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ORIGINAL ARTICLE

Gestational trophoblastic neoplasia with brain metastasis at initial presentation: a retrospective study

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Abstract

Objective To evaluate the survival and functional outcome of patients with brain metastasis due to gestational trophoblastic neoplasia (GTN).

Methods A 17-year retrospective study based on case review of women with brain metastasis from GTN identified by the electronic databases held in the French Reference Centre. Primary outcome measure: 5-year overall survival calculated with the Kaplan–Meier method. Secondary outcome measures: causes of death, prognostic factors and functional outcomes.

Results 21 patients had GTN brain metastasis and were treated with multidrug chemotherapy without concomitant whole-brain radiation therapy. Three patients died early (< 4 weeks) of cerebral hemorrhage, 3 died ≥ 1 months after treatment initiation and 15 were alive at the date of last contact. The overall survival rate at 5 years was 69.8% (95% CI 44.3–85.3). After excluding early deaths, the survival rate at 5 years was 81.5% (95% CI 52.3–93.7). No predictive factor of survival was identified. Although 11 of the 12 (92%) surviving patients contacted still reported sequelae, nine of them (75%) had resumed a normal life.

Conclusions After excluding early deaths, this study implies a high survival rate in patients with brain metastasis from GTN. These results were achieved in the total absence of whole-brain radiotherapy and almost completely without the need for intrathecal methotrexate.

Keywords Choriocarcinoma · Gestational trophoblastic neoplasia · Brain metastases · Quality of life

Introduction

Gestational trophoblastic diseases include premalignant conditions (complete and partial hydatidiform moles) and malignant conditions. The latter are called gestational trophoblastic neoplasia (GTN) represented by invasive moles, gestational choriocarcinomas (CC), placental site trophoblastic tumors (PSTT) and epithelioid trophoblastic tumors (ETT). Among GTN, choriocarcinomas constitute the most aggressive entity in terms of metastasis [1]. Their incidence ranges from 1 to 9 in 40,000 pregnancies according to ethnic characteristics [2], and they spread quickly through the blood. The overall risk of developing GTN with brain metastasis is approximately 2–3 cases per million pregnancies [3].

Although the development of brain metastases is rare in GTN, with only 222 cases reported in the literature until 2014, the incidence of brain metastases in patients with choriocarcinomas is 11% [1]. Brain metastases by virtue of their strong hemorrhagic potential and risk of neurological sequelae are considered factors for poor prognosis [4–6]. Patients with brain metastases are classified at disease stage IV and, by adding 4 points to the FIGO (International Federation of Gynecology Obstetrics) score, they contribute to patients being systematically classified in the high-risk GTN group [7] for treatment with multidrug chemotherapy regimens.

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The reference multidrug chemotherapy for high-risk GTN remains the EMA-CO protocol (etoposide, methotrexate and dactinomycin alternating weekly with cyclophosphamide and vincristine) with, in the case of brain metastasis, an increase in the dose of Methotrexate to 1 g/m^2 [EMA-CO CNS (central nervous system)] [8, 9]. The recently observed decrease in early mortality using a low-dose induction protocol with 1–2 courses of cisplatin and etoposide in the most severe forms of GTN, suggests that therapy for GTN with brain metastasis should start with this protocol before continuing with EMA-CO CNS or EMA-EP (etoposide, methotrexate, and dactinomycin alternating weekly with etoposide and cisplatin) [10]. The use of intrathecal chemotherapy and/or brain radiotherapy in addition to intravenous (IV) multidrug chemotherapy is associated with toxicity hence treatment protocols need to be individualized [3, 7]. Treatment of GTN with brain metastases currently has survival rates of up to 85% [3, 11], which is close to the overall survival rate for high-risk GTN which is 80–90% [5, 7], despite the presence of a poor prognostic indicator.

We present a cohort of 21 non-pretreated patients diagnosed with GTN with brain metastases and assess their survival rate, causes of death, neurological outcome, and possible predictors of survival.

