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Recurrent Metastatic Neuroblastoma Followed by Myelodysplastic Syndrome: Possible Leukemogenic Role of Temozolomide

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Abstract

An 8-year old child had a pelvic *MYCN*-nonamplified neuroblastoma (NB) with retroperitoneal nodal extension. Multi-modality therapy achieved complete remission (CR). Small recurrences confined to left supraclavicular nodes were treated with surgery alone at 4.9, 6.5, 7.5, 9.5, and 12.9 years from diagnosis. Monitoring through 12 months after the last resection showed CR. When she returned 34 months later (16.8 years from diagnosis), she had massive disease in the left neck and upper trunk, without osteomedullary metastases. Salvage therapy featured 11 cycles of temozolomide. She developed myelodysplastic syndrome with 45,XX,der(7)t(7;21) (p15;q11), −21 at age 24 and refused treatment; 19 months later she was transfusion-dependent but her NB remained in CR.

Keywords

alkylating agents; chromosomal aberrations; topoisomerase II inhibitors

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INTRODUCTION

Common treatments for resistant neuroblastoma (NB) include cyclophosphamide-topotecan,[1] irinotecan-temozolomide (TMZ),[2,3] and radiotherapy (RT). Dreaded sequelae include secondary leukemia (SL) and myelodysplastic syndrome (MDS).[4] The two main kinds of SL/MDS are those associated with topoisomerase-II inhibitors and marked by an early onset of leukemia with translocations of the *MLL* gene at chromosome band 11q23,[5] and those associated with alkylating agents and marked by a latency period of 2–8 years, a preleukemic phase, and deletions involving the long arms of chromosomes 5 or 7.[6]

TMZ is an alkylator that has recently attracted attention because of its activity against brain tumors,[7] excellent oral bioavailability,[8] and modest toxicity.[8,9] Pediatric phase I and II studies identified TMZ 200-to-215 mg/m^2/day x5 days every month as active against NB.[8–10] In combination with irinotecan, TMZ has been dosed at 100 or 150 mg/m^2/day x5 days.[2,3,11] TMZ, like other alkylators, may be leukemogenic but has been associated with only two cases reported to date,[12,13] possibly due to the relatively small size and the short survival of the exposed population. We now describe a third case of MDS in which TMZ is implicated as a causative factor in a patient with a remarkable clinical course of NB.

CASE REPORT

An 8-year old female with a pelvic NB plus retroperitoneal nodal extension to the diaphragm, but no bone or bone marrow (BM) metastases, was in complete remission (CR) after 4 cycles of cyclophosphamide (4200 mg/m^2), doxorubicin (45 mg/m^2), and vincristine, 2 cycles of cisplatin (120 mg/m^2) and etoposide (450 mg/m^2), surgery, and RT (2100 cGy) to the primary and nodal sites of disease.

Periodic small recurrences confined to left supraclavicular nodes were managed with surgery alone at 4.9, 6.5, 7.5, 9.5, and 12.9 years from diagnosis. Studies of resected NB showed chromosomal constancy, with hyperdiploidy and *MYCN*-nonamplified (3–8 copies, reflecting hyperdiploidy). Monitoring through 12 months after the last resection showed CR. She did not return until 34 months later (46 months from the prior resection, 16.8 years from diagnosis). At that time, she was 24 years old and, hidden under her long hair, was a massive recurrence in the left neck and upper anterior and posterior trunk. Bone and BM were not involved.

Retrieval therapy began with 2 cycles of cyclophosphamide (1250 mg/m^2) and topotecan (3.75 mg/m^2),[1] but her disease progressed. A cycle of ifosfamide (10 g/m^2), carboplatin (1000 mg/m^2), and etoposide (500 mg/m^2) and a cycle of carboplatin (1000 mg/m^2) plus irinotecan (250 mg/m^2) resulted in a minor response. The tumor was debulked. BM tests, including surveillance fluorescence *in-situ* hybridization (FISH) studies for SL/MDS, revealed no abnormalities. Specifically, FISH evaluation following hybridization with locus specific and centromeric probes did not reveal 5q deletion, monosomy 5, del (7q), trisomy 8, or translocation or deletion of 11q23 and del (20q) in any of the interphases examined. Peripheral blood findings were normal, including platelet counts >200,000/μl.

In the next 11.5 months, treatment included 3 five-day cycles of irinotecan (250 mg/m^2) and TMZ (750 mg/m^2);[3] RT (4320 cGy) to the left neck/upper trunk; 8 five-day cycles of TMZ (1000 mg/m^2)[10] used with continuous daily thalidomide (300–500 mg) and celecoxib (200 mg); resection of residual NB; and more RT (1500 cGy). During the three months of treatment with irinotecan-TMZ, thrombocytopenia (nadir: <20,000/μl) was attributed to chemotherapy and concomitant RT. Then, until shortly after completion of the fifth five-day cycle of TMZ alone, platelet counts were unremarkable, ranging between 58,000–127,000/μl, as expected from chemotherapy effects. Subsequently, the TMZ cycles #6, 7, and 8 were started when the platelet counts were in the 30,000/μl range. This thrombocytopenia was attributed to cumulative toxicity from chemotherapy and RT. The erythrocyte mean corpuscular volume was 113 fl (normal 82–98), which is a common finding following chemotherapy.

