CORRESPONDENCE

Epigenetic Therapy in a Rare Ovarian Cancer — A Double-Edged Sword

TO THE EDITOR: The field of solid-tumor oncology has made tremendous advances in targeted and immune therapies. However, far fewer advances have been made in tackling epigenetic alterations.

A 32-year-old woman presented with abdominal pain, vomiting, and constipation and was found to have a large, complex left ovarian mass; the serum calcium level was 16.7 mg per deciliter (reference range, 8.5 to 10.5). Histopathological results from oophorectomy revealed small-cell carcinoma of ovary hypercalcemic type (SCCOHT), a rare, aggressive gynecologic cancer associated with a median overall survival of 24 months despite the receipt of multimodal therapies.

SCCOHT is similar to childhood rhabdoid tumors and is characterized by pathognomonic biallelic loss of the *SMARCA4* tumor suppressor gene that encodes BRG1–BAF190, a component of the SWI–SNF chromatin remodeling complex, leading to epigenetic reprogramming and malignant transformation.[1] Pathogenic variants in the SWI–SNF complex are implicated in nearly 20% of human cancers.[2] Tumor genomic sequencing showed biallelic loss of *SMARCA4* with two pathogenic splicing variants: one somatic and one germline. These truncating mutations result in loss of function of the SWI–SNF complex and unopposed activity of oncogenic EZH2, which disrupts cellular processes including proliferation, migration, and differentiation.[3]

The patient's treatment course was notable for rapidly and multiply recurrent peritoneal carcinomatosis despite debulking surgery and multiple lines of intensive chemotherapy and immunotherapy. The patient then started off-label tazemetostat at a dose of 800 mg twice daily (Fig. 1).

Tazemetostat, an EZH2 inhibitor, induces synthetic lethality in cancers with SWI–SNF deficiency and has been approved by the Food and Drug Administration for patients with follicular lymphoma and advanced epithelioid sarcoma.[4] Approximately 1 year after the initiation of tazemetostat, the patient had a durable near-complete response. After 4 years of receiving continuous tazemetostat therapy, new cervical lymphadenopathy was seen on surveillance scans. A nodal biopsy revealed T-cell acute lymphoblastic lymphoma and leukemia (T-ALL). Although previous chemotherapy or immunotherapy may have been implicated in this secondary cancer, tazemetostat has also been associated with the development of such cancers. Loss-of-function variants in EZH2 are recurrently found in T-ALL and are strongly associated with disease pathogenesis, although no such variants were detected in this patient. We hypothesize that prolonged EZH2 inhibition by tazemetostat may have recapitulated this pathogenic state, whereby altered epigenetic control induced dysregulated hematopoiesis and malignant transformation.[5]

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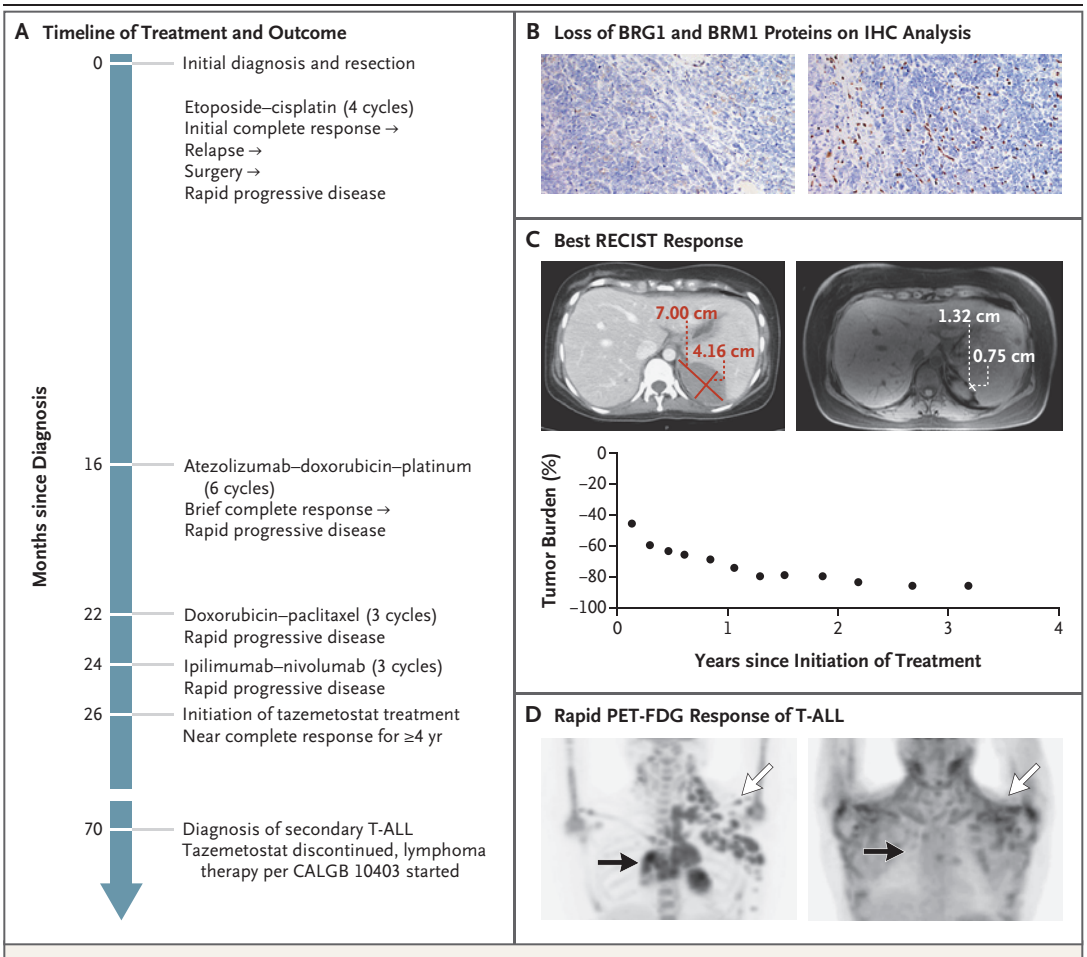

Figure 1. Treatment Course, Diagnostic Studies, and Imaging in the Study Patient.

