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Review Article

Prognostic Value of Complex Karyotype and del(17p) in Patients with Chronic Lymphocytic Leukemia

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Summary

Complex karyotype has been treated as a single adverse category in chronic lymphocytic leukaemia for two decades. The largest analysis of the question found it is nothing of the kind: five or more abnormalities are adverse regardless of anything else, three or four matter only alongside a TP53 lesion, and one particular complex pattern is associated with better survival than a normal karyotype.

Objectives: To review the published evidence on complex karyotype and del(17p) in chronic lymphocytic leukaemia: how each is defined and detected, how often they occur and co-occur, what each predicts under chemoimmunotherapy and under targeted therapy, and whether karyotypic complexity carries information independent of TP53 status.

Material and Methods: Narrative review of cytogenetic cohort analyses, trial correlative studies, sequencing work, consensus guidelines and methodological comparisons indexed in PubMed and the major haematology journals. Studies were eligible if they reported the frequency or prognostic effect of karyotypic complexity or TP53 aberration in a defined chronic lymphocytic leukaemia population. No new patient data were generated and no patients were recruited; every estimate quoted is one published by the original investigators.

Results: Deletion of 17p occurs in 4 to 10 per cent of patients at diagnosis and in up to 40 per cent at relapse after chemoimmunotherapy, with the remaining TP53 allele mutated in around 80 to 90 per cent of deleted cases. In a series of 3,539 patients, five or more chromosomal abnormalities defined a high-complexity group comprising 233 patients (6.5 per cent) with the shortest overall survival, independent of immunoglobulin mutational status and TP53 status. Three or four abnormalities were clinically relevant only in the presence of a TP53 lesion. Complex karyotypes characterised by trisomy 12 with trisomy 19 were associated with longer survival than in patients without a complex karyotype. Complexity retained prognostic value in patients treated with ibrutinib and with venetoclax, and in one series was associated with median progression-free survival of 34 against 40 months.

Conclusion: Counting abnormalities is not the same as measuring risk. A threshold of three, still widely used, groups together patients whose outcomes differ in both directions, and the composition of the karyotype matters as much as the count.

Abbreviations: CLL – Chronic Lymphocytic Leukaemia, CK – Complex Karyotype, hCK – High Complex Karyotype, CBA – Chromosome Banding Analysis, FISH – Fluorescence In Situ Hybridisation, IGHV – Immunoglobulin Heavy Chain Variable Region, M-CLL – IGHV-Mutated CLL, U-CLL – IGHV-Unmutated CLL, CIT – Chemoimmunotherapy, TTFT – Time to First Treatment, OS – Overall Survival, PFS – Progression-Free Survival, CLL-IPI – CLL International Prognostic Index.

Keywords: Chronic Lymphocytic Leukaemia; Complex Karyotype; del(17p); TP53; Prognostication

Introduction

Chronic lymphocytic leukaemia is unusually heterogeneous, with survival ranging from months to decades according to the underlying genetics [1,2]. For more than twenty years the framework organising that heterogeneity has been a hierarchical model built on interphase fluorescence in situ hybridisation, which assigns patients to risk categories by the presence of specific deletions and trisomies [3].

That model, together with immunoglobulin heavy chain variable region mutational status and TP53 gene status, has dictated treatment choice throughout the chemoimmunotherapy era [4,5,6]. Deletion of 17p13, which removes one copy of TP53, is the pre-eminent adverse marker and identifies an ultra-high-risk group [3,7,8].

Chromosome banding analysis captures something the targeted probes cannot: the overall burden of chromosomal change. Complex karyotype, conventionally defined as three or more abnormalities, has been reported as adverse across many cohorts [9,10,11]. Whether it adds information beyond TP53 status, and whether a single threshold is appropriate, has been harder to establish [12,13].

This review sets out how each marker is defined and detected, how often they occur and overlap, what each predicts under chemoimmunotherapy and under pathway inhibitors, and what the largest analyses have concluded about the adequacy of a three-abnormality threshold.

