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Minimal residual disease and the prediction of survival outcomes in chronic lymphocytic leukaemia: A pooled analysis of observational and clinical trial data

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INTRODUCTION

Despite the improvement in survival in chronic lymphocytic leukaemia (CLL). seen with newer immunochemotherapy regimens, most patients with a clinical response will eventually relapse due to residual disease.

Minimal residual disease (MRD) is a sensitive measure of the remaining tumour load after treatment and is an indicator of the depth of response to treatment. New techniques, such as polymerase chain reaction (PCR)–based and 4-colour flow cytometry, have made the assessment of MRD more feasible, accurate and sensitive.

MRD-negativity is generally defined as fewer than 1 leukaemic cell per 10,000 (10-4) lymphocytes from peripheral blood (PB) or bone marrow (BM).

Prospective clinical trials provide clear evidence that patients who achieve MRD-negativity after treatment have significantly longer overall survival (OS) and progression free survival (PFS) than those with higher levels of residual malignant cells.

AIM

To conduct a systematic literature review to identify studies considering MRD status and survival outcomes (OS and PFS) in CLL.

To conduct meta-analyses to evaluate the association of MRD with survival outcomes (OS, PFS) and the predictive relevance of MRD in patients with CLL, using studies identified by the systematic literature review.

METHOD

Systematic literature review

We systematically searched PubMed, Embase, the Cochrane library, heoro.com and 8 grey literature sites in December 2018.

We searched for studies that reported MRD and survival or quality of life in CLL.

We identified 3,065 studies **(Figure 1),** 485 of which met initial inclusion criteria and were included in an Evidence Map **(Figure 2)**.

All full text primary publications that reported on the association between MRD status and OS or PFS, plus those that compared PB with BM assessments of MRD, were identified for inclusion in the review.

Additional abstract-only publications that were relevant to licensed targeted therapies in CLL (ibrutinib, idelalisib and venetoclax) were also included if they reported useful data on the research questions.

Meta-analysis

The association of MRD with outcomes was assessed for PFS and for OS by line of therapy (first-line, subsequent-line), where data allowed.

Meta-analysis was conducted using a random effects model, which weighted studies using the inverse-variance method. Studies were combined on the scale of the logarithm of the hazard ratio (HR) and the corresponding standard error.

For each meta-analysis, the percentage of variation across studies that was due to heterogeneity rather than chance was assessed by performing the I^2, which is an intuitive and simple expression of inconsistency.

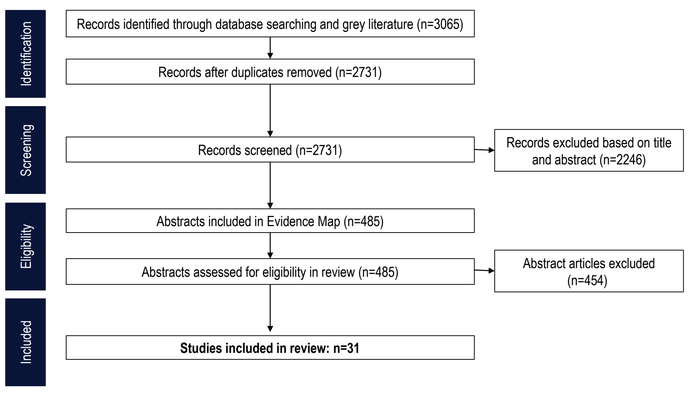
As complementary analysis, the prediction interval which presents the expected range of true effects in future similar studies was also computed for each set of meta-analysis.

Where HRs for outcomes were not reported in the original studies, HRs were estimated using either individual patient data (IPD) from Kaplan-Meier (KM) curves or survival data at specific time-points were computed.

The analysis used the package “metafor” in the R Statistical Platform.

Scenario analysis was performed including studies that had been previously excluded on the grounds that the proportional hazard assumption did not hold.

Figure 1. PRISMA diagram



RESULTS

Figure 2. Evidence Map, a screen shot of the Evidence Mapper showing the number of abstracts included by study methodology and outcomes reported

1. Select the first category to be included in the Evidence Map. This will show as a series of rows in the Map
First dimension: Study methodologies

2. Then select the second category to be shown as the columns of the Map, or leave blank
Second dimension: Outcomes

	MRD-Correlated with survival	MRD-PB vs BM
Unallocated	0	0
Case-control	0	0
Clinical Trial	24	19
Cohort	30	3
Cross Sectional	0	0
Economic Model	0	0
Pooled Analysis	12	7
RCT	10	13
SLR	2	0

We identified 31 publications that met the pre-defined inclusion criteria.