Materials and methods

Patient management

This study was carried out at the French Trophoblastic Disease Reference Centre (FTDRC). Informed consent for the prospective registration at the FTDRC was obtained from each patient, and ethical approval was guaranteed from the local ethical authority. The recommended initial imaging assessment, which enables the calculation of the disease stage and the FIGO 2000 score, includes endovaginal pelvic ultrasound with Doppler, magnetic resonance imaging (MRI) of the pelvis, thoracoabdominal computed tomography (CT) (complemented by a chest X-ray in the case of pulmonary metastasis) and a MRI brain scan [9].

For GTN with brain metastases, French guidelines recommend since 2010 EMA-CO CNS multidrug chemotherapy, with a higher dose of methotrexate, specifically 1 g/m^2 [9]. Thus, some patients treated before 2010 received classical EMA-CO, but those treated after 2010 mostly received EMA-CO CNS. Since 2012, an induction protocol of 1–2 courses of low-dose EP (Etoposide 100 mg/m^2 + Cisplatin 20 mg/m^2) has been implemented prior to multidrug chemotherapy for patients with brain metastasis or a FIGO score ≥ 13 [5, 10]. For the whole duration of the treatment, monitoring was performed through weekly serum human chorionic gonadotropin (hCG) measurements. The number of courses to be taken was determined by the time required to reach a negative hCG level. Since hCG measurements were performed in local hospitals, normalization thresholds varied among patients between 3 and 10 IU/L, but were constant along each patient's follow-up. The treatment was then extended with 2 consolidation courses after obtaining the first negative hCG level. A monthly hCG follow-up was then required for at least 18 months and subsequent follow-up was more spaced out [12]. In the daily practice of our center, whole-brain irradiation or intrathecal chemotherapy are generally not used concomitantly with multidrug chemotherapy. Brain decompression surgery is performed in the case of severe bleeding complications. EMA-CO resistant tumors are usually treated with the EMA-EP therapeutic regimen and possibly with surgery [13].

Study flow

Among the patients registered at the FTDRC between November 1999 and April 2016, we identified those who had one or more brain metastases at GTN diagnosis and who had not been treated previously. We excluded seven patients who developed brain metastases while on treatment. We studied their survival rate and assessed the outcome of survivors, i.e., quality of life, professional activity, and sequelae through phone or e-mail contact in early 2016, after the end of treatment using a standardized questionnaire from our clinical department (Table 1). For deceased patients, we analyzed the causes of death. Early death was defined as death occurring within the first 4 weeks of treatment initiation. The first 4 weeks of treatment in high-risk GTN patients can thereby be considered as a crucial time beyond which the risk of hemorrhagic complications decreases. We also investigated whether the following parameters could be used as prognostic factors for survival: FIGO score, age at diagnosis, initial hCG level, number of metastases, interval between last pregnancy and GTN diagnosis, nature of antecedent pregnancy, renal, hepatic or splenic metastases, histology of choriocarcinoma, EP induction chemotherapy or not, and symptomatic character or not of cerebral metastasis.

Statistics

Data were extracted from our database with PARADOX 9 software (Corel, Ottawa, Canada). Statistical analysis was performed using SAS v9.2 (SAS Institute, Cary, NC, USA). The descriptive analysis (Table 2) shows the distribution of patients according to different factors studied. The heterogeneity of distributions included early death patients and was tested using a Fisher's exact test. The mean difference was tested using the nonparametric Wilcoxon–Mann–Whitney test. Tests with $p < 0.05$ were considered significant. The survival rate was calculated using the Kaplan–Meier

Table 1 English translated version of quality of life questionnaire for patients treated for high-risk gestational trophoblastic neoplasia with brain metastasis

Do you live at home or in an institution?
If in an institution, why?
Do you need help with everyday gestures?
Do you need home support?
Do you need help with walking?
If yes, do you have to use a wheelchair (paraplegia or hemiplegia)?
Do you walk with a cane (hemiparesis)?
Do you have memory problems?
Are you able to manage your administrative tasks on your own (taxes, invoices)?
Do you have motor deficits?
Do you have sensory deficits?
Do you have epileptic seizures?
What are your current treatments?
Have you taken up a professional activity again?
If yes, is it the same as prior to treatment?
Do you consider you have resumed a normal life?

method, from the first day of treatment in all patients and from 1 month after the start of treatment once early deaths were excluded. The survival rate curves, according to different factors studied, were compared with the Wilcoxon test.

