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Therapy-related acute myeloid leukemia in the context of Methotrexate treatment

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Abstract

In adults, acute myeloid leukemia (AML) is the commonest type of leukemia and carries a high burden of mortality worldwide. Various risk factors have been identified to date, including environmental exposures, systemic anti-cancer treatment and radiotherapy. Therapy-related acute myeloid leukemia (t-AML) is a distinct subtype with characteristic genomic alterations, poor prognosis, and increasing incidence in recent years. This is particularly relevant with increasing survival of cancer patients after receiving more aggressive systemic anti-cancer therapy and the wide use of myelosuppressive agents in benign rheumatological conditions. This review shines the light on t-AML and the implication of Methotrexate in its development.

Keywords: Acute Myeloid Leukemia (AML), Methotrexate, carcinogenesis, therapy-related acute myeloid leukemia

Introduction

Acute Myeloid Leukemia (AML) is a morphologically and genetically heterogeneous disease characterized by malignant clonal proliferation of immature myeloid cells in the bone marrow, peripheral blood, and occasionally other body tissues. Approximately 91% of leukemia patients are diagnosed above the age of 20 with a median age at diagnosis of 67 years **(DeSantis C.E., et al., 2014).** In adults, AML is the most common type of leukemia, accounting for 25% of all leukemia subtypes. Pediatric cases account for 7% of AML cases and its biology is distinct from that of adults, with a significantly lower incidence of aggressive disease **(Dores G.M., et al., 2012).**

In the United States, there are approximately 18,800 new cases diagnosed on annual basis and the estimated death is as high as 10000, ranking AML as the sixth highest cancer-related death in

male population **(Zhou J., et al., 2014).** AML is much more common in older age, with a continuous slow rise in young adulthood turning into a rapidly increasing incidence by age from 50 years. The peak incidence occurs at approximately 80 years of age. The age profile of AML could be explained by single-hit mutations, prior myelodysplastic syndrome (MDS) and acquisition of multiple mutational events during lifetime **(Juliusson G., et al., 2012).**

Etiology of AML:

Leukemogenesis is a multi-step process requiring the susceptibility of a hematopoietic progenitor cell to mutational events at multiple consecutive stages. The different subtypes of AML may have distinct causal mechanisms, which suggests a functional link between a particular molecular abnormality and the causal agent. Several risk factors have been hypothesized to be implicated in the development of AML, such as genetic disorders, chemical agents, radiotherapy and systemic anti-cancer treatment **(Deschler B. and Lubbert M., 2006).**

In the pediatric population, genetic defects were identified as important risk factors for AML development. For instance, Down syndrome increases the risk of AML by 15 folds and causes a unique disease entity characterized by a relatively high frequency of copy number alterations (CNAs), suggestive of genomic instability **(Blink M., et al., 2012).** Among adults, acquired chromosomal mutations have been found in 50-70% of AML cases, with rising incidence in patients with therapy-related leukemia or older age **(Deschler B. and Lübbert M., 2006).**

Environmental factors that increase the risk of developing AML include smoking, benzene exposure, and pesticides **(Ferrara F. and Schiffer C.A., 2013).** Benzene is a prototype environmental leukemogen and chronic exposure significantly increases the risk for AML. The pattern of clonal molecular abnormalities observed in benzene-exposed AML patients seems to closely resemble that found in de novo than therapy-related AML **(Irons R.D., et al., 2013).** Smoking is a well-known culprit in mutagenesis and the intensity of smoking has a stronger correlation to the odds of developing AML compared to the duration of smoking in adults **(Merriam P., et al., 2013).** Interestingly, pre- and post-natal exposure to carcinogens were also linked to AML development in children. These include exposure to pesticides, alcohol consumption, ionizing radiation, and diagnostic X-rays **(Rathee R., et al., 2014).**

