89 (72%) of patients diagnosed with APA, whereas the remaining 25/89 (28%) patients with APA were diagnosed based on radiologic findings. Patients' characteristics are detailed in Table 1.

Table 1 Characteristics of the patients included in the current analysis

Age tertiaries *n* (%)	
1st tertiary (<50 years)	40/107 (37%)
2nd tertiary (50–64 years)	37/107 (34%)
3rd tertiary (≥65 years)	30/107 (28%)
Female gender *n* (%)	49/107 (46%)
Ethnicity *n* (%)	
Caucasian	72/107 (67%)
African-American	27/107 (25%)
Other/unknown	8/107 (7%)
Positive histology/microscopic confirmation *n* (%)	
Yes	82/107 (77%)
No	25/107 (23%)
Tumor extent *n* (%)	
Local	30/107 (28%)
Regional	59/107 (55%)
Distant	18/107 (17%)

Table 2 Comparison of demographic characteristics in patients with aggressive pituitary adenoma vs. pituitary carcinoma

	Aggressive pituitary adenoma	Pituitary carcinoma	*p* value
Age tertiaries *n* (%)			0.9
1st tertiary (<50 years)	34/89 (38%)	6/18 (33%)	
2nd tertiary (50–64 years)	30/89 (34%)	7/18 (39%)	
3rd tertiary (≥65 years)	25/89 (28%)	5/18 (28%)	
Female gender *n* (%)	40/89 (45%)	9/18 (50%)	0.4
Ethnicity *n* (%)			0.07
Caucasian	58/89 (65%)	14/18 (78%)	
African-American	25/89 (28%)	2/18 (11%)	
Other/unknown	6/89 (7%)	2/18 (11%)	
Diagnosis year *n* (%)			0.6
<2006	36/89 (40%)	6/18 (33%)	
≥2006	53/89 (60%)	12/18 (67%)	

Trends of PCs vs. APAs prevalence

The prevalence of PC and APA were comparable between periods ($p = 0.6$) and between gender ($p = 0.4$) and age strata ($p = 0.9$). Comparison of characteristics of patients harboring PC vs. APA is detailed in Table 2.

Patients harboring any pituitary tumor (PC or APA) had comparable risk ACM and disease-specific mortality between the two time periods ($p = 0.3$ and $p = 0.7$ respectively, Fig. 2a, b). However, among patients harboring PC,

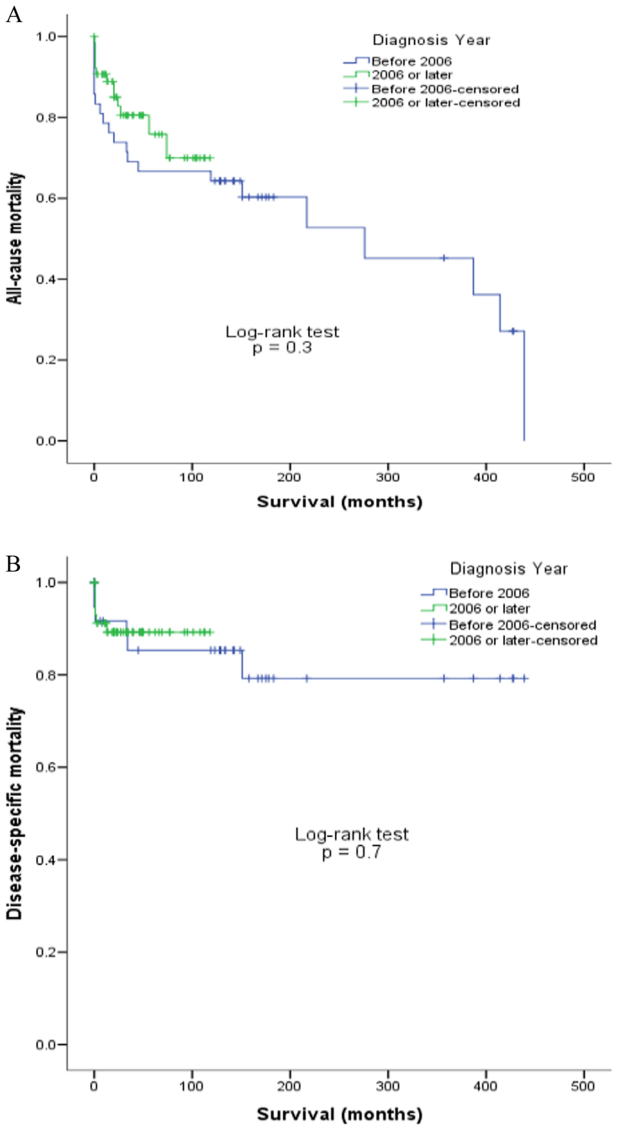

Fig. 2 Kaplan–Meier Survival analysis of the risk for all-cause mortality **a** and disease-specific mortality **b** in patients diagnosed with pituitary tumor before vs. at/after the year 2006

the risk for ACM was significantly lower in period 2 vs. period 1 ($p = 0.021$, Fig. 3), becoming comparable to the risk of ACM in patients diagnosed with APA after 2006 ($p = 0.48$, Fig. 4).