Results

Among the 1251 GTN patients registered at the FTDRC, 201 had high-risk GTN. Twenty-one of these had one or more brain metastases at diagnosis. Their characteristics are shown in Table 2. All patients had a FIGO score ≥ 9 and 17 (81%) had a score ≥ 13. Nine patients (43%) had a single brain metastasis, 6 (28.6%) had two and 3 (14.3%) had three. One patient had 7 brain metastases while the number of metastases was not identifiable in 2 patients because of cerebral hemorrhaging. The mean largest metastasis size was 24 mm (range 6–59 mm). Histology was available in 14 patients and the diagnosis was choriocarcinoma in all cases. Genotyping analysis to confirm gestational origin was not performed in any case.

The location of brain metastases was known for 18 patients. Seventeen patients had cortical metastasis: parietal ($n=7$), frontal ($n=8$), temporal ($n=1$), occipital ($n=1$), parieto-occipital ($n=2$) and fronto-parietal ($n=2$). One patient had cerebellar metastasis and one other had a metastasis at the head of the right caudate nucleus. Fifteen patients (71%) had neurological symptoms at diagnosis. Eleven patients (52%) had simultaneous utero-adnexal tumoral location.

The treatment strategy is shown in Fig. 1. Intravenous multidrug chemotherapy was individualised for patients after multidisciplinary team meeting. Three early deaths by cerebral hemorrhage occurred; one of these was following emergency neurosurgery, but before the start of medical treatment. One of the 9 patients who received a low-dose EP induction protocol regimen died early during the first course of EP. One of 11 women who did not receive this regimen died early during the first course of multidrug chemotherapy treatment.

Concerning first-line treatment, the EMA-CO protocol was used for 14 patients (67%), 12 of which with the increased dose of methotrexate (1 g/m^2). The APE protocol (dactinomycin, cisplatin, etoposide) was used twice, and the EMA-EP and BEP protocols (bleomycin, etoposide, cisplatin) once each. Two of the 4 patients who had the conventional EMA-CO protocol received intrathecal methotrexate. No patient received whole-brain radiotherapy and 1 patient received stereotactic radiotherapy consolidation treatment after chemotherapy and a brain metastasectomy. Among 10 patients treated after 2012, 9 received low-dose induction EP and 1 had initial surgery for intracranial hemorrhage followed by EMA-CO CNS. Treatment details are presented in Table 3.

Nine patients (43%) underwent surgical treatment including 4 for brain decompression surgery because of brain hemorrhaging. Among patients with brain neurosurgery, no significant difference was noted in terms of previous EP low-dose induction chemotherapy, number or largest brain metastasis size. After chemotherapy, one patient underwent a brain metastasectomy as a result of clinical signs, and then an adrenal metastasectomy as imaging tests highlighted the residual presence of a tumor. In another patient, a cerebral and pulmonary metastasectomy was performed before the diagnosis of a gestational choriocarcinoma.

Median follow-up was 22.8 months (Table 2). Of the 21 patients, 15 were still alive in April 2016. The overall survival rate at 5 years was 69.8% (95% CI 44.3–85.3) (Fig. 2). Three early deaths were due to brain hemorrhages. After excluding early deaths, the survival rate at 5 years was 81.5% (95% CI 52.3–93.74). Three late deaths occurred at 2, 5 and 30 months and were the result of cerebral hemorrhaging, sepsis and chemoresistance, respectively. Tumor lysis syndrome was systematically tested for using biology (serum electrolytes and creatinine level) and/or clinical tests, but was not found for any patient.