Therapy-related AML (t-AML) occurs as a late complication of systemic anti-cancer treatment and/or radiation therapy, whereas secondary AML (s-AML) is defined as that occurring after an antecedent myeloid disease regardless of prior cytotoxic therapy for these disorders**(Swerdlow SH, et al., 2008).**Two main subgroups of t-AML have been described, one comprising leukemia occurring 5-10 years after alkylating agents or radiotherapy, and the second occurring within 2-5 years after topoisomerase II inhibitors. The former tends to be associated with abnormalities of chromosomes 5q and/or 7q, while the latter is often associated with a translocation involving 11q23 (*MLL*) or 21q22 (*RUNX1*) **(Dohner H, et al., 2010).** However, more complex mutational pathways have also been recently described in therapy-related AML development, such as TP53, RUNX1, and RAS **(Weinberg OK, et al., 2022).** Interestingly, when classified by latency period duration, t-AML arising after extended latency (>10 years) is more likely to be associated with history of multiple malignancies and young age at the time of receiving systemic anti-cancer treatment, compared to t-AML arising after ordinary latency (1-10 years) **(Liu YC, et al, 2022).**

In a large population-based study of 3,055 AML patients, s-AML and t-AML were observed in 19.8% and 6.6% of patients, respectively. Therapy-related AML patients were observed to harboradverse-risk cytogenetics compared with secondary and de novo AML patients. This over-expression of complex and monosomal karyotypes most likely reflects clonal selection of

chemotherapy - resistant p53-mutated hematopoietic cells in the presence of previous cytotoxic therapy. Moreover, t- and s-AML were independently associated with increased risk of death **(Ostgard L.S.G., et al., 2015).** The notoriously poor clinical outcomes in t-AML could be partly attributed to organ injury from prior therapy, depletion of normal hematopoietic stem cells, damage to bone marrow stroma and chronic immunosuppression **(Strickland SA, et al, 2022).**

Pathogenesis:

The pathogenesis of therapy-related acute leukemia is a complex interplay of multiple factors that lead to high mutational burden. Pre-leukemic mutations are identified in specific genes with clear prognostic impact in AML, including ASXL1, *DNMT3A*, *IDH1*, *IDH2*, and *CBFB-MYH11*. It has been postulated that pre-leukemic hematopoietic stem cells can survive chemotherapy and contribute to hematopoiesis during remission, generating myeloid cells that harbor pre-leukemic mutations **(Strickland SA, et al, 2022).** In addition, relapsed AML follows diverse clonal evolutionary patterns, some of which are consistent with involvement of pre-leukemic hematopoietic stem cells. This provides key insights into the evolutionary processes that govern leukemia onset and progression, and identify pre-leukemic stem cells as a cellular reservoir in remission that is poised to generate relapsed disease. The variation in driver mutations in t-AML indicates the stochastic nature of myeloid leukemogenesis, yet the patterns of co-occurrence and mutual exclusivity suggest a molecular synergy between them. (**Corces-Zimmerman M. R., et al., 2014), (Zhou J. and Chng W.J, 2014).**

For decades, the accepted model of leukemogenesis was established to be a “two-hit hypothesis”, which suggests that two different types of genetic mutations were required for malignant transformation of a myeloid precursor **(Welch et al., 2012).** Mutations involving BCR-ABL, FLT-3, and RAS genes typically lead to uncontrolled cellular proliferation and evasion of apoptosis, whereas mutations involving NPM1, CEBPA, and CBFB-MYH11result in inhibition of differentiation and transcriptional dysregulation **(Conway O’Brien E., et al. 2014).** The order of mutation acquisition can be determined by comparing the patterns of co-occurring mutations in residual leukemia stem cells. In one study, many mutations including *NPM1*and*TET2*were detectable in the residual leukemia stem cells, but others such as *FLT3-ITD* and *IDH1* were not, indicating that these were probably late events in the leukemogenesis process**(Jan M., et al., 2012).** More recently, Weinberg et al reported high incidence of TP53 mutations in t-AML which predicted for worse clinical outcomes and confirmed the significance of multihit status of the TP53 mutation in driving an aggressive disease behavior **(Weinberg OK, et al., 2022).** Interestingly, further subclassification of t-AML into normal and abnormal karyotype based on the mutational burden is evolving. Tariq et al demonstrated higher prevalence of mutations in NPM1, TET2, ASXL1, and RUNX1 as well as lower prevalence of TP53 mutations in normal karyotype t-AML, compared to abnormal karyotype t-AML, translating into higher survival outcomes **(Tariq H, et al, 2022).**

