Testicular Relapse of T-Cell Acute Lymphoblastic Leukemia in an Adult 11 years after Allogeneic Stem Cell Transplantation: A Case Report

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Introduction

Acute lymphoblastic leukemia (ALL) is a malignant hematologic disease characterized by the proliferation of immature lymphoid cells—B-cells, T-cells, or Natural Killer cells. The utilization of genomewide profiling has led to a better understanding of the structural genetic alterations and mutations that contribute to leukemogenesis in ALL and provides information for directing personalized medicine approaches with novel, targeted therapies. As a result of the incorporation of MRD testing, the improvement of risk-directed chemotherapeutic regimens, and the advent of allo-HCT, the survival for patients with ALL have dramatically improved. Despite these advances however, adult-ALL still portends a poorer prognosis, with survival rates being 20% to 40%. Moreover, relapsed ALL remains a harrowing for dismal outcomes with median survival rates ranging from a mere 10% to approximately 25%.

Specifically, extramedullary relapse in leukemia, although not a frequent recurrence in leukemia, remains an intriguing and notable cause of treatment failure in patients with ALL. The central nervous system and testes have been long regarded as immunological sanctuaries for cancer cells due to the physiologic blood-brain and blood-testes barriers, respectively. Advances in the therapeutic management of ALL have virtually eliminated the utility of prophylactic craniospinal irradiation to the CNS or local irradiation versus orchietomy to the testes. Guidance for the management of leukemic relapse involving the testis is not standardized especially in the adult patient population, and even more specifically, in those who are status-post allo-HSCT, with case reports comprising much of the available literature. Therefore, given the rarity of this presentation and the paucity of definitive evidence for guiding treatment, extramedullary relapse of ALL, particularly of the testis in adults in the post-allo-HSCT setting is a notable topic for discussion.

Case Presentation

Initial Treatment Course

A 43-year-old male was diagnosed with T-cell acute lymphoblastic leukemia (T-ALL) involving the mediastinum and with multi-compartmental adenopathy on both sides of the diaphragm without clinical evidence consistent with central nervous system nor overt testicular involvement. He received hyperCVD plus nelauroxim, alternating with intrathecal methotrexate and cytarabine, on protocol 2006-0328, achieving complete remission after 1 cycle. He went on to receive POMP maintenance and delayed intensification with nelauroxim, during which he developed MRD positivity on flow cytometry. As a bridge to allo-HSCT, he received 2 cycles of MOAD, and then proceeded to a MUD allo-HSCT with a busulfan plus fludarabine conditioning regimen (on protocol 2009-0209) twenty-months after his initial diagnosis of T-cell ALL.

Presentation

Eleven years following his allo-HSCT, the patient, now 56-years-old, presented to his urologist with concerns over unilateral, non-painful testicular swelling. He was diagnosed with left-sided, acute epidiidymo-orchitis and was treated with a short course of ciprofloxacin. When his symptoms failed to resolve, he presented to his hematologist-oncologist. Bilateral testicular ultrasound showed an enlarged left testicle with heterogeneous architecture as well as increased vascularity throughout the left testicle and epididymis (Fig. 2). Subsequent pathology from left-sided orchietomy was consistent with relapse of his T-ALL (Table 1). Further work-up with a BMA revealed medullary relapse (Table 2).

Follow-Up & Outcome

The patient received 2 cycles of hyperCVD with venetoclax and 4 lumbar punctures with alternating methotrexate and cytarabine IT chemotherapy. He achieved complete remission after his first cycle of therapy with flow cytometry negative for MRD; a PET scan showed no evidence of disease uptake. However, the patient was observed to pursue additional cycles of intensive, salvage chemotherapy, additional IT chemotherapy prophylaxis, and a second allo-HSCT given the impact on his overall quality of life (QoL). However, he did go on to complete testicular radiation to the tests and scrotum (24Gy, 12 fractions), which he tolerated well. Until now, 6 weeks after completion of radiation therapy, the patient remains without evidence of disease relapse, systemically and in the remaining, right testicle. His most recent bone marrow aspiration and biopsy (performed prior to the initiation of local radiation therapy and 6 weeks prior to the completion of this poster) revealed no morphologic or immunophenotypic evidence to support residual T-ALL; flow cytometry was negative for MRD, and PCR analysis was negative for monoclonal TCRG rearrangements.

Discussion

The clinical and diagnostic presentation of leukemic infiltration of the testis can mimic that of more common ungeriatric inflammatory processes, such as orchitis or epididymitis; however, a high index of suspicion for relapsed disease must be maintained in this patient population. Literature describes the occurrence of testicular relapse of T-ALL across all ages, but more uncommon among the adult populations; moreover, such an occurrence in a post-allo-HSCT setting is exceptionally rare. As such, the consequence for patients with testicular leukemia relapse post-allo-HSCT is still not well standardized. However, research has shown that the presence of testicular relapse occurs within months of testicular radiation or orchietomy administered alone, and thus, treatment should be one of a systemic approach, with local testis-directed therapy potentially an adjunct to intensive systemic chemotherapy such as hyperCVD.

Some reports describe successful treatment of patients with only systemic chemotherapeutic and local therapy to the testes with irradiation with or without orchietomy1,4, whereas another case report described treatment with orchietomy alone in a pediatric patient status-post allo-HSCT. However, given the dismal post-relapse survival statistics for these patients, especially in T-ALL, consideration for aggressive management with a second allo-HSCT after re-induction to induce MRD negativity may portend the best durable remission, and has been recommended by others. The role and efficacy of more novel therapeutics such as venetoclax, navitoclax, and daratumumab, everolimus, CD5- or CD7- engineering CAR-T therapy are being investigated via early phase clinical trials, and the results may provide better guidance on the use of such rare recurrences of T-ALL.

Conclusions

With the development of high-intensity chemotherapeutic regimens that incorporate chemotherapeutic agents which are known to penetrate the blood-testes barrier, the need for testicular-directed local therapies has been largely removed from the treatment algorithms for ALL. Leukemic relapse of the testes following allo-HSCT in the adult patient is an exceedingly rare clinical scenario, making it difficult to evaluate the literature for well-established management protocols to guide therapy. However, salvage treatments for testicular leukemic relapse, whether in a clinically isolated relapse or not, should mimic a systemic approach given the high likelihood of systemic relapse soon after extramedullary recurrence, despite localized treatment with testicular irradiation or orchietomy2,5. Nonetheless, the rarity of T-ALL testicular relapse is a detriment for clinicians working to establish definitive, transformative therapeutic management regimens for patients in the relapse refractory setting. Ultimately, the approach for management should integrate a multidisciplinary team approach to include hematology-oncology, urology, and radiation oncology.

References