Case Report

Temozolomide-related acute lymphoblastic leukemia with translocation (4;11)(q21;q23) in a glioblastoma patient

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A B S T R A C T

Temozolomide (TMZ), an alkylating agent, is widely used for treating high-grade gliomas. TMZ has been reported to cause secondary myelodysplastic syndrome and acute myeloid leukemia. However, TMZ-related acute lymphoblastic leukemia is rare. Here we describe a 54-year-old woman with glioblastoma multiforme, who developed precursor-B acute lymphoblastic leukemia with translocation (4;11)(q21;q23) after 15 months of TMZ treatment.

1. Introduction

Temozolomide (TMZ) has been increasingly reported to cause secondary myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) [1]. However, TMZ-related acute lymphoblastic leukemia (ALL) has rarely been reported [2–5]. We describe a 54-year-old woman with glioblastoma multiforme (GBM) who developed precursor-B–ALL with translocation (4;11)(q21;q23) after 15 months of TMZ treatment.

2. Case report

A 54-year-old Taiwanese woman was diagnosed with a GBM tumor in the left frontoparietal lobe by stereotactic biopsy in August 2011. However, she refused to undergo surgery after the diagnosis. She received TMZ-based concurrent chemoradiation (total dose of 6000 cGy in 30 fractions and TMZ 75 mg/m²/day for 42 days) and TMZ maintenance therapy (150 mg/m²/day for 5 days in a 28 day cycle) for eight cycles. Disease progression was observed in July 2012, and she underwent an operation to remove the brain tumor. The patient received three cycles of TMZ maintenance therapy after the surgery. She developed leukopenia with anemia, which began in August 2012 and persisted. She remained stable until November 2012, following which she presented with rapid progression of generalized weakness and drowsiness. Brain MRI showed tumor recurrence. Moreover, complete blood count showed marked leukocytosis (white blood cell count, 104 × 10³/μL, normal range, 4.5–11 × 10³/μL) including 1% neutrophils, 2% lymphocytes, and 97% blasts), anemia (hemoglobin 8.0 g/dL, normal range, 13.5–18.0 g/dL), and thrombocytopenia (platelet count 54 × 10³/μL, normal range, 150–400 × 10³/μL). A diffuse growth pattern of blasts with scant cytoplasm and nuclear hyperchromatism was detected after bone marrow biopsy. Peripheral blood flow cytometry revealed CD19 and HLA-DR expression; immunohistochemistry of the bone marrow biopsy specimen revealed CD79a expression. CD34, CD3, CD5, CD10, CD20, kappa/lambda, and terminal deoxynucleotidyl transferase were negative in both examinations (Fig. 1). Consequently, precursor-B–ALL was diagnosed. Bone marrow cytogenetics revealed translocation (4;11)(q21;q23) but was negative for Philadelphia chromosome (Fig. 2). Dexamethasone was administered to alleviate the peritumoral edema and B-ALL related leukocytosis. We provided supportive care only to the patient due to her poor performance status. She died of profound sepsis in one month later. The total cumulative dose of TMZ in this patient was 11,400 mg/m².

3. Discussion

Alkylating therapeutic agents are clearly related to secondary AML/MDS and are associated with deletions or loss of the long arms of chromosomes 5 and 7 [6]. Alkylating agent-induced leukemia is generally preceded by MDS [7].
Translocation (4;11)(q21;q23) leads to MLL-AF4 fusion gene formation and accounts for approximately 10% of newly diagnosed B-cell ALL in adult patients [8]. Chromosomal 11q23 rearrangements are the most common karyotypic alterations in therapy-related ALL, and most of these abnormalities are caused by previous topoisomerase II inhibitor exposure [9]. Translocation (4;11)(q21;q23) has been reported in secondary ALL, but most are case reports. However, it has not been reported in TMZ-related acute leukemia. To our knowledge, this is the first report to describe TMZ-related ALL with translocation (4;11)(q21;q23).

Cranial radiotherapy is the standard treatment after surgery for high-grade glioma. The clinical review by Perry et al. proposed that...
conventional external beam radiotherapy does not increase the risk of acute leukemia compared with chemotherapy alone in patients with malignant glioma [10]. In the Gruppo Italiano Malattie Ematologiche Maligne dell’Adulto (GIMEMA) archive of adult acute leukemia, 5.1% (200 out of 3934) of patients had secondary AML and ALL, and 77 of the evaluated 148 patients had undergone previous chemotherapy and/or radiotherapy. Only two patients had primary central nervous system malignancy [11,12]. Therefore, cranial radiotherapy seems to have limited influence, and we believe that TMZ plays a major role in the pathogenesis of secondary acute leukemia.

Villano et al. reported that 17 of 3490 patients treated with TMZ developed leukemia [13]. TMZ-related ALL has been increasingly reported in the literature (Table 1) [2–5]. Interestingly, the latency between previous cancer treatment and leukemia development is long after treatment with most alkylating agents (3–8 years) [7]. However, TMZ-related ALL seems to have a shorter latency (4–57 months).

4. Conclusion

TMZ is a mainstay treatment for high-grade gliomas and other malignancies; however, physicians should monitor the therapeutic efficacy and myelotoxicity of TMZ closely and be aware of treatment-related leukemogenesis.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References


Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age</th>
<th>Diagnosis</th>
<th>Chemoradiation strategy</th>
<th>Latency</th>
<th>Immunophenotype</th>
<th>Cytogenetics</th>
<th>Leukemia-related death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [2]</td>
<td>M/40</td>
<td>Glioblastoma multiforme</td>
<td>60 Gy with 70 mg/m2/daily, 200 mg/m2/daily x 1 cycle</td>
<td>4 months</td>
<td>Pre-B ALL</td>
<td>45, XY, t(9;22)</td>
<td>No data</td>
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<td>2 [3]</td>
<td>F/12</td>
<td>Anaplastic astrocytoma</td>
<td>60 Gy with 75 mg/m2/daily, 150 mg/m2/daily x 8 cycles</td>
<td>13 months</td>
<td>Pre-B ALL</td>
<td>Normal</td>
<td>8 months</td>
</tr>
<tr>
<td>3 [4]</td>
<td>M/26</td>
<td>Astrocytoma and oligodendroglioma WHO grade II</td>
<td>60 Gy with 75 mg/m2/daily, 150 mg/m2/daily x 6 cycles</td>
<td>17 months</td>
<td>Pre-B ALL</td>
<td>Normal</td>
<td>No data</td>
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<td>4 [5]</td>
<td>F/49</td>
<td>WHO grade II astrocytoma</td>
<td>80 Gy with 75 mg/m2/daily, 150 mg/m2/daily x 6 cycles</td>
<td>57 months</td>
<td>Pre-T ALL</td>
<td>Normal</td>
<td>No data</td>
</tr>
<tr>
<td>Present patient</td>
<td>F/54</td>
<td>Glioblastoma multiforme</td>
<td>60 Gy with 75 mg/m2/daily, 150 mg/m2/daily x 11 cycles</td>
<td>15 months</td>
<td>Pre-B ALL</td>
<td>t(4;11)(q21;q23)</td>
<td>1 month</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia, der = derivative chromosome, F = female, M = male, t = translocation, WHO = World Health Organization.