None of the following tested parameters was found to be a predictive factor of survival: FIGO score, age, initial hCG level, number of metastases, interval between last pregnancy and GTN diagnosis, antecedent pregnancy, kidney, liver or spleen metastases, histology of choriocarcinoma, EP induction chemotherapy, and symptomatic character of cerebral metastasis. For the latter factor, which was not significant, one

Table 2 Characteristics of patients with brain metastases at the diagnosis of gestational trophoblastic neoplasia ($n=21$)

Characteristic	Total cases, $N=21$	Cured cases, $n=15$	Fatal cases, $n=6$	Exact p value
Age at diagnosis	31 (18–45)	32 (22–39)	28 (18–45)	0.48
Median time between last known pregnancy and start of treatment (months)	6.8 (0.2–30.9)	7.5 (0.2–30.9)	5.85 (1.9–10.9)	0.52
Median hCG level before treatment	182,948 (107–2,365,500)	140,545 (107–1,266,885)	433,367 (8215–2,365,500)	0.49
Median FIGO score	15 (9–19)	14 (9–19)	16 (11–18)	0.60
FIGO Score				
7–12	4 (19)	3 (75.0)	1 (25.0)	0.38
13–16	11 (52.4)	9 (81.8)	2 (18.2)	
17–19	6 (28.6)	3 (50.0)	3 (50.0)	
Antecedent pregnancy				
Hydatidiform mole	1 (4.8)	1 (100)	0 (0.00)	0.72
Abortion or ectopic pregnancy	7 (33.3)	4 (57.1)	3 (42.9)	
Childbirth	13 (61.9)	10 (76.9)	3 (23.1)	
Interval from index pregnancy				
Less than 4 months	5 (23.8)	4 (80.0)	1 (20.0)	0.18
4–6 months	6 (28.6)	3 (50.0)	3 (50.0)	
7–12 months	4 (19)	2 (50.0)	2 (50.0)	
13 months or more	6 (28.6)	6 (100)	0 (0.00)	
Interval from index pregnancy				
Less than 6 months	11 (52.4)	7 (63.6)	4 (36.4)	0.63
6 months or more	10 (47.6)	8 (80.0)	2 (20.0)	
Pre-treatment hCG level				
< 1000 UI/L	2 (9.5)	2 (100)	0 (0.00)	1
1000–10,000 UI/L	2 (9.5)	1 (50.0)	1 (50.0)	
10,000–100,000 UI/L	4 (19)	3 (75.0)	1 (25.0)	
> 100,000 UI/L	13 (61.9)	9 (69.2)	4 (30.8)	
Pre-treatment hCG level				
< 100,000 UI/L	8 (38.1)	6 (75.0)	2 (25.0)	1
> 100,000 UI/L	13 (61.9)	9 (69.2)	4 (30.8)	
Number of identified metastases				
1–4	6 (28.6)	6 (100)	0 (0.00)	0.15
5–8	3 (14.3)	2 (66.7)	1 (33.3)	
More than 8	12 (57.1)	7 (58.3)	5 (41.7)	
Number of identified metastases				
1–8	9 (42.9)	8 (88.9)	1 (11.1)	0.18
More than 8	12 (57.1)	7 (58.3)	5 (41.7)	
Site of metastases				
Lung	21(100)	15	6	
Liver	6 (28.6)	3	3	0.29
Kidney	8 (38.1)	6	2	1
Spleen	5 (23.8)	3	2	0.60
Other site[a]	6 (28.6)	4	2	
Histology				
Choriocarcinoma	14 (66.7)	10 (71.4)	4 (28.6)	1
Low-dose induction etoposide cisplatin				
Yes	9 (42.9)	6 (66.7)	3 (33.3)	1
No	12 (57.1)	9 (75.0)	3 (25.0)	
Symptomatic				
Yes	15 (71.4)	9 (60.0)	6 (40.0)	0.12
No	6 (28.6)	6 (100.0)	0 (0)	