Material and Methods

Search strategy: PubMed and the archives of the major haematology journals were searched for studies of cytogenetics in chronic lymphocytic leukaemia. Search terms combined chronic lymphocytic leukaemia with complex karyotype, karyotypic complexity, del(17p), TP53 aberration, chromosome banding analysis, prognosis, ibrutinib and venetoclax. Reference lists of retrieved cohort analyses, guidelines and reviews were screened by hand.

Eligibility: Studies were included if they reported the frequency, definition or prognostic effect of karyotypic complexity or TP53 aberration in a defined chronic lymphocytic leukaemia population, or addressed the methodology of complexity scoring. Genomic array and sequencing studies are cited where they bear on detection or on clonal evolution, and are identified as such.

Data extraction and handling: Design, cohort size, detection method, complexity definition, treatment received and reported outcome estimates were extracted as published. Detection method is stated alongside every frequency figure, because banding analysis, fluorescence in situ hybridisation and genomic arrays resolve different lesions and yield different complexity counts on the same sample. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The classic hierarchy and its frequencies: The most frequent cytogenetic aberrations involve chromosomal subbands 13q14 in 50 to 60 per cent of patients, 14q32 in 12 to 15 per cent, 11q22 in 10 to 20 per cent and 17p13 in 5 to 10 per cent, with trisomy 12 in 15 to 25

per cent (Figure 1) [1,3]. Each group carries a distinct prognosis, and the hierarchical arrangement of these lesions has served as the backbone of diagnostic practice for two decades [3,14].

Adverse markers beyond del(17p) include del(11q), unmutated immunoglobulin status, use of the IGHV3-21 gene segment and expression of ZAP70 or CD38 [7,15,16]. Stereotyped B-cell receptor immunoglobulins carry independent clinical effect [17], and tailored approaches grounded on immunogenetic features have been proposed to refine prognostication further [18].

Molecular markers were added to this framework as sequencing matured. Immunoglobulin mutational status and CD38 expression were shown to combine with genomic aberrations in predicting survival [7], and the value of molecular genetic markers for risk assessment was assessed systematically soon afterwards [15]. Cytogenetics and genomics are now considered together rather than as alternatives [16].

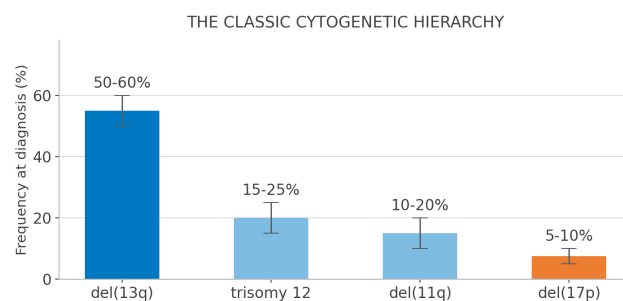


Figure 1: Frequency of the principal cytogenetic aberrations at diagnosis [1,3]

del(17p) and TP53 disruption: Loss of the short arm of chromosome 17 arises through deletions, translocations, isochromosomes and ring chromosomes, all removing one copy of TP53 at 17p13 [19,20]. The remaining allele is mutated in more than 90 per cent of cases by one account [19] and in around 80 per cent by another [21], so biallelic dysfunction is the usual state and appears to be the mechanism driving progression in this subgroup [21].

Frequency depends on when the sample is taken. Deletion appears in 4 to 10 per cent of cases at diagnosis and in up to 40 per cent of cases relapsing after chemoimmunotherapy (Figure 2) [21,22]. That enrichment reflects selection: TP53-disrupted clones survive genotoxic therapy preferentially, so the marker becomes commoner in exactly the population in which it matters most [21,23].

TP53 mutation without deletion carries adverse prognosis independently, which is why deletion and mutation are considered together as TP53 aberrations [8,24]. Mutation is present in roughly 10 per cent of cases at diagnosis [21]. Deletion also frequently accompanies isochromosome 17q formation, and cases with the isochromosome showed a tendency toward more associated chromosomal aberrations [20].