Evaluations one month after the last TMZ (16.5 months from the start of retrieval) confirmed CR, but BM showed refractory anemia with excess blasts (RAEB-1) (World Health Organization Classification and Criteria for Myelodysplastic Syndromes[14]). BM had a modal karyotype of 45,XX,der(7)t(7;21) (p15;q11), −21. Despite being informed of the dismal prognosis (median survival time after the diagnosis of SL/MDS associated with chromosome 7 abnormalities is 9 months[15]), the then 24-year woman refused treatment. Over the ensuing 19 months, she has remained clinically well, despite requiring transfusions of platelets and red blood cells every other week, and her NB is in CR.

DISCUSSION

The patient's clinical course was noteworthy for five recurrences of NB over an 8-year period that were always isolated, in the same left supraclavicular area, and readily managed with minor surgery (and no cytotoxic therapy). Remarkably, the sixth recurrence was again isolated despite the enormous size it had attained during the 34 months the patient was lost to follow-up. The many recurrences limited to the same site point to biological attributes that might confer a propensity for nodal-soft tissue trafficking versus hematologic-osteomedullary spread.

The persistence of MDS for 19+ months without leukemic transformation, and the absence of *MLL* aberrations, implicate an alkylator in causation. Further, the patient's lifetime exposure to topoisomerase II inhibitors (doxorubicin 180 mg/m^2, etoposide 1400 mg/m^2) was much less than the dosages associated with SL/MDS (doxorubicin 240 mg/m^2, etoposide >5000 mg/m^2);[16,17] in contrast, her exposure to alkylators was considerable. However, 16.2 years elapsed between completion of her first treatment program for NB (which included a total cyclophosphamide dosage of 16,800 mg/m^2), and the initiation of retrieval chemotherapy. That extraordinarily long period greatly exceeds the usual time-frame for SL/MDS.[6] One can speculate about whether cyclophosphamide imparted a susceptibility to SL/MDS in our patient: reflecting the uniqueness of the clinical course of her NB, no detailed published report, to our knowledge, provides substantial data on pediatric patients whose initial therapy for a solid tumor included high doses of alkylators, followed only >10 years later by more chemotherapy.

Our patient received RT, first to a field (pelvis and retroperitoneal nodes) encompassing extensive BM space and, 16.5 years later, to a smaller field (left neck and upper trunk). Local RT is routine in patients with pediatric solid tumors, so its leukemogenic role, if any, cannot be defined in this population. Limited-field RT appears to be a weak leukemogen,[18] and one might expect weak-to-absent leukemogenicity if local RT completely ablates BM within the RT field.

The initial retrieval therapy included total doses of alkylators that would not be expected to cause SL/MDS, but could have been a contributory factor. Subsequent peripheral blood counts (before TMZ) were normal, and routine surveillance BM tests showed no evidence of SL/MDS by histology, karyotype, and FISH. Nevertheless, backtracking studies using cryopreserved BM have revealed early and unexpected chromosomal SL/MDS-associated rearrangements.[19,20]

She then received 3 cycles of a recently described irinotecan-TMZ regimen[2] that included a 50% higher dosage of TMZ than in the only other detailed reports[2,11] on combined use of those agents in children – namely, 150 versus 100 mg/m^2/day, x5 days/cycle. She next received 8 five-day cycles of the standard monthly TMZ regimen of 200 mg/m^2/day,[10] plus daily continuous thalidomide and celecoxib. Thalidomide and the related lenalidomide are treatments for MDS.[14]

Two other cases have been reported detailing a possible leukemogenic effect of TMZ. In one, a 44 year old female with a brain tumor received TMZ 100 mg/m^2/day x5 days in the first cycle and 200 mg/m^2/day x5 days in the next 6 cycles; MDS with a cytogenetic study showing del (3)(q11.1) was diagnosed 8.4 months from initial exposure to TMZ, and 19.4 months from initial exposure to the only other chemotherapeutic agent she received (the nitrosourea, ACNU [nimustine]).[12] Thus, that patient, like ours, developed MDS after a latency period shorter than the 2–8 years typically associated with alkylating agents.[6] The findings raise the possibility of an interaction – additive or synergistic effect - between TMZ and previously used alkylating agents.

In the other case,[13] after resection of a brain tumor, a 66 year old female received involved-field RT (6000 cGy), followed by one cycle of procarbazine, lomustine, and vincristine (PCV). Six months later, a recurrence was resected and carmustine-loaded wafers were implanted. After 22 monthly cycles of TMZ (150 mg/m^2/day, x5 days), cytopenias and macrocytosis were noted. At 51 months from the initial exposure to chemotherapy (PCV), and 40 months from the start of TMZ (25 cycles), BM studies revealed MDS, with multiple complex cytogenetic abnormalities, including deletions of chromosomes 1, 5, 6, 7, 11, and 16. The clinical picture, including latency, were typical for alkylator-induced MDS.[6]

TMZ is now part of the treatment for NB, brain tumors, and other cancers. As TMZ gains wider usage, and as patients receiving TMZ survive longer, the full spectrum of its risks, including possible leukemogenicity which remains speculative, should become clearer.

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