- 20 full texts and 11 abstracts.
- 15 reported data that could be included in a meta-analysis. One paper (Dimier et al., 2018[1]) had information for 3 separate trials (CLL8, CLL10 and CLL11).
- Of the trials, 8 were in first-line treatment and 9 were in either mixed (n=4) or subsequent line therapy (n=5).

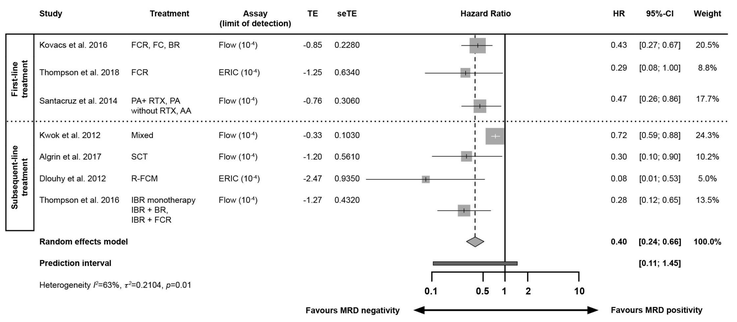
Most studies used multiparametric flow cytometry to detect MRD with a threshold of less than 1 in 10^{-4} malignant cells for MRD-negativity.

Overall survival

For OS, data was available from 7 studies (3 in first line[2,3] and 4 in subsequent-line treatment populations[4-8]). It was decided to combine all 7 studies into 1 meta-analysis because the subsequent-line and mixed-line studies included 2 small studies of <65 people.

Meta-analysis of all 7 studies (706 patients with a negative MRD test [MRD-], 562 with a positive MRD test [MRD+]) showed that MRD-negative status was significantly associated with increased OS as compared with MRD+ (HR 0.40, 95% CI 0.24, 0.66) **(Figure 3).**

Figure 3. Meta-analysis results for MRD-negativity and OS including all studies regardless of proportional hazard assumption



AA: Alkylating agents, BR: Bendamustine + rituximab, ERIC: European Research Initiative on CLL, FLOW: 4 or more parameter flow cytometry, FCR: Fludarabine + cyclophosphamide + rituximab, FCR: Fludarabine + cyclophosphamide + rituximab, IBR: Ibrutinib, PA: Purine analogues, R-FCM: Rituxumab + fludarabine, cyclophosphamide and mitoxantrone, SCT: Stem cell transplant, Mixed: Chemotherapy, chemoimmunotherapy, SCT, targeted therapy

Sensitivity analyses were carried out excluding studies where there was uncertainty around the proportional hazard assumption.

- In 3 studies (all of which were in subsequent-line or mixed-line therapy): Algrin et al., 2017[8], Dlouhy et al., 2012[7] and Thompson et al., 2016[4], the proportional hazards did not hold.
- For studies in any line of treatment (n=4), the HR (95% CI) was 0.53 (0.31, 0.90), with a prediction interval which crossed 1 (0.14, 2.00) and a reasonable level of heterogeneity (I^2 57%, τ^2 0.0670, p=0.07.
- For the 3 first-line studies, the HR (95% CI) was 0.43 (0.29, 0.63), with a prediction interval which crossed 1 (0.08, 2.30) and no heterogeneity (I^2 0%, τ^2 0.0094, p=0.78.

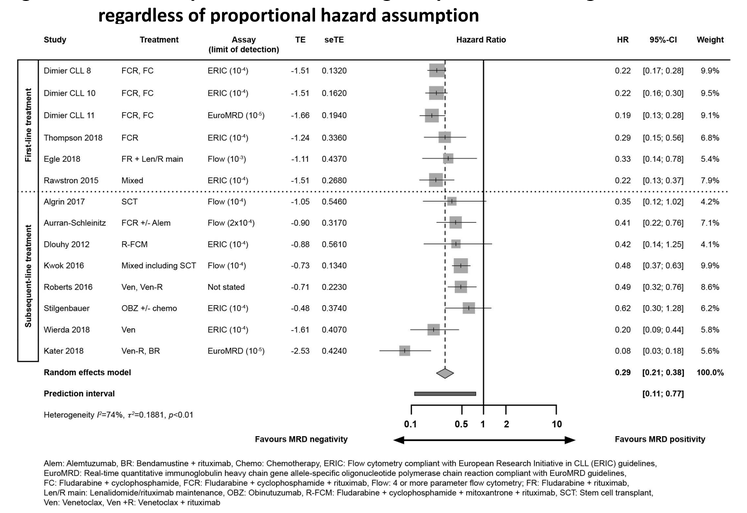
All HRs for OS were in the same direction favouring those patients who achieved MRD-negativity. However, prediction intervals crossed 1, indicating variation in effect estimates in different settings and what can be expected in future studies.

