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The molecular mechanisms of alkylating agent-related acute myeloid leukaemia

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Alkylating chemotherapy agents are used with considerable success to treat numerous human malignancies, including lung cancer, breast cancer, Hodgkin lymphoma and multiple myeloma. Alkylating agents encompass a broad range of structurally diverse agents that includes nitrogen mustards, methylating agents, platinating agents and nitrosoureas. They exert their anti-cancer effect by interacting directly with DNA to generate base damage,[1] which can subsequently lead to DNA crosslinking, DNA strand breakage and abnormal DNA base pairing, and ultimately cytotoxicity. In addition, many of the primary and secondary DNA lesions induced by alkylating chemotherapy agents are also mutagenic and clastogenic, and may contribute to cellular transformation. Indeed, the majority of alkylating agents used therapeutically are suspected or demonstrated human carcinogens.[2]

Although cancers have been reported at most sites in the body after therapeutic exposure to alkylating agents, research efforts have focused particularly on acute myeloid leukaemia (AML).[3] One reason for this is that the relative risk of developing AML after alkylating chemotherapy is considerably higher than the risk of developing cancer at other sites in the body,[4] which is a reflection of the inherent sensitivity of the bone marrow, including the $CD34^{+ve}$ putative target cell for transformation, to the mutagenic and clastogenic effects of this group of agents. Low activity of critical DNA repair enzymes may partly explain why the bone marrow is so susceptible to alkylating agent-induced transformation;[5,6] which has prompted efforts to protect the bone marrow using gene therapy.[7-9] The gross chromosomal abnormalities associated with alkylating agent-induced AML are well characterized, and typically include unbalanced aberrations such as chromosome 5 and/or 7 monosomy and long-arm deletion.[10,11] Whilst it is likely that these lesions directly contribute to transformation, along with P53, RAS and other gene mutations,[11] understanding how and when they develop during the pathogenesis of AML and establishing a causal link to alkylating exposure is of high priority. Unlike AML that develops after therapy with topoisomerase inhibitors there is little evidence implicating alkylating agent exposure as directly causative of lesions predicted to be ultimately transforming, although this has yet to be extensively investigated. Rather, the relatively long latency between alkylating exposure and disease onset (typically between 2 and 7 years) and initial presentation as a pre-malignant dysplasia in many cases[10] is suggestive of a multi-step mechanism of transformation, possibly involving the early acquisition of a genomic instability phenotype. A high frequency of microsatellite instability and concomitant DNA mismatch repair loss in alkylating chemotherapy-induced AML[12-14] provides some support for this general model. Moreover, mutations in genes encoding components of the homologous recombination repair system in alkylating chemotherapy-related AML implicates abrogated DNA double strand break repair in the pathogenesis of this disease.[15] Systematic deregulation of homologous recombination in stem cell clones treated with leukaemogenic alkylating agents suggests a plausible mechanism by which these exposures might give rise to a genomic instability phenotype predisposing to unbalanced chromosome aberrations.[16] Furthermore, a role for the Fanconi anaemia gene products in DNA strand break repair,[17] inherent susceptibility to myeloid leukaemia in Fanconi patients,[17] and reported dysfunc-

tion of the Fanconi anaemia pathway in *de novo* and therapy-related myeloid leukaemia,[18,19] all support the notion of acquired genomic instability predisposing to myeloid leukaemia with unbalanced aberrations.

Taken together, the epidemiologic, molecular and cellular data suggest a general mechanism for alkylating agent-induced myeloid leukaemogenesis involving the cumulative acquisition of mutations and deletions in key genes and pathways, possibly mediated via an underlying alkylating agent-induced genomic instability.

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