Discussion

In the current analysis we compared the risk for mortality in patients harboring PC/APA, and the risk dynamics over the years 1975–2015, based on the SEER database. The period included in the analysis was divided into two: 1975 up to 2006, the year of the first report on TMZ treatment in PC and from 2006 onwards. We found a decrease in the risk for ACM among patients with PC during period 2 vs. period 1.

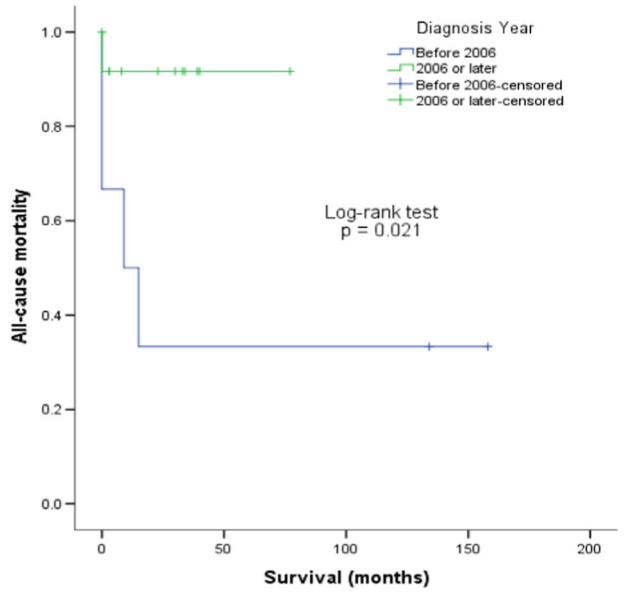

Fig. 3 Kaplan–Meier survival analysis, comparing risk for all-cause mortality in patients diagnosed with pituitary carcinoma before vs. at/after the introduction of temozolomide in 2006

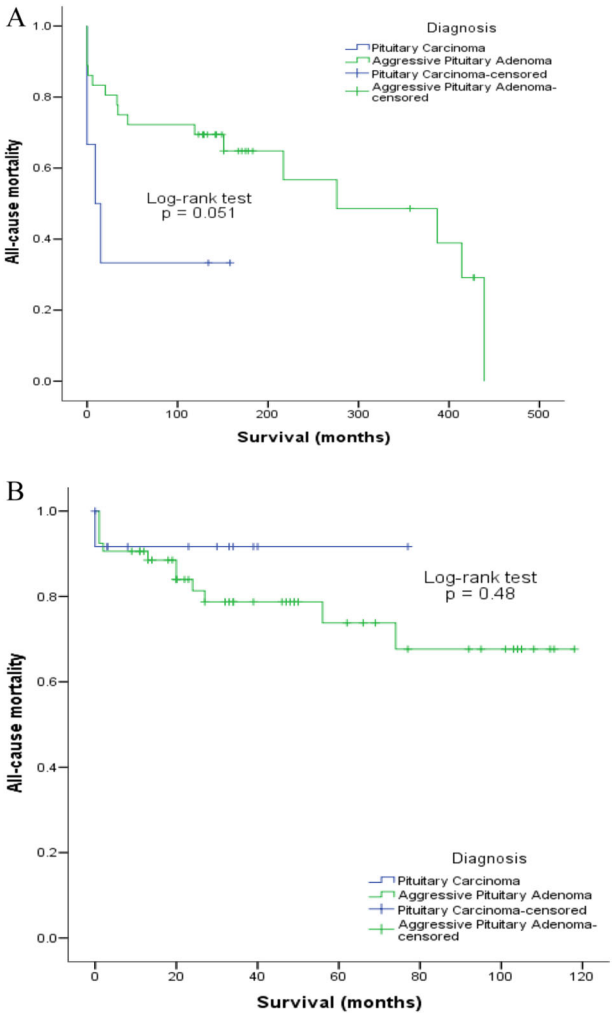

Fig. 4 Kaplan–Meier survival analysis, comparing the risk for all-cause mortality in patients diagnosed before 2006 **a** and after 2006 **b**

Moreover, the increased risk for ACM among patients with PC compared with APA diagnosed during period 1, has significantly decreased during period 2, after the introduction of TMZ for these patients.

