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A network meta-analysis of progression free survival and overall survival in first-line treatment of chronic lymphocytic leukemia

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ABSTRACT

Background: A limited evidence exists regarding comparisons of clinical effectiveness of available therapies for first-line treatment of chronic lymphocytic leukemia (CLL).
Methods: We compared available therapies for treatment-naïve, symptomatic CLL regarding progression free survival (PFS) and overall survival (OS) in all the identified random control trials and in subgroups composed of younger/fit and older/unfit patients, using a Bayesian network meta-analysis.
Results: In younger/fit patients we obtained median of projected mean PFS of: 19, 26, 31, 43, 51 and 75 months for chlorambucil, fludarabine, alemtuzumab, fludarabine with cyclophosphamide (FC), bendamustine and fludarabine with cyclophosphamide and rituximab (FCR), respectively. We noted median OS of: 59, 66, 66, 70 months for FC, chlorambucil, FCR and fludarabine, respectively. In older/unfit patients we noted PFS of: 16, 17, 24, 30, 60 months for chlorambucil, fludarabine and chlorambucil with ofatumumab (OClb) or rituximab (RClb) or obinutuzumab (GClb), respectively. We obtained median OS of: 44, 58, 59 and 90 months for fludarabine, RClb, chlorambucil and GClb, respectively.
Conclusions: Our results suggest that: (1) FCR has higher potential of preventing CLL progression in younger/fit patients over four therapy options, which were subject of previous meta-analysis but also over bendamustine; (2) in these patients FCR does not entail prolonging of OS in comparison with chlorambucil and it is outperformed by fludarabine; (3) in older/unfit patients GClb demonstrates longer projected PFS than all assessed comparators; (4) in this group GClb has also the highest potential of increasing OS.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common subtype of mature B-cell neoplasms with the overall age-standardized incidence rate equal to 3.8 and 4.2 per 100,000 per year in Europe and in the United States, respectively [1,2]. The incidence increases rapidly with increasing age. About 70% of all CLL cases is diagnosed in the population aged 65 and over [2]. The disorder is more common in men with a male to female ratio of approximately 1.5:1 [1]. The median survival at diagnosis varies between 1 and more than 10 years.

Many people with CLL do not have any symptoms when it is diagnosed. A few studies demonstrated that treatment of patients with early-stage disease does not prolong survival [3–5]. Thus, the standard treatment of patients with early disease is a watch-and-wait strategy, while progressive or symptomatic disease requires therapy [6,7]. Indications for treatment include: massive or progressive splenomegaly, massive node or progressive lymphadenopathy, general symptoms (weight loss, fatigue, sweat and fever without infections), lymphocyte doubling time shorter than 6 months, anemia and/or thrombocytopenia not responsive to corticosteroids and the advanced clinical staging [6].

A few therapy options are currently available for symptomatic, progressive CLL that make use of alkylating agents (e.g. chlorambucil, bendamustine), purine nucleoside analogues (e.g. fludarabine), and/or monoclonal antibodies (e.g. alemtuzumab, rituximab) either in a monotherapy or in a combination therapy. Efficacies of some of these treatments for symptomatic previously untreated CLL patients have been compared directly in the randomized control trials (RCTs) in terms of the progression-free survival time (PFS) and/or overall survival (OS). However, the available data are sparse and most of the therapy options have not been compared directly.

Several systematic reviews and meta-analyses of the first-line treatments in CLL patients have been published for the last two decades, becoming a valuable source of information on efficacy of different therapy options in terms of the response rates or sur-

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vival [8–11]. In each of these reports, results of individual RCTs were aggregated to compare direct effects of two selected therapy options (e.g. fludarabine *vs.* alkylator-based regimen, purine analogues *vs.* alkylating agents, etc.) that were tested head-to-head in the source RCTs. In 2012, Cheng et al. [12] reported results of the network meta-analysis using a Bayesian analytic framework applied to the survival data obtained from RCTs [13–17] identified during the systematic literature review in order to simultaneously analyze therapies that previously have not been directly compared in terms of PFS. In this meta-analysis two hazard models were considered and the Weibull model was demonstrated to fit the data taken from the RCTs more closely than log–logistic one. The study suggested that combination of fludarabine with cyclophosphamide and rituximab (FCR) resulted in relatively longer PFS than other therapy options that were compared, i.e. chlorambucil, fludarabine, fludarabine with cyclophosphamide (FC) and alemtuzumab. One of a few limitations of this meta-analysis is related to the fact that only two hazard functions were considered and, consequently, that the selected Weibull model might have not fit the experimental data optimally. Another report comparing different treatment options for the first-line CLL therapy used a Cox regression model for the PFS outcome relaying on the proportional hazards assumption that might have been not plausible [18].

The objective of the current study was to conduct a network meta-analysis to compare survival data of therapies for previously untreated CLL, modeling the hazard function of competing interventions with fractional polynomials. Such an approach provides a general framework for modeling of a broad family of parametric survival functions including some of the commonly used (e.g. Weibull, Gompertz) and it does not rely on the constant hazard ratio assumption [19].