Panel A shows the treatment course of the study patient with small-cell carcinoma of ovary hypercalcemic type (SCCOHT). On presentation, the patient underwent left salpingo-oophorectomy and infracolic omentectomy, with pathological analysis showing SCCOHT. She received adjuvant chemotherapy and remained disease-free on imaging for 10 months. Recurrent abdominal masses with peritoneal carcinomatosis developed, and the patient underwent surgical cytoreduction with hysterectomy and right salpingo-oophorectomy, with pathology-confirmed relapse. She received multiple lines of therapy, with any response followed by rapid disease progression. At 26 months after diagnosis, she started off-label tazemetostat, which was followed by substantial clinical improvement and near-complete radiologic response sustained for more than 4 years before the development of a secondary cancer. C denotes cycle, CALGB Cancer and Leukemia Group B, CR complete response, PD progressive disease, and T-ALL T-cell acute lymphoblastic lymphoma and leukemia. Panel B shows the results of immunohistochemical (IHC) analysis, indicating loss of BRG1 (at left) and BRM1 (at right), findings that are characteristic of *SMARCA4*-deficient tumors. Panel C shows the patient's tumor response to tazemetostat, according to Response Evaluation Criteria in Solid Tumors (RECIST). Baseline computed tomography (CT; top row at left) shows a large perisplenic implant, as compared with magnetic resonance imaging (MRI; top row at right) after receipt of tazemetostat for 1 year. The patient had a near-complete response according evaluation of two target lesions (perisplenic implant and mesenteric implant) on serial MRI of the abdomen and pelvis (bottom row), according to Response Evaluation Criteria in Solid Tumors, version 1.1. Panel D shows the response to treatment for secondary T-ALL. Baseline ^{18}F-fluorodeoxyglucose (^{18}F-FDG)–positron-emission tomography (PET) and CT (at left) shows numerous enlarged FDG-avid lymph nodes in the left axillary and cervical regions (white arrow), as well as mediastinal adenopathy (black arrow). Restaging FDG–PET–CT (at right) shows a substantial reduction in size and resolved FDG avidity of the previously observed adenopathy within 1 month after the initiation of lymphoma-directed treatment.

The patient discontinued tazemetostat and started to receive lymphoma therapy as described in the Cancer and Leukemia Group B (CALGB) 10403 trial. The patient had an excellent response and no recurrence of SCCOHT 9 months later.

This remarkable response to an otherwise fatal disease underscores the potential of targeted epigenetic therapies. However, further investigation is needed to understand the double-edged nature of such treatments. The association of this novel drug with secondary cancer presents not only a risk to mitigate but also a new avenue to explore oncogenesis.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Jelinic P, Mueller JJ, Olvera N, et al. Recurrent SMARCA4 mutations in small cell carcinoma of the ovary. Nat Genet 2014;46:424-6.
2. Kadoch C, Crabtree GR. Mammalian SWI/SNF chromatin remodeling complexes and cancer: mechanistic insights gained from human genomics. Sci Adv 2015;1(5):e1500447.
3. Wang Y, Chen SY, Karnezis AN, et al. The histone methyltransferase EZH2 is a therapeutic target in small cell carcinoma of the ovary, hypercalcaemic type. J Pathol 2017;242:371-83.
4. Gounder M, Schöffski P, Jones RL, et al. Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study. Lancet Oncol 2020;21:1423-32.
5. Julia E, Salles G. EZH2 inhibition by tazemetostat: mechanisms of action, safety and efficacy in relapsed/refractory follicular lymphoma. Future Oncol 2021;17:2127-40.

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Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

TO THE EDITOR: In the ANNEXA-I trial (Trial of Andexanet Alfa in Intracranial Hemorrhage Patients Receiving an Oral FXa Inhibitor) conducted by Connolly et al. (May 16/23 issue),[1] investigators evaluated the use of andexanet alfa in cerebral hemorrhage associated with factor Xa use, which is currently the subject of debate, given that guidelines are contradictory.[2,3] We are concerned about the potentially unbalanced data presentation.

In contrast to the andexanet group, in which 98.2% of the patients received the trial drug, only 85.5% of the patients in the usual-care group received prothrombin complex concentrate. This situation disadvantages the control group. If 98.2% of the patients in the usual-care group had received prothrombin complex concentrate, 139 patients (instead of 121) could potentially have met the criteria for hemostatic efficacy (the primary end point), which would have resulted in similar outcomes in the two groups. A per-protocol analysis that includes the dose and composition of prothrombin complex concentrate would be valuable.

Moreover, the number of patients with a modified Rankin scale score of 0 to 3 (range, 0 [no deficit] to 6 [death]) at 30 days was lower in the andexanet group than in the usual-care group, and the number of patients with ischemic stroke was substantially higher in the andexanet group. These results are reminiscent of those in the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial, which showed no clinical benefit despite the reduction in hematoma expansion with recombinant activated factor VIIa.[4]

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1. Connolly SJ, Sharma M, Cohen AT, et al. Andexanet for factor Xa inhibitor-associated acute intracerebral hemorrhage. N Engl J Med 2024;390:1745-55.
2. Rossaint R, Afshari A, Bouillon B, et al. The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition. Crit Care 2023;27:80.
3. Kietaibl S, Ahmed A, Afshari A, et al. Management of severe peri-operative bleeding: guidelines from the European Society of