Therapy-related leukaemias are becoming an increasing healthcare problem as more patients survive their primary cancers. The nature of the causative agent has an important bearing upon the characteristics, biology, time to onset and prognosis of the resultant leukaemia. Agents targeting topoisomerase II induce acute leukaemias with balanced translocations that generally arise within 3 years, often involving the \( MLL \), \( RUNX1 \) and \( RARA \) loci at 11q23, 21q22 and 17q21 respectively. Chromosomal breakpoints have been found to be preferential sites of topoisomerase II cleavage, which are believed to be repaired by the non-homologous end-joining DNA repair pathway to generate chimaeric oncoproteins that underlie the resultant leukae-

mias. Therapy-related acute myeloid leukaemia (t-AML) is the most common malignancy to occur following therapy for a primary carcinoma. This complication was first recognised over 30 years ago [2], and now accounts for 10–30% of all AML [3].

Traditionally therapy-related leukaemias have been classified into two subgroups according to the nature of the agents to which the patient was exposed [4, 5]. Treatment with drugs targeting DNA topoisomerase II, including epipodophyllotoxins (e.g., etoposide), anthracyclines (e.g., epirubicin) and anthracenediones (e.g., mitoxantrone) predisposes to the development of a subgroup of secondary leukaemias characterised by balanced translocations, particularly involving \( MLL \) at 11q23, \( NUP98 \) at 11p15, \( RUNX1 \) at 21q22 and \( RARA \) at 17q21 [4–8]. Such leukae-

mias typically present with a relatively short latency period (1.5–3 years) from time of first drug exposure, with no intervening myelodysplastic phase. In contrast, the other classic subtype of t-AML that arises following treatment with anti-metabolites, alkylating agents or radiation expo-

sure generally presents after a much longer latency period (typically 5–7 years), may be preceded by a myelodysplastic phase and is characterised by a complex karyotype often featuring loss or deletion of chromosome 5q and/or 7, and a high prevalence of \( TP53 \) mutation [4, 8].

However a major problem in distinguishing such sub-
types of t-AML is that the majority of patients who develop this complication have been exposed to combination thera-
pies that make it difficult to identify the causative agent in any particular case. This is taken into account in the most

**Keywords** Topoisomerase · Therapy-related AML · Alkylating agents

**Introduction**

Secondary leukaemias arising after successful treatment of a malignancy represent the worst possible complication of cytotoxic therapy. However, these are becoming more prevalent as the population ages and more patients survive their primary cancers due to better treatment strategies [1]. Therapy-related acute myeloid leukaemia (t-AML) is the most common malignancy to occur following therapy for a primary carcinoma. This complication was first recognised over 30 years ago [2], and now accounts for 10–30% of all AML [3].

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types of t-AML is that the majority of patients who develop this complication have been exposed to combination thera-
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recent World Health Organisation (WHO) classification of AML in which no distinction is made between cases arising following alkylating agents, radiotherapy or drugs targeting topoisomerase II, and which are categorised according to their cytogenetic and molecular features, which more effectively capture disease biology and likely response to treatment [9]. Therapy-related acute promyelocytic leukaemia (t-APL) with the t(15;17)(q22;q21) leading to fusion of the PML and RARA genes is the most common second malignancy arising following breast cancer therapy involving epirubicin, mitoxantrone and/or radiotherapy and is associated with a relatively favourable prognosis [10, 11]. The disease typically responds well to anthracycline chemotherapy combined with all-trans retinoic acid (ATRA), which effectively targets the underlying PML-RARα oncoprotein [12]. In patients who are close to the anthracycline ceiling or who are unfit for conventional therapy, molecularly targeted therapy using arsenic trioxide (ATO) provides a highly effective alternative treatment approach [12]. Patients with t-AML with chromosomal rearrangements involving genes encoding components of the core binding factor (CBF) haematopoietic transcription factor complex (i.e., with t(8;21)(q22;q22) or inv(16)(p13q22)/t(16;16) (p13;q22) leading to RUNX1-RUNX1T1 and CBFB-MYH11 fusions, respectively) may also have a relatively favourable prognosis [13]. Poorer outcome is generally observed in patients with secondary leukaemias involving the MLL locus at 11q23; while t-AML with loss of chromosome 5 and/or chromosome 7 material and cases with complex karyotype are associated with a dismal prognosis due to high rates of primary resistance and rapid relapse in those showing an initial response to chemotherapy [13].

Considering that the spectrum of cytogenetic and molecular lesions observed in t-AML mirrors that found in the disease arising in individuals with no history of chemotherapeutic or radiotherapy exposure, study of the mechanisms underlying the development of t-AML could provide valuable insights into the pathogenesis of de novo leukaemias. This review considers the mechanism of action of drugs targeting topoisomerase II, as well as alkylating agents used for the treatment of primary carcinomas and their relevance to induction of secondary leukaemias.

Role of topoisomerase II in the pathogenesis of t-AML

Every human cell contains a vast amount of DNA that, when unwound, extends to ~2 m in length [14]. In order to manage this state of affairs and gain access to the genetic information encoded within the genome, enzymes are required to relax supercoiled DNA and resolve knotting. The enzymes that are responsible for regulating the topological state of the genetic material are the topoisomerases. These ubiquitous enzymes have the ability to regulate the under- and over-winding of DNA, as well as creating transient single- and double-stranded breaks in order to untangle knotted DNA. Topoisomerases are essential to cell survival and play key roles in chromatin structure, replication of DNA and mitosis/meiosis in eukaryotic cells [14–16]. There are two classes of topoisomerase, namely type I (cleaves one strand of DNA at a time) and type II (cleaves both strands of the DNA) [16]. This review will be focusing on the mechanism of action of topoisomerase II and the ways in which cytotoxic drugs poison this enzyme, to turn it from being essential to cell survival to a mediator of DNA damage, which has the capability to fragment the genome.

Catalytic cycle of topoisomerase II

Topoisomerase II regulates the topological state of DNA by a ‘double-stranded DNA passage reaction’ [16] (see Fig. 1). The first step in the catalytic cycle of topoisomerase II is the covalent binding of the enzyme to DNA. Topoisomerase II–DNA interactions are not well defined; although a large number of recognition sequences have been described, the topological structure of the DNA is highly