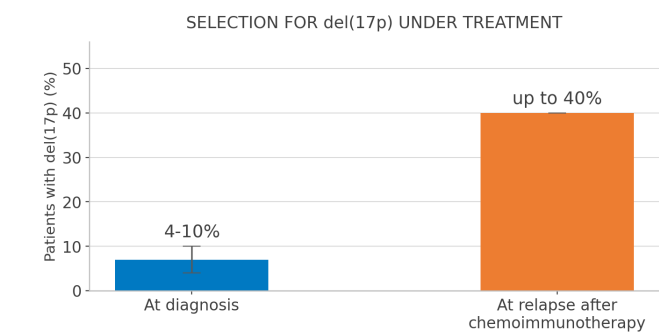


Figure 2: Frequency of del(17p) at diagnosis against at relapse after chemoimmunotherapy [21,22]

Study	n	Focus	Principal reported finding
Döhner et al. 2000 [3]	—	FISH hierarchy	Genomic aberrations define survival categories
Baliakas et al. 2014 [9]	—	Translocations	Systematic reappraisal of classic cytogenetic data
Herling et al. 2016 [10]	—	Chemoimmunotherapy	Complexity with KRAS and POT1 mutations affects outcome
Baliakas et al. 2019 [12]	3,539	Complexity	Five or more abnormalities define the adverse group
Kittai et al. 2021 [25]	—	Ibrutinib	Increasing complexity and evolution affect survival
Jondreville et al. 2020 [13]	Review	Methodology	Diagnostic recommendations for complexity scoring

Table 1: Principal studies reviewed, with focus and the finding as reported by the original investigators

Complexity is not one category: The decisive analysis examined 3,539 patients and led to a hierarchical model rather than a binary one. Patients with five or more abnormalities, numbering 233 or 6.5 per cent of the series, showed the shortest overall survival (Figure 3), and that effect held independently of immunoglobulin mutational status and of TP53 status [12,13].

Below that threshold the picture changes entirely. Three or four aberrations were clinically relevant only in the presence of a TP53 lesion, meaning that a patient with four abnormalities and intact TP53 does not belong in an adverse category [12]. And complex karyotypes characterised by trisomy 12 together with trisomy 19 were associated with longer overall survival than in patients without a complex karyotype at all (Figure 4) [12].

That last finding is the one that most undermines a simple count. A karyotype meeting the conventional definition of complexity can carry a better prognosis than a normal one, which means the definition is capturing something other than risk. An earlier analysis of 1,001 patients with banding data obtained within six months of diagnosis and before treatment had found complexity in 157 cases, strongly associated with unmutated immunoglobulin genes and with del(17p), and independently predictive of shorter time to first treatment [9,26].

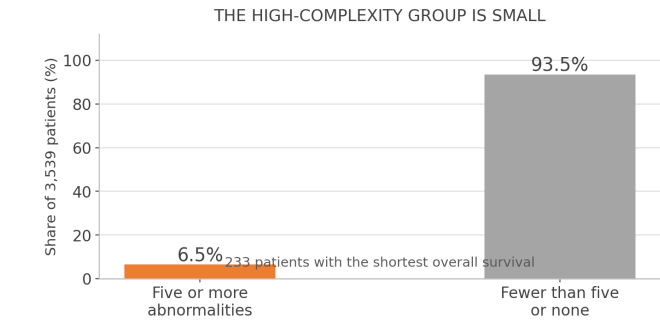


Figure 3: Size of the high-complexity group within a series of 3,539 patients [12]

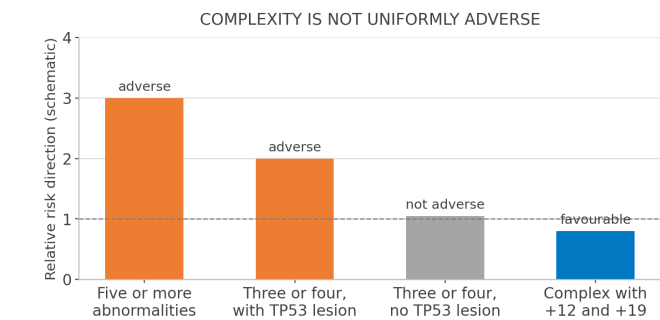


Figure 4: Direction of prognostic effect by complexity subtype and TP53 status [12]

Complexity under targeted therapy: The introduction of pathway inhibitors raised the question of whether cytogenetic risk would persist, and it largely has. Karyotypic complexity affects survival in patients treated with ibrutinib [25] and with venetoclax [27], and complexity defined as three or more abnormalities remains prognostic in relapsed and refractory disease treated with either [28].