Data are given as n (%), median (min–max range)

hCG human chorionic gonadotropin, *FIGO* International Federation of Gynecology and Obstetrics

[a]Including pancreas, adrenal gland, heart atrium, vagina, jejunum, intraperitoneal

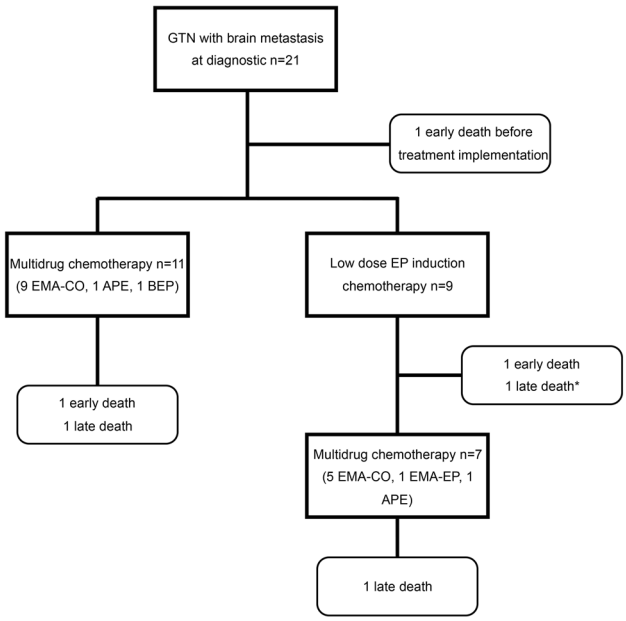

Fig. 1 Early and late deaths as a function of the type of initial chemotherapy. *APE* dactinomycin, cisplatin, etoposide, *BEP* bleomycin, etoposide, cisplatin, *EMA-CO* etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine, *EMA-EP* etoposide, methotrexate, dactinomycin, etoposide, cisplatin, *EP* etoposide, cisplatin, *GTN* gestational trophoblastic neoplasia. *EMA-CO not initiated due to post-EP sepsis

death occurred among the 6 patients with asymptomatic brain metastases (17%), while 5 patients died among the 15 symptomatic patients (33%). Among the 4 patients who received classic EMA-CO, 3 and 1 patients were still alive at 5 years and 3 years after treatment initiation, respectively.

We were able to contact twelve of the 15 surviving patients again. Eleven of them (92%) had sequelae, which are presented in Fig. 3. The sensory deficits found were as follows: one occurrence of visual field loss, one of grade 1 sensory neuropathy, and one of proprioception deficit. Furthermore, four of the eleven had superficial sensitivity deficit. Two patients had a hip osteonecrosis requiring an implant. Despite these sequelae, nine patients (75%) considered that they had resumed a normal life. Among the 10 patients professionally active before the disease, 6 resumed their activity as follows: 3 worked full-time, while 1 and 2 worked 80% and 50% of the time, respectively. Two of the 6 patients had to undergo professional retraining because of the effects of the disease. Four patients were on disability benefit.

Discussion

The present study involved 21 patients registered over a period of 17 years and treated for GTN with brain metastases discovered at diagnosis. In the UK, early centralization of incident GTN cases in the 1970s enabled the Charing Cross Hospital team to identify 27 cases over 23 years. The data from two centers, UK and France combined provide quite a reliable assessment of the rarity of GTN with brain metastases in Europe and justifies the need to provide specialized care in expert centers. It also worth noting that despite an increased rate of brain metastases among GTN patients between the period 1962–1978 and the period 1979–2012, Neubauer et al. reported a concomitant improvement of overall survival from 46 to 64% [14]. The proportion of post-term GTN (13/21 patients) as well as the 100% coincidence with lung metastasis was extremely high among patients with brain metastasis, which is in accordance with previous data from the New England Trophoblastic Disease Centre [15].