Progression free survival

For PFS, relevant data was provided by 6 studies in first-line therapy[1,3,9,10] and in 8 in subsequent-line therapy[6-8,11-15].

Regardless of line of treatment, meta-analysis of 14 studies (n=1,021 MRD-, n=1,289 MRD+) showed that MRD negativity was a strong predictor for PFS: HR 0.29 (0.21, 0.38), with a narrow PI of 0.11, 0.77.**(Figure 4)**.

Figure 4. Meta-analysis results for MRD-negativity and PFS including all studies regardless of proportional hazard assumption



Alem: Alemtuzumab, BR: Bendamustine + rituximab, Chemo: Chemotherapy, ERIC: Flow cytometry compliant with European Research Initiative in CLL (ERIC) guidelines, EuroMRD: Real-time quantitative immunoglobulin heavy chain gene allele-specific oligonucleotide polymerase chain reaction compliant with EuroMRD guidelines, FC: Fludarabine + cyclophosphamide, FCR: Fludarabine + cyclophosphamide + rituximab, Flow: 4 or more parameter flow cytometry; FR: Fludarabine + rituximab, Len/R main: Lenalidomide/rituximab maintenance, OBZ: Obinutuzumab, R-FCM: Fludarabine + cyclophosphamide + mitoxantrone + rituximab, SCT: Stem cell transplant, Ven: Venetoclax, Ven +R: Venetoclax + rituximab

First-line PFS

Pooled data from 6 first-line studies (n=644 MRD-, n=818 MRD+) also showed a strong association between MRD negativity and PFS: HR 0.22 (0.19, 0.26), with a narrow prediction interval of 0.16, 0.31 and no heterogeneity (I^2 0%, τ^2 0.0207, p=0.83).

The proportional hazard did not hold in 1 study in first-line treatment (Rawstron et al., 2015[9])

For all remaining studies (n=5) the HR (95% CI) was 0.22 (0.18, 0.27), with a narrow prediction interval of (0.14, 0.35) and no heterogeneity (I^2 0%, τ^2 0.0146, p=0.72).

Second-line PFS

Meta-analysis of all 8 subsequent-line studies (n=377 MRD-, n=471 MRD+) gave a significant HR for PFS of 0.34 (0.20, 0.59), with a prediction interval of 0.08, 1.50 and moderate levels of heterogeneity (I^2 67%, τ^2 0.3119, p<0.01).

The proportional hazard did not hold in 3 studies in subsequent-line treatment (Aurran-Schleir et al., 2011[13], Dlouhy et al., 2012[7] and Roberts et al., 2016[14]).

For all remaining studies (n=5) the HR (95% CI) was 0.29 (0.10, 0.79), with a prediction interval which crossed 1 (0.02, 3.76) and a high level of heterogeneity (I^2 81%, τ^2 0.5200, p<0.01.

All HRs for PFS were in the same direction favouring those patients who achieved MRD-negativity. There was a strong association between MRD negativity and PFS, which was particularly noticeable in patients after their first-line of treatment.

CONCLUSIONS

All studies included in the meta-analyses consistently confirmed the significant association of MRD status with OS and PFS, regardless of therapies used, indicating that the predictive value of MRD status is independent of study design, MRD assessment and type of treatment used.

A narrow prediction interval indicates the benefit of MRD testing in the prediction of PFS; however, lack of high-quality estimates for OS resulted in some uncertainty.

Sensitivity analyses removing studies in which the proportional hazards did not hold increased the degree of uncertainty as indicated by a wider prediction intervals, however, this approach is more robust and will be used as the base case in future work.

These results support the role of MRD status as a surrogate endpoint for outcomes in patients with CLL.

Further research is necessary to determine the impact of MRD-negativity on quality of life in CLL. This work has been updated with a new systematic literature review and meta-analysis to capture the most up to date information.

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