In therapy-related AML, there is growing evidence to support both linear and branching patterns of clonal evolution. A comparison of paired primary and relapsed AML samples revealed two patterns of clonal evolution during relapse. In some cases, only a single mutation cluster was found in the primary tumor which gained additional mutations at relapse, consistent with a linear pattern of evolution. In the remaining cases, multiple mutation clusters corresponding to different subclones were detected in the primary sample. A subclone survived therapy, gained additional mutations and expanded at relapse exemplifying a branching evolution model **(Ding L., et al., 2012).**

Besides germline genome, the micro-environment plays a cardinal role in tumor growth dynamics. Axl has been shown to mediate the proliferation and survival of AML cells and is upregulated following cytostatic treatment. In addition, AML cells induce expression of the Axl ligand growth arrest-specific gene 6 (Gas6) by bone marrow-derived stromal cells (BMDSCs). Gas6 in turn mediates proliferation and chemo-resistance of Axl-expressing AML cells. This Gas6-Axl paracrine crosstalk between AML cells and BMDSCs establishes a chemo-protective tumor cell niche. The Gas6-Axl pathway has translational relevance because Axl is expressed by approximately 50% of AML patients and Axl-targeting approaches can block growth of human AML cells **(Janning M., et al., 2015).**

Methotrexate role in t-AML development:

Methotrexate plays an integral role in the treatment of various cancerous and non-cancerous conditions, such as rheumatoid arthritis. Its long-term use carries the risk of a multitude of complications, including carcinogenesis and leukemogenesis. There is growing evidence to suggest that methotrexate administration under unfavorable conditions, such as other diseases, lowers its tolerability and increases its toxicity profile **(Kim YI, 2004).**The development of t-AML in such cases may either be directly caused by Methotrexate or related to the changes in folate metabolism in the context of Methotrexate therapy.

A few studies have reported t-AML following Methotrexate therapy for benign and malignant conditions. In one series, two patients developed t-AML following low-dose methotrexate for rheumatoid arthritis and psoriasis **(Al-Anazi KA, et al, 2009).** Another case report confirmed the development of t-AML, following low-dose methotrexate for rheumatoid arthritis, harboring the t(3;21)(q26.2;q22) translocation which is almost exclusively present in therapy-related acute myeloid leukemia **(Tanaka K, et al, 2017).** In addition, the cryptic NUP98/PRRX2 rearrangement was identified in another case report of t-AML following methotrexate therapy in rheumatoid arthritis **(Chonabayashi K, et al, 2019).** More recently, a case series of 9 patients

who developed t-AML following treatment for solid malignancies revealed a grim median survival of only 10 months. Of note, two of those patients had received Methotrexate for previously diagnosed breast cancer **(Yang J, et al, 2022).** In another study involving 225 t-AML patients, 16 patients had received myelosuppressive agents including Methotrexate **(Gross S, et al, 2022).**

To date, the exact mechanism of Methotrexate-induced t-AML is yet to be fully understood. It was hypothesized that the rapidly proliferating hematopoietic cells are particularly vulnerable to mutations in folate deficient patients as these cells have the greatest requirements for DNA synthesis **(Robien K, et al, 2003) (figure 1).** Additionally, gene polymorphisms affecting methylenetetra hydrofolate reductase (MTHFR) enzyme have also been implicated. Two distinct polymorphisms, C677T and A1298C, in the gene coding for MTHFR enzyme have been observed to alter enzymatic activity and susceptibility to acute myeloid leukemia **(Choi S.W., et al, 2000).**

