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Editorial

Emergency craniotomy: a life-saving procedure as part of multi-modal therapy of GTN

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▸ See the article "Effectiveness of craniotomy and long-term survival in 35 patients with gestational trophoblastic neoplasia with brain metastases: a clinical retrospective analysis" in volume 33, e33.

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While the majority of patients with gestational trophoblastic neoplasia (GTN) achieve complete remission with modern multiagent chemotherapy, there remains an ultra-high-risk subgroup with significantly higher risk of both early and late deaths [1]. Patients with brain metastases are typically considered among this subgroup with approximately 70%–85% long term survival in contemporary studies [2,3]. Early deaths typically occur within 4 weeks of admission due to complications such as acute hemorrhage and raised intracranial pressure, while late deaths arise from multidrug resistant disease months or years later [2]. Standard approaches to managing GTN brain metastasis include chemotherapy regimens incorporating high dose (1 g/m^2) intravenous methotrexate to enhance brain penetration [4], intrathecal (IT) methotrexate and locoregional consolidation with radiotherapy and surgery [1]. However, to reduce the risk of early complications it is critically important to commence chemotherapy gently, for example with low dose etoposide and cisplatin [5]. Some have also advocated giving whole brain radiotherapy as part of initial management [6], but this likely adds to long-term toxicities and there is no evidence that it reduces bleeding or improves overall survival. Nevertheless, several important questions remain to be resolved.

Firstly, what is the optimal management of emergency presentations of GTN brain involvement, including active intracranial hemorrhage, raised intracranial pressure and risk of imminent cerebral herniation? Previous case reports and small series suggest emergency surgery followed by chemotherapy is effective [2,7]. This notion is further supported by Li et al. [8] who now present the largest case series to date of patients undergoing brain surgery for GTN.

The authors report a series of 35 patients who underwent craniotomy at the Peking Union Medical College Hospital between 1990–2018, the majority (26) of whom underwent emergency decompressive surgery. Notably, 8 patients had previously failed chemotherapy so these were not all initial presentations of disease. The estimated 5-year overall survival rate of 80.4% is in line with a contemporary series reported from our institution and others [2,3]. Interestingly, 9 patients underwent elective craniotomy for tumors of unknown origin. Although the authors do not present data separately on survival outcomes for patients treated in the emergency setting, this would be expected to be no lower than 73% in the worst case scenario that all observed deaths before 5 years were in this group.

Secondly, what is the optimal post-surgical systemic therapy regimen? While the essential role of gentle induction chemotherapy with, for example, low dose etoposide and cisplatin given weekly for 1–3 cycles followed by multiagent chemotherapy in this setting is agreed on [9], the best regimen remains unknown. One unknown area is the role and optimal administration route of methotrexate. While all 35 patients in the current report were treated with various multiagent chemotherapy regimens post-surgery, these included combinations with intravenous methotrexate (EMA/CO [etoposide, methotrexate, and actinomycin D/cyclophosphamide and vincristine], EMA/EP [etoposide, methotrexate, and actinomycin D/etoposide and cisplatin]) or without this agent (FAV [5-fluorouracil/floxuridine, actinomycin D, and vincristine], FAEV [5-fluorouracil/floxuridine, actinomycin D, etoposide, and vincristine]). However, the vast majority (33 of 35 patients) received IT methotrexate. In contrast, a recent study from the French Centre for Trophoblastic Diseases [3] suggested IT methotrexate may not be required to achieve equivalent outcomes among those treated with chemotherapy regimens including high dose intravenous methotrexate. Given the potential hematological and mucosal toxicities associated with high dose intravenous methotrexate, the question of whether this is necessary as part systemic chemotherapy of resected brain metastases or whether IT methotrexate is sufficient, is pertinent. While an analysis of survival in relation to chemotherapy regimen was unlikely to be feasible in the current study due to limitations of cohort size, future work should focus on this question.

More recently, immunotherapy with agents such as pembrolizumab has emerged as an effective and well tolerated treatment for GTN with complete responses of brain metastases reported [10]. Further work is required to determine the optimal use of this modality in combination with resection of brain metastases in cases where emergency surgery is necessary. One possibility is combination immunotherapy with less toxic chemotherapy regimens.

Thirdly, when should chemotherapy be commenced? Legitimate concerns around recovery time post brain surgery may discourage some oncologists from starting chemotherapy in the days following the procedure. However, at Charing Cross Hospital we start emergency induction chemotherapy on admission and in rare cases needing urgent surgery will commence chemotherapy within 48 hours of the operation. In this study, Li et al. [8] provide further evidence that early initiation of chemotherapy is a potentially critical contributor to enhanced overall survival. In univariable analysis, chemotherapy delayed over 1-week post-surgery was found to be associated with significantly worse survival. In view of the rapid growth of these aggressive tumors, minimizing delays to commencing systemic therapy is therefore strongly advised.

Finally, what is the role of consolidation radiotherapy? Data from all 3 of the largest studies to date suggest whole brain radiotherapy is unnecessary, and patients should be spared the neurological toxicity of this approach particularly given that long term survival is anticipated in the majority of cases. Across studies, small numbers of patients have received consolidation stereotactic radiotherapy to treat residual disease. While this remains standard practice across centers, the contribution of this approach to long term outcomes is unknown and the procedure carries a risk of radiation necrosis. Future studies including immunotherapy – chemotherapy combinations may render radiotherapy to be unnecessary.

Overall, survival prospects of patients with brain metastases including those with emergency presentations are now very good. Answering remaining questions around optimal use of the therapeutic tools available will require effective multi-institutional collaboration in this very rare disease setting.

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