In one series of patients receiving ibrutinib with venetoclax, complex karyotype was associated with del(17p) in 24 cases ($p = 0.0049$) and with significantly worse progression-free survival, at a median of 34 against 40 months ($p = 0.00028$) [29]. Extended follow-up of a randomised ibrutinib trial examined high-risk prognostic factors in previously treated patients [30], and complexity has been shown to affect outcome independently of the international prognostic index [31].

Near-tetraploidy has been associated with Richter transformation in patients receiving ibrutinib, which links extreme complexity to a specific adverse event rather than to attrition alone [13,32]. Allogeneic transplantation retains a role in this population, and its indications have been reconsidered in the pathway inhibitor era [33,34].

Karyotype category	Prognostic effect	Independent of TP53?
Five or more abnormalities	Shortest survival	Yes [12]
Three or four with TP53 lesion	Adverse	No; requires the lesion [12]
Three or four without TP53 lesion	Not clinically relevant	Not applicable [12]
Complex with +12 and +19	Longer survival than non-complex	Distinct entity [12]
Near-tetraploidy	Linked to transformation	Reported separately [13,32]

Table 2: How different complexity categories behave prognostically

How complexity should be measured: Chromosome banding analysis requires successful mitotic stimulation and metaphase preparation, and the count obtained depends on culture conditions and on scoring convention [13,35]. Direct comparison of scoring guidelines found that different conventions applied to the same karyotype yield different complexity assignments [35], which affects any threshold-based classification.

Genomic arrays offer an alternative that does not require dividing cells, and array-based screening at diagnosis and follow-up has been evaluated [36,37]. Multicentre work identified high-risk disease by genomic complexity using arrays [38], and whole-genome sequencing has been validated to clinical grade for detecting low-frequency variants and copy number alterations together [39]. These approaches count different lesions from banding, so thresholds are not transferable between platforms [13,35,38].

The underlying mutational landscape has been characterised by sequencing [40,41], including non-coding recurrent mutations [42], and subclonal architecture evolves under treatment [43]. Gene mutations including KRAS and POT1 modify outcome alongside complexity [10], and results from trial correlative studies have connected specific mutations to treatment response [44].

The double-hit subgroup: A small group carries both TP53 disruption and gain or translocation of MYC at 8q24, and it behaves worse than either lesion alone. Cases with del(17p) together with 8q24 gain were described as an aggressive subgroup [20], and the combination has since been characterised as double-hit disease with very poor prognosis [19].

MYC translocation and MYC gain proved mutually exclusive in that analysis, with translocation present in the major clone and gain mainly subclonal [19]. Whether the combination retains its adverse weight under targeted therapy has been identified as requiring evaluation rather than assumed [19,28].

Detection method	What it resolves	Limitation
Interphase FISH	Defined recurrent lesions	Cannot assess overall complexity [3,13]
Chromosome banding	Whole-genome complexity count	Requires mitotic stimulation; scoring varies [13,35]
Genomic arrays	Copy number without dividing cells	Counts differ from banding; no agreed threshold [36,38]
Whole-genome sequencing	Variants and copy number together	Clinical-grade validation recent [39]

Table 3: Methods for assessing cytogenetic risk and what each can and cannot establish

Discussion

The central finding is that a category in routine use does not behave as a category. Complex karyotype defined at three or more abnormalities groups together patients whose outcomes differ in opposite directions: a high-complexity group with the shortest survival in the series, a middle group whose risk depends entirely on TP53 status, and a trisomy 12 with trisomy 19 subtype that does better than patients with no complexity at all [12].

Retaining the three-abnormality threshold therefore mixes three populations. For a patient with four abnormalities and intact TP53, being labelled complex conveys an adverse implication the data do not support [12]. For a patient with the favourable trisomy pattern it is actively misleading.

