Dichloroacetate and Arsenic Trioxide as an Acute Myeloid Leukemia Combination Therapy

Summary

Few therapeutic options are available for patients with relapsed or refractory acute myeloid leukemia. Targeting the inherent metabolic dysregulation of leukemia cells using a combination of dichloroacetate and arsenic trioxide has shown a synergistic anti-leukemic effect when used either simultaneously or sequentially and is well-tolerated in the clinical setting.

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Technology
Therapeutic compunds
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Available for licensing

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External Reference
Perturbation of cellular oxidative state induced by dichloroacetate and arsenic trioxide for treatment of acute myeloid leukemia.
Emadi A, et al. Leuk Res. 2015 Jul;39(7):719-29

Market

Acute myeloid leukemia (AML) is a rapidly progressing blood cancer that affects premature white blood cells (blast cells), resulting in the accumulation of immature, nonfunctional, and abnormal blood cells. This accumulation may lead to serious infections and organ failure if it is not treated. There are approximately 20,000 new cases of AML each year in the United States with a 5-year survival rate of ~25% (NCI, 2017). AML is more common in adults aged 65 and older and among men compared to women. Moreover, AML is the second frequent type (after acute lymphocytic leukemia) of leukemia diagnosed in infants. While considered a relatively rare disease, it is currently very challenging to treat due to the heterogeneity and unknown interplay between cells stemming from various mutations and abnormalities. The combination of cytarabine and anthracycline as the mainstay of treatment for AML has not changed significantly for the last forty years and it has been reported that multidrug resistance could be mechanism of chemotherapy failure in AML. At present, the costs of diagnosing AML amount to $3,200. Remission-induction treatments cost on average $46,400 and the harvest of bone marrow or peripheral blood stem cells costs $6,500. The costs of the transplantation varies between $25,500 and $44,100.

Given the upsurge in AML cases and limited treatment options, there is an unmet medical need to develop more targeted and effective therapeutic options. The global AML therapeutics market is estimated at $616.4 million in 2015 and is expected to grow at a CAGR of 20.0% to reach $1.5 billion by 2020, driven primarily by an aging population, strong product pipeline, high-unmet medical need, and entry of quality products.

Technology

UMB research has been directed at a synergistic combination drug formulation of dichloroacetate and arsenic trioxide to treat AML. AML cells, compared to normal cells, have an increased susceptibility to the disruption of balance of oxidative forces. Selective targeting of the oxidative state, which is a tightly balanced fundamental cellular property, is an attractive strategy for developing novel anti-leukemic chemotherapeutics with potential applications in the treatment of AML. Published studies show that dichloroacetate (DCA) inhibits PDK1, a key gate-keeping enzyme that regulates the flux of fuel supply into the mitochondria. Additionally, arsenic trioxide is approved for treatment of patients with acute promyelocytic leukemia (APL) whose disease failed to respond to or relapsed following all-trans retinoic acid/anthracycline therapy. The combination therapy has been shown to have synergistic cytotoxic effects against a wide range of AML cells, including cells with FLT3-ITD mutation, at concentrations at or below those currently being clinically tested.

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