The strategy to treat patients who have GTN and brain metastases with intravenous multidrug chemotherapy, but without concomitant whole-brain radiotherapy or intrathecal MTX, led to a survival rate at 5 years of 81.5% after excluding early deaths, which is comparable with those from combined strategies. The 2013 Cochrane review [16] could not come to a conclusion on what the most effective multidrug chemotherapy regime was to treat high-risk GTN. However, the EMA-CO combination is most commonly used with, in the case of brain metastases, an increased dose of Methotrexate from 300 to 1000 mg/m^2 (EMA-CO CNS), as recommended by the FTDRC.

Some teams combining systemic chemotherapy and intrathecal MTX, have reported a patient survival rate of between 71.5 and 85% [3, 6, 11, 17] while others combining whole-brain radiotherapy with multidrug chemotherapy have reported survival rates of up to 75% [4, 18–20]. The high survival rates reported in our study with a strategy of intravenous multidrug chemotherapy without intrathecal MTX highlight the need to reconsider the role of intrathecal MTX in the treatment of brain metastases associated with GTN. The effectiveness of increased doses of intravenous methotrexate may also be questioned since a dose of 1000 mg/m^2 administrated over 24 h is probably below the cytotoxicity threshold [21]. Thus, the role of etoposide, which CNS concentrations are higher, may explain similar remission rates between centers using intrathecal methotrexate, whole-brain radiotherapy and/or high dose methotrexate EMA-CO.

The latter point may be corroborated by the efficiency of EP induction, of APE and of BEP, which do not contain MTX. For these reasons in daily practice of our center, intrathecal MTX with concomitant intravenous multidrug chemotherapy in GTN patients with brain metastases is generally not used. As for whole-brain radiotherapy, given the irreversible cognitive risk that it may create to some patients and the high-survival rates reported without it [3], the FTDRC does not advocate it in patients with brain metastases at initial diagnosis.

Table 3 Patient and disease characteristics, treatment and results

Patient no./age	Antecedent pregnancy	Neurological symptoms	hCG level (IU/L)	FIGO Score	Treatment	No. of brain metastases	Status
1/39	Abortion	None	1,266,885	15	15 EMA-CO	1	NED
2/32	Term pregnancy	Headache, vision changes, hemiparesis, cerebellar ataxia	240,000	16	6 EMA-CO with IT MTX ; 4 EMA-CO CNS	2	NED
3/32	Term pregnancy	Seizures	49,516	11	7 EMA-CO	1	NED
4/37	Term pregnancy	Vision changes, headache	107	13	3 APE; SBI; brain metastasectomy	1	NED
5/29	Abortion	Headache, coma	190,896	14	8 EMA-CO CNS	NI	NED
6/22	Abortion	None	47,600	16	8 EMA-CO CNS	2	NED
7/24	Term pregnancy	None	175,000	19	14 EMA-CO CNS; 5 EP-EMA; 5 TIP	3	NED
8/39	Molar pregnancy	None	106,090	16	4 BEP, hysterectomy	2	NED
9/30	Term pregnancy	Hemiparesis, seizures	105,360	14	2 LD EP; 10 EP-EMA CNS	1	NED
10/27	Term pregnancy	Headache	2145	11	2 LD EP; 4 EMA-CO with IT MTX	1	NED
11/29	Term pregnancy	None	84,271	14	2 LD EP; 9 EMA-CO CNS; 4 EP; 4 paclitaxel, APBSCT	1	Under treatment
12/32	Abortion	None	978,800	19	2 LD EP, 9 APE	NI	NED
13/35	Term pregnancy	Headache, vomiting, vision changes	NA	9	Brain metastasectomy; 5 EMA-CO CNS	1	NED
14/38	Term pregnancy	Headache, mental status changes	250,000	14	2 LD EP; 6 EMA-CO CNS; 4 APE	3	NED
15/31	Term pregnancy	Central facial palsy, hemiparesis	338,970	17	2 LD EP; 8 EMA-CO CNS	2	NED
16/28	Term pregnancy	Headache	42,449	13	DBT	2	DOD/brain hemorrhage
17/18	Term pregnancy	Headache	205,450	17	1 EMA-CO CNS	1	DOD/brain hemorrhage
18/26	Term pregnancy	Headache	867,450	17	8 EMA-CO CNS; 4 BEP; 4 TIP; 4 paclitaxel-thiotaxol-ICE, APBSCT	2	DOD/PD
19/45	Abortion	Headache	661,284	18	2 LD EP, 2 EMA-CO CNS; 3 BEP	1	Dead/sepsis
20/28	Abortion	Headache	2,365,500	15	1 LD EP	3	DOD/brain hemorrhage
21/38	Ectopic pregnancy	Headache	8215	11	1 LD EP	7	DOD/brain hemorrhage

