t(15;17) in acute promyelocytic leukemia

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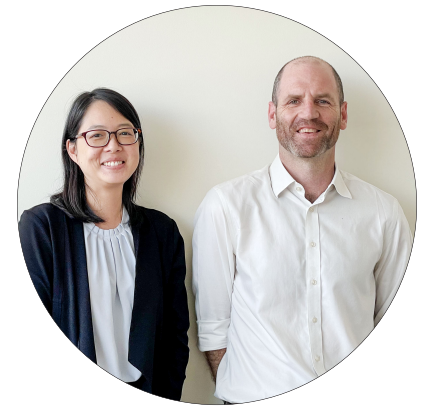
https://doi.org/10.3324/haematol.2022.282577



TITLE	Evidence for a 15;17 translocation in every patient with acute promyelocytic leukemia
AUTHORS	Larson RA, Kondo K, Vardiman JW, Butler AE, Golomb HM, Rowley JD.
JOURNAL	American Journal of Medicine. 1984;76:827-841. PMID: 6586073.

Since its first description by Hillestad in 1957, acute promyelocytic leukemia (APML) has been recognized as a distinct subtype of acute myeloid leukemia (AML) because of its pathognomonic 'M3' morphology, fulminant clinical presentation with life-threatening coagulopathy and, more recently, exquisite responsiveness to molecularly targeted differentiation therapy. The diagnostic translocation t(15;17) between chromosomes 15 and 17, which is responsible for the distinctive biology of APML, was definitively established in a seminal publication by Richard Larson, Janet Rowley and colleagues in 1984.[1] This manuscript brought together the meticulous characterization of the clinical, microscopic and karyotypic features of a multicenter cohort of 27 patients with APML, in which the t(15;17) was found in all patients.

Following case reports and small case series (including one from Rowley's group)[2] of an abnormal chromosome 17, subsequently noted to reflect a balanced translocation between chromosomes 15 and 17 in APML, Larson *et al.* examined 27 patients with *de novo* APML from the University of Chicago, USA and other Chicago centers; at least four of the patients had the atypical 'microgranular' variant. Transmission electron microscopy analysis revealed that 'microgranular' and granular variant granules are on a continuum of size, thereby leading to the proposal that the names represented an arbitrary division rather than a biologically significant dichotomy. The clinical cohort had a bimodal age distribution skewed towards a younger age (median 26 years). The responses to treatment (mainly cytarabine + anthracycline-based) were a harrowing com-

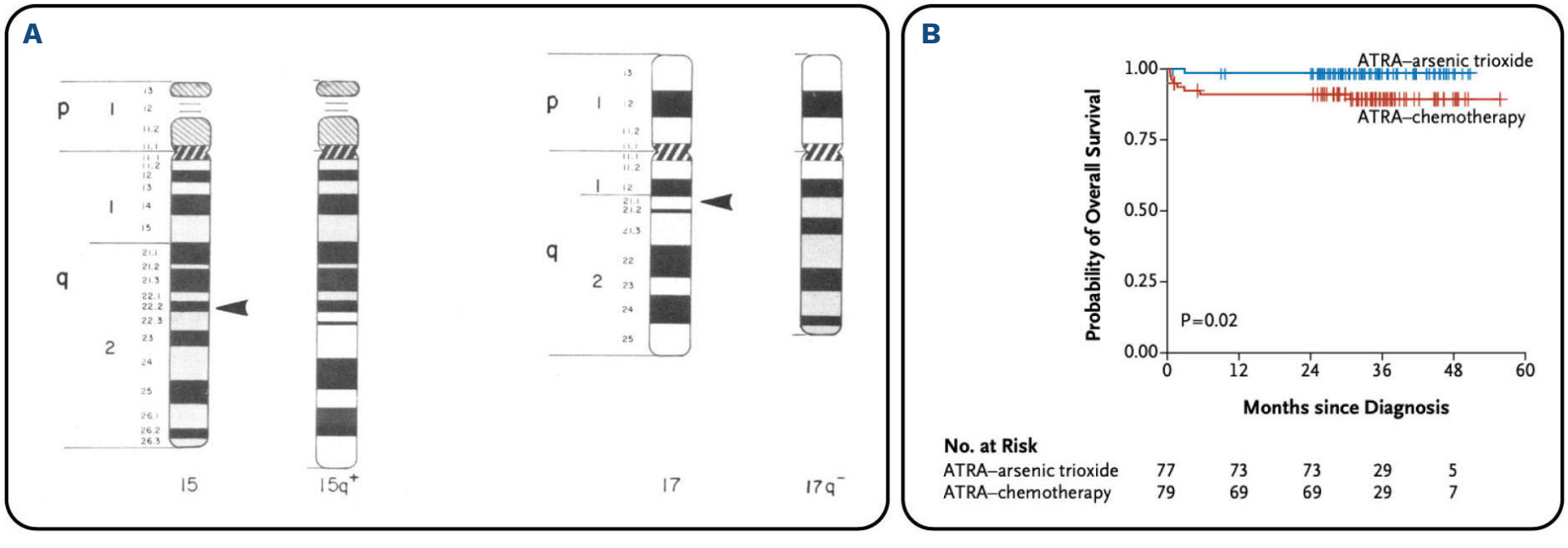


Figure 1. The diagnostic translocation and treatment efficacy in acute promyelocytic leukemia. (A) Schematic of the identical 15;17 translocation identified in every patient of the cohort reported by Larson and colleagues (taken from Larson *et al.* Am J Med. 1984; with permission).[1] (B) Treatment of acute promyelocytic leukemia with all-*trans* retinoic acid (ATRA) and arsenic trioxide produces almost 100% cure rates (taken from Lo Coco *et al.* New Engl J Med. 2013; with permission).[4]

parison to current clinical outcomes, with less than half of patients achieving remission and a median survival of only 8 weeks. The clinical complications of this early cohort reflect the sobering natural history of APML with 40% of patients succumbing to intracranial hemorrhage and reminds us that early effective and protocoled management of coagulopathy in APML are still key for today's high rates of cure to be realized.

The first legacy of this paper was the careful cytogenetic analysis of each patient utilizing specific culture conditions and corroborating banding techniques. Through these karyotypic analyses, the authors identified a t(15;17) with identical breakpoints at 15q22 and 17q21.1 in every patient of their cohort (Figure 1A). They suggested that methodological issues explained the previously reported uneven geographical distribution of t(15;17) in APML. With modern techniques, this has proven to be true with more than 95% of cases of APML containing the described t(15;17).

Subsequent to the discovery of t(15;17)(q22;q21.1), a number of groups identified the fusion to be between *PML* (on chromosome 15) and *RARA* (on chromosome 17), also providing the biological explanation for clinical differentiation responses to all-*trans* retinoic acid (ATRA) observed in the late 1980s.[3] ATRA, now accompanied by arsenic trioxide, forms the backbone of APML therapy[4] and has been transformative in converting a highly fulminant, chemotherapy-resistant entity into one with a more than 95% cure rate (Figure 1B). These responses are unprecedented in any other subtype of AML or advanced cancer. Exemplified by APML, genetic characterization of AML is now a fundamental requirement, with numerous pathogenic reciprocal translocations and molecular mutations guiding AML classification, prognostication, selection for allogeneic transplantation and rationally designed targeted therapies.

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors contributed equally.

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