Methods

Systematic literature review

We conducted a literature search in the NCBI PubMed and Cochrane Library for RCTs databases for studies published in the English language prior to January 2014 using search terms that included names of drugs used as primary agents in CLL therapy that we identified as the first-line therapy options for CLL using National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines. In our search query we included also terms "CLL", "drugs" and "treatment". We used references of the identified papers to search for additional eligible studies. We found 467 studies reported in papers containing the searched terms or being referenced in these papers. For each study identified, we reviewed the title and abstract to exclude studies that described one drug, concerned not treatment naïve patients or reported results of non RCT. Then the main text of the identified papers was checked to include studies that measured a survival endpoint (PFS and/or OS), provided respective survival curves and reported the number of patients at risk below the survival curves at different times during follow-up. A lack of information on the number of patients at risk below the survival curves precluded an inclusion of some otherwise eligible studies, including RCTs reporting on monotherapy or combination therapy with cladribine [20–22].

Fig. 1 shows scheme of the literature search that was applied. The eligible studies were scored according to the Jadad et al. [23] scale independently by two researchers. We analyzed base-line characteristics of the study groups and treatment schedules including the dosing schemes to assess potential heterogeneity between studies.

We used G-test to assess significance of differences in proportion of male patients, patients aged below 60 years, patients aged above 70 years, patients with the advanced stage disease defined as stage III/IV according to Rai or stage C according to Binet, patients with ECOG score equal to zero and patients with cytogenetic abnormalities, i.e. del 17p, del 11q or mutation of IgVH. We also applied the Marascuilo procedure to identify pairs of the studies that contributed to the detected differences. The results were considered to be statistically significant for $p < 0.05$. Based on the results of this analysis and considering the inclusion criteria and other base-line characteristics of the study groups in each RCT we divided the whole group of the eligible RCTs into two subgroups including younger/fit patients and older/unfit patients. The network meta-analysis was conducted using the whole group and these two subgroups of RCTs.

Hazard model

In the current study a multi-dimensional treatment effect approach was used as an alternative to a network meta-analysis of survival data, in which the treatment effect is represented by a single parameter [19]. We used hazard model represented with several parameters defined using first and second order fractional polynomials. In this model, for the simplest case of the first order fractional polynomial, the log hazard (h_{At}) of treatment A at time t is given as $\ln(h_{At}) = b_{0A} + b_{1A}t^p$ with $t^0 = \log(t)$ [19].

If we use the first order polynomials for a single RCT comparing two treatments (A and B), parameters of the model for treatment B are given as $b_{0B} = b_{0A} + d_0$ and $b_{1B} = b_{1A} + d_1$ where vector $(d_0\ d_1)$ reflects the difference in b_0 and b_1 of the log hazard curve for treatment B relative to A. Meta-analysis models for the comparison of treatment B *vs.* A can be extended to models allowing simultaneous comparisons of B *vs.* A as well as C *vs.* A. When individual pair-wise trials are comparable in terms of covariates affecting the relative treatment effect then a network of studies can be built using trials with common arms to allow for both direct and indirect comparisons preserving the strength of randomization. In a network meta-analysis of a binary outcome an indirect estimate for the relative effect of C *vs.* B (d_{BC}) can be obtained from the direct estimates of A *vs.* B and C *vs.* A using the following equation $d_{BC} = d_{AC} - d_{AB}$. For a network meta-analysis of survival data, the comparison of treatments is performed on the log hazard ratio (HR), and the following relation should apply to every timepoint t: $\ln(HR_{BC}(t)) = \ln(HR_{AC}(t)) - \ln(HR_{AB}(t))$ with $HR_{BC}(t)$ reflecting the hazard ratio of C relative to B at time t. Hence, in the fractional polynomial log hazard model the differences in the model parameters b_0 and b_1 are independent of time and these differences for the B *vs.* C comparison can be described by the differences in b_0 and b_1 for the A *vs.* C comparison and A *vs.* B comparison. Therefore, a network meta-analysis can be performed based on the differences in b_0 and b_1 of log hazard curves across studies. Thus, applying different p values a wide range of curve shapes can be tested and network meta-analysis of survival can be performed using a model that fits the experimental data most closely [19].

To select the best models we first digitalized survival curves for PFS and OS from the individual RCTs. The scanned Kaplan–Meier curves were divided into multiple 2-months-long consecutive intervals (Δt) over the follow-up period adjusting the data for censoring according to the method described by Jansen [19]. In each interval $[t, t + \Delta t]$ in each study j and in each treatment k the number of patients at risk at the beginning of the interval (n_{jkt}) and the incident number of endpoint events (r_{jkt}), i.e. disease progressions in case of PFS and deaths in case of OS, were calculated.

We used binomial likelihood distributions $r_{jkt} \sim \text{bin}(p_{jkt}, n_{jkt})$ to describe the number of endpoint events r_{jkt} in each interval $[t, t + \Delta t]$ based on n_{jkt} and p_{jkt}, which is the observed cumulative incidence of the disease progressions and/or deaths in treatment k of the j-*th* study in the particular interval. The hazard rate is