hCG human chorionic gonadotropin, *IU/L* international units per liter, *FIGO* International Federation of Obstetrics and Gynecology, *EMA-CO* etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine, *IT MTX* intrathecal methotrexate, *CNS* central nervous system, *APE* actinomycin D, cisplatin, etoposide, *SBI* stereotactic brain irradiation, *EP-EMA* etoposide, cisplatine, etoposide, methotrexate, actinomycin D, *TIP* paclitaxel, ifosfamide, and cisplatin, *BEP* bleomycin, etoposide, cisplatin, *LD EP* low-dose induction etoposide cisplatin, *APBSCT* autologous peripheral blood stem cell transplantation, *DBT* dead before treatment, *ICE* ifosfamide, carboplatin, etoposide, *NI* not identifiable, *NED* no evidence of disease, *PD* progressive disease, *DOD* dead of disease, *NA* not available

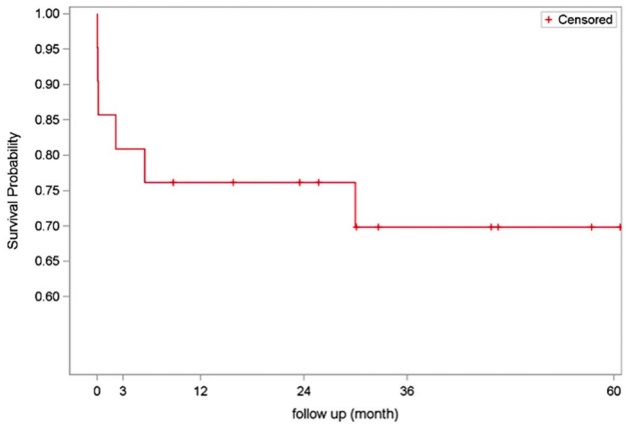

Fig. 2 Five-year overall survival of gestational trophoblastic neoplasia patients from the French cohort with brain metastases at diagnosis from 1999 to 2016 ($n=21$)

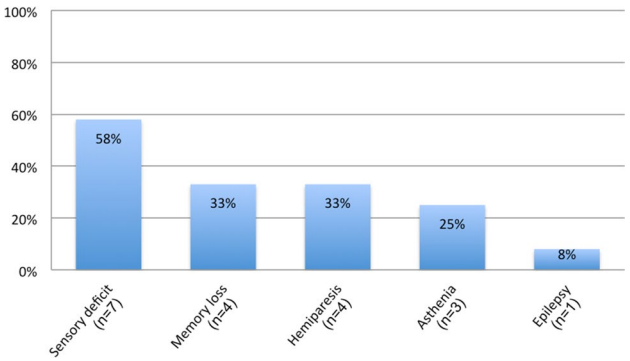

Fig. 3 Sequelae in surviving patients after therapy for gestational trophoblastic neoplasia with brain metastases ($n=12$). Patients with history of treated brain metastasis from gestational trophoblastic neoplasia were contacted in early 2016 to gather information on persistent sequelae

Although the role of surgery in the treatment of high-risk trophoblastic neoplasia is difficult to define, it is necessary to be able to perform an emergency craniotomy in the case of hemorrhagic complications or intracranial hypertension [8]. Four of our patients benefited from such an intervention, leading to long-term survival for 3 of them. It is important, therefore, that patients with brain metastases are treated in centers, which have rapid access to a neurosurgery unit.

