Relapsed Intracranial Non-Germinomatous Germ Cell Tumours: is it possible to achieve long-term survival?

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Abstract

Non-germinomatous germ cell tumours of the central nervous system (CNS NG-GCT) have no standardized treatment at relapse and prognosis is dismal. Additionally, limited patient numbers preclude any clinical trials in this setting. Here we report the case of an adolescent with relapsed metastatic pineal yolk sac tumour treated with induction chemotherapy, high dose chemotherapy followed by autologous stem cell transplant and radiotherapy who is alive and progression-free 5 years after end of treatment. This experience illustrates the importance of tumour marker surveillance and that multimodal treatment can salvage children with relapsed CNS NG-GCT.

Introduction

The central nervous system (CNS) is the second commonest site for extragonadal germ cell tumours (GCT)[1]. Primary CNS GCTs can be histologically divided into germinomas and non-germinomatous GCTs (NG-GCTs), with the latter group comprising almost one third of primary CNS GCTs[2–5]. Although germinomas are more sensitive to chemotherapy and radiotherapy than NG-GCTs[5–10], 75-82% of children with CNS NG-GCTs can still be cured[5]. However, at relapse, most patients succumb to their disease[8,11–13]. Hereby, we report the case of an adolescent with a relapsed metastatic yolk sac tumour (YST) who received multimodal treatment and remains alive and progression-free at 5 years from his last end of treatment. This encouraging case contributes to the limited existing body of literature on the management of relapsed CNS NG-GCT.

Case Report

A 12 year-old male, previously fit and well, presented with a 2-week history of headache, nausea, vomiting, ataxia and drowsiness. A head CT scan showed a homogenous enhancing lobulated lesion within the right thalamic/pineal region which extended inferiorly to the right midbrain. The head and spine magnetic resonance (MR) examination demonstrated a lobular mass which appeared to be extra-axial and in continuity with the pineal gland with no evidence of disease involvement of the spine (Figure 1). Testicular ultrasound was normal. Serum alpha-fetoprotein (AFP) was 1,832 ng/ml and serum beta-human chorionic gonadotropin (β-HCG) was 16 IU/L. Cerebrospinal fluid (CSF) cytology did not show any malignant cells and AFP in CSF was 34.9 ng/ml (β-HCG not available).

The child underwent endoscopic third ventriculostomy, stereotactic biopsy of the posterior third ventricular lesion, and insertion of a Rickham reservoir. The initial biopsy was inconclusive. A second biopsy was

obtained together with insertion of an external ventricular drain, which was later replaced by a ventriculoperitoneal shunt. The second biopsy showed a malignant GCT with predominant features of YST (Figure 2). Immunohistochemistry confirmed focal positivity with AFP, pan-cytokeratin and in occasional cells with HCG. PLAP, synaptophysin and GFAP were negative while INI1 (BAF47) was normally expressed in the tumour cells. The tumour showed high proliferation index (Ki67: 70%).

The child was treated as per SIOP CNS GCT 96 protocol off-trial with 4 cycles of cisplatin, etoposide and ifosfamide (PEI). Following the 4th cycle of chemotherapy, MR assessment showed partial response according to Response Evaluation Criteria in Solid Tumors, version 1.1[14]. Serum tumour markers also normalized. Subsequently, he received radical volumetric modulated arc therapy (VMAT) to the residual tumour (54 Gy in 30 fractions) with a single arc VMAT plan. Following that, MR brain scan revealed a stable subcentimetre tumour residuum with negative serum tumour markers.

Two years after the end of treatment, routine serum tumour markers showed AFP 56.6 ng/ml with β-HCG <2 IU/L. MR brain and spine demonstrated stable intracranial disease, with a new solitary plaque of enhancing tissue over the surface of the spinal cord posteriorly on the left side at the level of T10 disc space (Figure 1). The child received alternating carboplatin/etoposide and ifosfamide/etoposide for a total of 4 cycles as per SIOP CNS GCT II trial (NCT01424839). After 4 cycles of chemotherapy, shrinkage of the T10 meningeal spinal metastasis was seen on MRI; serum AFP was 4.8 ng/ml. He then received high dose thiotepa and etoposide followed by autologous stem cell transplant (ASCT). Finally, he received craniospinal irradiation CSI (30 Gy in 16 fractions) with a boost to the site of recurrence at T10 (20.8 Gy in 13 fractions).

The end of treatment MRI showed maintained response and serum AFP was normal. This young man is currently alive, with normal serum tumour markers and no evidence of further recurrence 5 years after completion of treatment.

