Successful treatment of extracranially metastasized pineal gland germinoma with high-dose methotrexate

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Received 15 February 2002; revised 22 April 2002; accepted 22 April 2002

Germinoma of the pineal gland is a rare disease usually confined to the brain which responds well to radiotherapy. Spinal seeding occurs in ~4% of cases and distant metastases are extremely rare. We report on a 27-year-old female with an intracranially metastasized pineal gland germinoma, meningeal carcinomatosis and distant bone metastases. Treatment was initiated with intrathecal methotrexate (MTX) and continued with high-dose intravenous MTX. The therapy was very well tolerated apart from reversible hepatic toxicity requiring a dose reduction. The patient was in complete remission after three courses followed by two consolidation cycles; the patient has now been in continuous complete remission for more than 22 months. This is the first report to show that MTX is a potent drug in treating pineal gland germinoma. Long-term side effects of radiotherapy such as reduced mental function or hypopituitarism can probably be avoided. Single-agent high-dose MTX may provide high efficacy with limited adverse effects, especially at a more advanced tumor stage with spinal seeding and extracranial disease.

Key words: chemotherapy, intracranial germ-cell tumor, metastasis, methotrexate

Introduction

Germ-cell tumors are primarily gonadal neoplasms but may also arise extragonadally in the midline structures of the body (retroperitoneal, mediastinal) including the central nervous system (CNS). Most pineal gland tumors are germ-cell tumors and can be subdivided into nongerminomatous germ-cell tumors and germinoma (seminoma) (Figure 1; modified from refs 1–3). Due to their excellent radiosensitivity, localized CNS germinomas are routinely treated with radiotherapy of the primary tumor bed with curative intention [1–8]. However, mental and pituitary hormonal dysfunctions are major drawbacks of radiotherapy [9–13]. Radiotherapy treatment is not sufficient for patients with spinal seeding, extracranial disease or disease relapse who will also require chemotherapy.

Like gonadal seminoma, CNS germinoma is a highly chemotherapy-responsive disease and successful treatment has been reported for both newly diagnosed and recurrent disease [1, 3, 14–16]. The chemotherapeutic regimens were, as in the treatment of primary gonadal neoplasms, platinum-based with the addition of other drugs like etoposide or vinblastine, bleomycin and ifosfamide. While some protocols favored a combined modality treatment with the additional use of reduced local radiotherapy [1], others used chemotherapy alone [14, 16]. Using a new chemotherapeutic monotherapy, we report the successful treatment of a patient with wide-spread primary CNS germinoma.

Case report

A 27-year-old female patient presented with vertigo, headache, emesis and progressive ataxia. The patient had a history...
of grand mal seizures since the age of 12; valproic acid had been successfully used as a prophylactic regimen during the previous 6 years.

A lumbar puncture showed 250.6 cells/µl with a total protein level of 1327 mg/l. Magnetic resonance imaging (MRI) localized a prominent tumor in the pineal gland with suprasellar and cerebellar metastases, edema and involvement of the petrous bone. Another MRI evaluation revealed cerebrospinal dissemination and spinal bone metastases (arch of L2, L3) (Figure 2A–C). α-Fetoprotein and β-human chorionic gonadotropin in serum and spinal fluid were not elevated; serum lactate dehydrogenase (LDH) was 161 U/l (range 120–240). There were no signs of impaired renal function or metabolic disturbances and liver enzymes [aspartate aminotransferase (AST), alanine aminotransferase (ALT)] were within normal range. Cholinesterase (2653 U/l, normal range 2800–7400) and total serum protein (60 g/l, normal range 66–87) were slightly reduced indicating impaired hepatic function possibly due to the long-term use of valproic acid.

Cytopathological analysis of the cerebrospinal fluid showed polymorphic tumor cells with basophilic cytoplasm surrounded by an inflammatory infiltrate of small lymphocytic cells. Mitotic figures were easily detected and nuclei centrally placed with one or two prominent nucleoli (Figure 3) as seen in cytological smear preparations of intracranial germinoma [17]. The tumor cells were negative for cytokeratin (using antibody MNF 116). The pathological diagnosis was germinoma.