We performed the current analysis, to assess the impact of TMZ on the survival of patients with PC. However, the improvement in survival of patients with any disease, and specifically those harboring PC, may stem from improvements in diagnostic modalities (leading to diagnosis at earlier stages with smaller primary tumors and less hazardous metastases), or improved management options other than TMZ. Nevertheless, we report a dramatic decrease in the risk for mortality from PC at/after vs. before the year 2006, with an opposite trend in the risk for ACM in PC vs. APA after the year 2006. Hence, we concluded that the introduction of TMZ as a potent chemotherapy for PC had changed the treatment paradigm of these patients and their survival.

Moreover, the inverse trend of reduced mortality after year 2006 in patients with PC vs. APA suggests that TMZ should be initiated not only in patients with PC but also in patients harboring APA. This assumption is supported by a recent report showing histological and clinical similarities between PC and APA [10].

The therapeutic options for PC can be divided into two groups: Agents aimed mainly at controlling biochemical secretion, such as dopamine agonists for prolactin secreting PC, and agents aimed at reducing proliferation or inducing apoptosis of the tumor [16]. Until the introduction of TMZ, many single agent and combination chemotherapy regimens had been explored, including alkylating agents, anthracyclines, antimetabolites, and adrenocortical suppressant [16]. However, no randomized controlled trials were conducted, and in the limited literature available, the general efficacy reported was low and the overall prognosis was poor [17].

TMZ is an alkylating agent and oral derivative of dacarbazine. It acts by methylation of the O6 position of guanine, resulting in DNA mismatch, and eventually apoptosis. It was suggested that low expression of the O(6)-methylguanine-DNA methyltransferase (MGMT) protein, involved in DNA repair, may be a potential predictor for poor response to TMZ [18].

TMZ, initially approved for the treatment of glioblastoma multiforme, was used "off-label" for treating patients with PC since 2006 [11, 19]. Several advantages, make this drug a good candidate for the treatment of PC; an oral agent, crossing the blood brain barrier, showing a

favorable side effect profile and proven to have good efficacy in other neuroendocrine tumors [20]. It has also been suggested as a radiosensitizing agent, based on in vitro studies [21, 22].

A number of small case series and larger studies reported variable response rates following treatment with TMZ, with rate of tumor regression ranging between 40 and 75% of the patients [11, 12, 18, 23]. Recently, a large study, including 166 patients harboring PC and other locally invasive pituitary tumors was published. This survey studied the outcomes of treatment with TMZ either as monotherapy (most cases), or in combination with other chemotherapy or with radiotherapy [6]. When used as first line monotherapy, TMZ induced biochemical complete response in 19% of patients, partial response in 34%, stable response in 27% and no response with disease progression in 21% of patients. The overall radiological response rate to TMZ was 37%. Concomitant TMZ and radiotherapy was associated with an increased response rate compared to TMZ monotherapy. A complete or partial response was observed in 71% of patients receiving TMZ and concomitant radiotherapy compared with 34% of those receiving TMZ monotherapy [6]. As to mortality, the median duration from initial diagnosis of pituitary tumor to death was 11 years across the cohort (range 1–31) [6]. Our population based-cancer database analysis shows improvement in survival of those patients since the introduction of TMZ, supporting the results reported by McCormack et al. in their study, and clearly showing a benefit in terms of ACM in patients harboring PC. This may be referred either to treatment with TMZ as monotherapy, or through synergistic effect when combined with other modalities.

The current study has several limitations. First, this was a retrospective analysis. Second, we lack the actual treatment regimens in the database, and inferred that the major change in treatment was the introduction of TMZ, based on the timing of TMZ approval by the FDA and the first report on its successful treatment of PC [11]. Third, reporting of pituitary tumors to the SEER database is potentially biased towards more aggressive neoplasms, explaining the small numbers of pituitary adenomas, and the relatively high rate of PC in our cohort. Forth, the APA label is based on the lack of histological evidence for metastases, which may lead to inaccurate comparison between APA and PC. Finally, the sample size is small, hence only univariate analysis was performed. Nevertheless, we adjusted for age at diagnosis by age stratification.

In conclusion, in this retrospective SEER database-based analysis, we report a pronounced decrease in the risk for ACM in patients with PC after the year 2006, after the introduction of TMZ as a potential treatment for PC. We propose that based on the accumulating data and the favorable results in the current analysis, TMZ should be investigated as a therapeutic option also in patients with APA.

Future larger studies are required to validate our results. Moreover, we should more accurately delineate the benefit from TMZ as a monotherapy, vs. combination therapy with other modalities, to assess their potential synergistic effect.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This manuscript was performed in compliance with ethical standards.

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