Discussion

Whilst most relapsed CNS germinomas can be salvaged, relapsed CNS NG-GCTs have a much worse prognosis[8,11,12]. There is no international consensus on salvage therapy for relapsed CNS NG-GCT and there are relatively few published case series with limited and heterogeneous cases[13]. Murray et al.[15] reported a cohort of 32 relapsed CNS NG-GCT patients with a 5-year overall survival (OS) of 9% (95%CI: 2-26). Of the 16 patients who received high dose chemotherapy (HDC) and ASCT, 13 died (range 3-35 months), one was alive with stable disease (at 88 months follow-up), and another 2 survivors were disease-free. Interestingly, these 2 patients were the only ones who received irradiation after HDC and ASCT. Similarly, Callec et al.[13] reported a retrospective multicenter study of 25 patients with relapsed CNS NG-GCT showing a 5-year OS of 72% (95%CI: 46-87) for patients who received HDC and 29% (95%CI: 4-61) for those who didn't (P=0.006). These observations and others have led the Third International CNS Germ Cell Tumor Symposium to recommend HDC, surgery, and irradiation, if feasible, for the management of relapsed CNS NG-GCTs[16].

Elevated serum AFP at initial diagnosis (>1000 ng/ml) was incorporated as a poor prognostic factor in the SIOP CNS GCT II trial (NCT01424839), following results of the SIOP CNS GCT 96 showing that among 19 patients with AFP >1000 ng/ml the 5-year progression-free survival (PFS) was 32% compared to 130 patients with AFP <1000 ng/ml, who had a 5-year EFS of 76%[17]. As a result of that, the SIOP CNS GCT II trial incorporated an experimental arm with two cycles of conventional PEI followed by 2 cycles of high-dose PEI with ASCT. The results of this trial have not been published at the time of this report.

As per the latest CCLG guidelines[18], management of relapsed CNS NG-GCT includes conventional dose platinum-based chemotherapy, which may either be PEI, Carboplatin/Etoposide or Gemcitabine/Paclitaxel/Oxaliplatin. This should be followed by surgical resection, if feasible, then high dose carboplatin, etoposide and thiotepa followed by ASCT. Irradiation should then be considered as consolidation.

This case also illustrates the importance of close surveillance with tumour markers for early detection of

recurrences in secreting GCTs, since the low volume of disease at the time of recurrence is likely to have played a role in his favourable long-term outcome. Additionally, our case could receive CSI because he had only had focal radiotherapy at initial diagnosis. However, those cases with metastatic disease at initial diagnosis who receive CSI upfront would not have this choice in case of a metastatic relapse. Of note, whilst this case was salvaged, this young man has to deal with with a number of late effects, including poor memory, cataracts, and hearing loss requiring hearing aids. Although he is able to live an independent live, the late effects associated with this intensive treatment should not be overlooked.

Relapsed CNS NG-GCTs have a dismal prognosis. Notwithstanding, this case with relapsed metastatic pineal YST illustrates the importance of close surveillance with tumour markers and that it is possible to achieve long-term survival with multimodal treatment, including induction chemotherapy, high dose chemotherapy with ASCT, and radiotherapy.

Conflict of Interest statement

The Authors declare that there is no conflict of interest.

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Legends

Figure 1: Series of head (axial T2-weighted turbo spin echo sequences) and spine (sagittal post-gadolinium T1-weighted turbo echo sequences) MR examinations. A 12 year-old male presented with a lobulated neoplastic pineal mass (A1; arrow), biopsy-proven to be a yolk sac tumour, approximately measuring 4 x 2.5 x 4 cm (ap tr cc/ob), markedly vascularised but non-high-cellular, and containing a couple of subcentimetric central cystic foci. This lesion compressed and distorted the third ventricle causing moderate obstructive hydrocephalus and exerted mass effect also onto the right dorsal medial thalamic nuclei and onto the ipsilateral dorsal midbrain along its aqueduct. No intracranial or spinal metastases at baseline (A2). Favourable response to chemotherapy and radical VMAT therapy was achieved 7 months after diagnosis with a minimal cystic residuum (B1; arrow) which has remained stable over time (C1, D1; arrow). However, 23 months after end of treatment a millimetric faintly enhancing leptomeningeal deposit overlying the cord at the level of T10-11 (B2; circle) developed. This resolved (C2) the following year, after completion of further chemotherapy, autologous stem cell transplant, and craniospinal irradiation and has not reoccurred (D2) to date, 5 years off treatment.

Figure 2: Yolk sac tumour from the second endoscopic biopsy. (A) Vacuolated tumor cells forming Schiller-Duval body around a blood vessel (haematoxylin and eosin). (B) Immunohistochemistry confirms focal positivity with alpha-fetoprotein (AFP).