In our patient with meningeal carcinomatosis and uncontrollable emesis we started treatment immediately with oral dexamethasone and intrathecal methotrexate (MTX), an anti-

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**Figure 2.** Magnetic resonance imaging of the brain and vertebral column at diagnosis (A, B and C) and after chemotherapy (D, E and F). Note the lesion in the pineal region (A, white arrow) representing the primary tumor as well as lesions in the preoptic region (B, white arrow) and lumbar vertebra 2 (C, white arrow). After three cycles of high-dose methotrexate chemotherapy the lesions in the pineal (D) and preoptic (E) region can no longer be identified. The high signal intensity in the plain T1 sequence of L3 (F) represents the fatty change after chemotherapy.
metabolite with broad activity in solid tumors and a variety of hemato-oncological diseases. Methotrexate 15 mg was applied by lumbar puncture on day 1, followed by intrathecal administration of MTX 10 mg via a C-port on days 2, 7, 10 and 13. The patient showed a rapid response with continuous improvement in nausea and emesis. A spinal tap on day 13 contained 11 cells/µl with some scattered tumor cells. Magnetic resonance imaging showed a 25% reduction in the tumor burden. In view of the meningeal improvement and morphological MRI findings, treatment was continued with high-dose methotrexate which offers sufficient systemic efficacy as well as blood–brain penetration [18]. Our patient received MTX 4 g/m² as a 4-h infusion with leucovorin rescue initiated after 24 h. Serum MTX levels after 24, 36 and 48 h were within the normal range, requiring no rescue intensification. Treatment was well tolerated without nausea, vomiting or infectious complications. The patient was discharged and readmitted after 3 weeks to continue therapy. Outpatient serum controls in the interval showed a 40-fold increase in both AST and ALT indicating hepatic MTX toxicity. Serum AST and ALT levels at readmission returned to normal, but we decided to reduce the total dose of methotrexate to 4 g; no hepatic toxicity or bone marrow suppression (WHO stage >1) were observed after any of the following cycles. After three cycles of chemotherapy, a control MR scan of the brain and lumbar spine showed complete tumor remission (Figure 2D, E and F); the Karnofsky index was 100%. Two consolidation cycles up to a total of five cycles high-dose methotrexate were administered and valproic acid was discontinued. The patient is currently being followed-up in our outpatient clinic.

Ten months after discontinuing therapy the patient reported a generalized seizure which had occurred at home. Magnetic resonance imaging scans showed no sign of tumor relapse and valproic acid as prophylactic anti-convulsive medication was restarted without any further convulsive episodes. Our patient, currently 22 months out of therapy, is in excellent general condition with no evidence of disease and has returned to work as an architect. She reports no cognitive deficits and shows no signs of hormone dysfunction (normal thyroid tests, regular menstrual cycle).

**Discussion**

Primary CNS germinomas are highly radiosensitive and localized disease is curable with involved field radiotherapy in up to 95% of cases [1–4, 6, 7, 19]. Synchronous involvement of the pineal and suprasellar region is seen in up to 12% of cases [20]. Cerebrospinal seeding occurs in about 4% [4], which requires craniospinal therapy. A CNS germinoma with spinal seeding and extracranial metastases is exceptionally rare [16, 21–23]; peritoneal seeding due to a ventriculoperitoneal

![Figure 3. Cytospin preparation (May–Giemsa–Grünwald staining). Large tumor cells with thin cytoplasmic rim, central nucleus and prominent nucleoli are infiltrated by small lymphocytes. Mitoses are frequent (magnification: A, 200×; B, 1000×).](image-url)
shunt may be responsible for widespread disease [24, 25]. Radiotherapy is not sufficient in the extracranially metastasized situation or for nongerminomatous germ-cell tumors of the pineal gland [3, 6]. Several studies have shown that CNS germinomas are chemo-sensitive [1–3, 14–16]; chemotherapy regimens were cisplatin- or carboplatin-based, as in the treatment of primary gonadal neoplasms.

Methotrexate is a very potent chemotherapeutic drug with a tolerable and well-known toxicity profile. When higher doses are applied systemically, adequate cerebrospinal and intracranial drug levels can be achieved, making MTX suitable for various leptomeningeal cancers as well as for primary CNS lymphoma therapy [18, 26]. Methotrexate has never been used before in the treatment of CNS germinoma.

In our patient with extracranially metastasized CNS germinoma we achieved a sustained complete remission with single-agent high-dose MTX chemotherapy; toxicity was confined to a reversible increase in liver enzymes.

In a recently published study by Oka et al. [9], 91.7% of all patients treated with radiotherapy for suprasellar germinoma required hormone replacement and 50% of the patients showed remarkably low mental function after radiotherapy. Several studies have demonstrated that children especially suffer from a multitude of neurocognitive deficits when treated with brain radiotherapy which worsen over time [10–12, 27]. Attempts have been made to reduce late effects by dose reduction [19] or a combination of reduced-intensity irradiation and chemotherapy [28]. A combined treatment with radiochemotherapy, however, has a higher risk of leukencephalopathic alterations [26, 29].

Successful, but less toxic, treatments with chemotherapeutic regimens, such as high-dose methotrexate, is now a new attractive therapeutic option with the potential of reducing radiotherapy use.

References

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