For patients with high-risk GTN, a key challenge is to reduce early deaths, which occurred for 3 patients in our study and for 8 in Xiao's study [11]. After exclusion of these deaths, the survival rate in our patients went from 69.8% to 81.5% at 5 years, which is in the same range as the 71% and 89% found in Xiao's and Newlands' studies, respectively [6, 11]. Given the potential effect of EP induction treatment on preventing early death [10], and the association of risk of early death with a FIGO score ≥ 13 [5], GTN patients with brain metastases and with a FIGO score ≥ 13 could benefit from this induction therapy.

It is likely that the use of brain surgery to relieve pressure, together with EP induction, can help to minimize early deaths by prompt care in highly specialized centers. It is interesting to note that none of the early deaths of our study was due to tumor lysis syndrome. This syndrome usually associated with large proliferating and chemosensitive onco-hematological tumors [22] has so far only been described once worldwide for patients with GTN [23].

Our study did not highlight significant predictors of survival. The death rate was twice as high (although not significant) in patients whose brain metastases were symptomatic as in those whose metastases were asymptomatic. This association between neurological symptoms and death was found to be significant in a different study examining 20 patients with brain metastases detected at diagnosis [19]. Another factor of poor prognosis found in the literature is the combination of liver and brain metastases at diagnosis, with one study reporting a survival rate as low as 10% in 15 patients [24]. We did not find this prognostic factor here, possibly due to the low frequency of this association in our study.

In our study, approximately 92% of the interviewed surviving GTN patients who had brain metastases at initial diagnosis, and had no whole-brain radiation therapy, reported treatment-associated sequelae. Neurological sequelae were mainly sensitive-sensorial, motor and memory-based disorders. These long-term effects are rarely reported in the literature, and when they are, it is not always possible to distinguish those potentially caused by whole-brain radiotherapy from those caused by the disease itself [4, 25]. Accordingly, in a study including whole-brain radiotherapy interventions, 4 cases of hemianopia, 2 cases of hemiparesis, 2 cases of epilepsy and an unspecified number of episodes of amnesia, headache, aphasia and cognitive deficits, were reported [25].

Another study reported a case of proliferative retinopathy specifically induced by whole-brain radiotherapy among 17 survivors [4]. Despite these frequent sequelae, 75% of our patients considered they had regained a normal life. This positive functional outcome was also found in a study in the UK which observed that the majority of the patients involved had a normal quality of life several months after the end of treatment [6]. As already suggested, it would be interesting to conduct standardized neurological examinations in these patients after treatment to better assess sequelae.

Some limitations to the present study deserve to be mentioned. First, we cannot exclude an inherent selection bias linked to the retrospective nature of the analysis and multicenter origin of patients. Second, a degree of heterogeneity in treatment existed as patients could be treated in non-expert centers and change of chemotherapy regimen with advent of newer protocols during the study period.

Patients with brain metastases at initial diagnosis of GTN have a high-survival rate with intravenous multidrug chemotherapy treatment without concomitant whole-brain radiotherapy and almost completely without the need for intrathecal methotrexate. This strategy, coupled with emergency brain surgery for severe neurological symptoms, can continue to be recommended in practice. The improved prognosis of GTN with high-risk of early death, will probably be the result of a combination between rapid referral to a center of expertise, the availability of a neurosurgical team and potentially, low-dose induction chemotherapy. Despite the presence of frequent functional sequelae, after completion of treatment, the majority of patients in our study reported they had a good quality of life.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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