Why del(17p) enriches under treatment

Rising from 4 to 10 per cent at diagnosis to up to 40 per cent at relapse is among the clearest demonstrations of clonal selection in haematological malignancy [21,22]. The deletion removes the principal mediator of the DNA damage response, so genotoxic chemoimmunotherapy selects for exactly the cells it cannot kill [21,24].

That has two consequences. Testing must be repeated before each line of therapy rather than performed once at diagnosis, since a patient negative at presentation may be positive at relapse [8,13]. And it supplies the rationale for non-genotoxic approaches in this subgroup, where pathway inhibitors have substantially improved outcomes without applying the same selective pressure [19,28,45].

Whether complexity adds to TP53 status

This is the question that most divides the literature, and the difficulty is confounding: complexity associates strongly with del(17p), so distinguishing their contributions requires either large numbers or careful stratification [9,26,46]. Several analyses report that the impact of complexity was hard to separate from that of TP53 aberration [11,46].

The 3,539-patient analysis addressed this directly by stratification and found that five or more abnormalities remained adverse independently of TP53 status while three or four did not [12]. Work examining complexity specifically within TP53-aberrant patients reached a compatible conclusion, finding that karyotypic complexity rather than any individual chromosome abnormality aggravated outcome in that subgroup [46].

Study limitations

The limitations belong to the underlying literature. Banding analysis requires mitotic stimulation, and failure rates and culture protocols differ between laboratories, so complexity is not measured identically across cohorts [13,35]. Complexity and TP53 aberration are strongly correlated, which makes their independent contributions difficult to separate outside very large series [9,11,46]. Most cohorts were treated with chemoimmunotherapy, and prognostic weights established in that era may not transfer to pathway inhibitors, although current evidence suggests they largely do [25,27,28]. Genomic arrays and sequencing count different lesions from banding and no threshold has been agreed across platforms [36,38,39]. And cohorts assembled at diagnosis differ systematically from those assembled at relapse, where del(17p) is several times commoner [21,22].

Two gaps deserve naming. No prospective study has tested whether treating patients differently on the basis of complexity subtype rather than a single threshold improves outcome [12,13]. And no study reviewed here establishes whether the favourable trisomy 12 with trisomy 19 subtype should be managed as low-risk disease, which is what its survival would imply [12].

Conclusion

Deletion of 17p occurs in 4 to 10 per cent of patients with chronic lymphocytic leukaemia at diagnosis and in up to 40 per cent at relapse after chemoimmunotherapy, with the remaining allele mutated in most cases, and it remains the pre-eminent adverse marker. Complex karyotype is a less coherent category than its routine use implies. Among 3,539 patients, five or more abnormalities identified 6.5 per cent with the shortest survival independently of immunoglobulin and TP53 status; three or four abnormalities carried no clinical relevance without a TP53 lesion; and complexity characterised by trisomy 12 with trisomy 19 was associated with longer survival than an absence of complexity.

Complexity retains prognostic weight under ibrutinib and venetoclax. The count matters less than what is being counted, and a three-abnormality threshold conflates populations that should be separated.

Two practical changes follow. Complexity should be reported as a count with the specific abnormalities listed, rather than as a binary complex or not complex, so that a reader can distinguish the high-risk group from the trisomy subtype [12,13]. And TP53 testing should be repeated before each line of therapy rather than performed once, given the several-fold enrichment observed at relapse [8,21,24].

Neither requires new technology or new evidence. Both follow from data already published, and both would change what a clinician can do with a cytogenetics report that currently compresses three distinct populations into one label [12].

Implications for trial design

If complexity subtypes carry different prognoses, then enrolling patients by a single threshold dilutes any treatment effect specific to the high-risk group. A trial recruiting all patients with three or more abnormalities includes a subgroup with favourable survival [12], which biases toward the null.

Stratifying by count rather than by threshold would be straightforward, since the information is already generated by the same test [12,13,35]. Reporting outcomes separately for five or more abnormalities, three to four with TP53 lesion, and the trisomy subtype would allow future analyses to be pooled meaningfully, which at present they cannot be [11,12,26].

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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