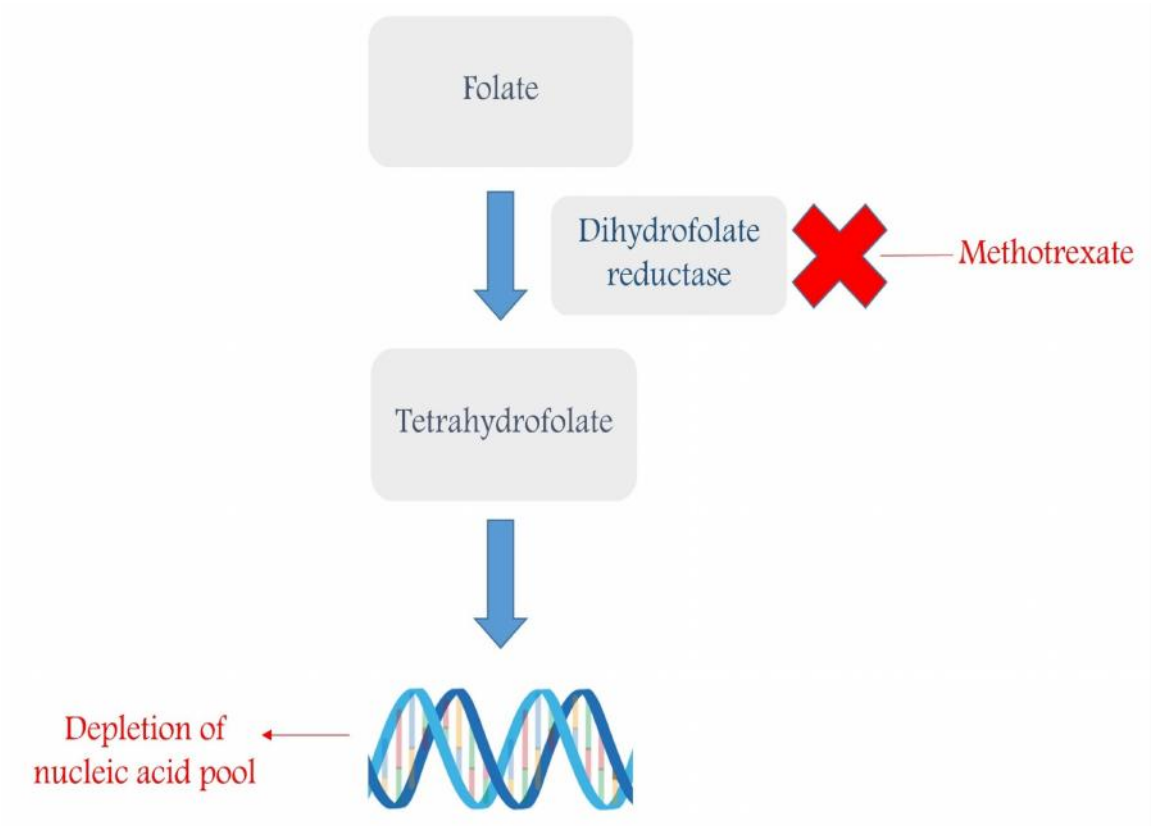

Figure 1: Mechanism of action of Methotrexate. Inhibition of Dihydrofolate reductase enzyme leads to impaired folate metabolism and inhibition of DNA synthesis, which in turn leads to depletion of nucleic acid pool.

Conclusion

Therapy-related acute myeloid leukemia is an increasingly identified subtype of AML, with characteristic chromosomal abnormalities and poor prognosis. Growing evidence supports the implication of Methotrexate in leukemogenesis, hence patients on long-term Methotrexate therapy should be carefully monitored for the potential development of t-AML. Further studies are required to elucidate the mechanism of Methotrexate-induced therapy-related acute myeloid leukemia.

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