Chronic Myeloid Leukemia survival in Europe from 1995 to 2007

Vener C,[1,2] Minicozzi P,[1] ...., Sant M,[1] and the EUROCARE Working Group

[1] *Analytical Epidemiology and Health Impact Unit, Department of Preventive and Predictive Medicine, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan, Italy*

[2] *Laboratory "G. A. Maccacaro", Department of Clinical Sciences and Community Health, University of Study of Milan, Milan, Italy*

Further authors to be involved (alphabetical order):

De Angelis R,[a]

Marcos-Gragera R,[b]

[a] *Cancer Epidemiology Unit, National Centre of Epidemiology, Italian National Institute of Health, Rome, Italy*

[b] *Epidemiology Unit and Girona Cancer Registry, Oncology Coordination Plan, Department of Health, Autonomous Government of Catalonia, Catalan Institute of Oncology, Girona Biomedical Research Institute (IdiBGi), and Universitat de Girona, Girona, Spain*

Rationale

European chronic myeloid leukemia (CML) incidence was 1.10 (per 100.000) in 2000-2002,[1] reaching about 4 (per 100.000) in patients aged 75-99 years at diagnosis. CML can be classified into 3 clinical phases: chronic (CP), accelerated (AP), or blastic (BP) phase, the last two representing about 4%, and 3%, respectively,[2,3] associated with different survival.[4]

For many years, CML remained a leukemic subtype in which little improvement was gained with regard to overall survival (OS), despite numerous trials investigating possible new treatments.[5] The introduction of imatinib mesylate, the first tyrosine kinase inhibitor (TKI), changed the treatment strategy in all CML phases.[6-9] Imatinib mesylate (formerly STI571; Glivec™; Novartis Pharma), is available in study protocols from 2000 (in Sweden) and has been approved by authorities in 2001 (in Europe).[2,10]

Nowadays, second-generation TKIs, dasatinib and nilotinib, are an effective and safe therapy option in CML; firstly approved in 2005 in UK,[11] then in 2007 and 2008 (dasatinib

and nilotinib, respectively) in Sweden,[2] they can be used as first-line therapy for CP or in subsequent CML phases.[11]

The introduction of imatinib/TKIs has dramatically improved CML survival and nowadays CML is considered as a chronic disease. Most studies based on population cancer registries (CRs) data, reported survival at five years after diagnosis. The population-based CR of Girona showed that in 1994-2008 the 5-year relative survival (RS) for CML patients treated with TKIs was around 80% compared to 44% for those who did not receive the selected treatment.[12] The EUROCARE-5 study showed that the 5-year RS increased from 1997 to 2008 in all European regions, particularly after 2000,[10] although wide differences in RS (>10%) were still evident among European countries.[13] Survival increased slightly in Southern Europe, more in the UK, and conspicuously in Northern, Central, and Eastern Europe, but improvements in Eastern Europe remained lower than elsewhere.[10] A low survival increase was seen among the elderly, possibly because of the underuse of imatinib (89.7% of 20–59 year-old received imatinib, 75.0% of 60–79 years, and 46.0% of ≥80 years) and second-generation TKIs.[14]

In CML, as well as in many other diseases, clinical management guidelines are mainly based on results from randomized clinical trials (RCT), performed on selected study populations in which elderly patients and those with significant and/or multiple comorbidities are underrepresented. Typically, RCT patients have been treated within a university hospital setting. Thus, collecting results from population-based CRs with full coverage of the target population would reduce the effect of selection on outcome and provide important complementary data to those obtained from RCT, providing information on effectiveness in daily clinical practice. Moreover, communicating reports from such CRs timely to all treating clinicians may also be a way to improve the quality of care.[15]

Thus the analysis of 10-year RS will be worthy of relevance and more informative than conventional 5-year survival. Notably, we will carry out the first European study on CML survival at 10 years.

Aims

By taking advantage of high-quality European population-based CRs, using EUROCARE data and HAEMACARE morphological groupings, we will estimate survival in relation to age, gender, and geographic region among CML patients (aged 15 years and older) diagnosed from Jan 1, 1995 up to Dec 31, 2007, and followed up to Dec 31, 2008.

In particular, our main aim is to estimate 10-year relative survival of CML patients, analysing differences by country, regions, age, gender.

Additionally, we also aim to estimate the conditional survival that will be analyzed as a proxy of different CML phases.

Materials and methods

For our analyses, carried out on individual data, we need information on adult (≥15 years) patients:

gender

date of birth and/or age at diagnosis

date of diagnosis

vital status

date of last vital status check

European region/cancer registry

morphology, coded according to the 3rd edition of ICD-O (ICD-O-3).[16] All morphological codes will be analysed in order to check the completeness of morphology codes and to be sure to carry out analyses on comparable data. However, for CML only the following codes will be included in the final analyses: 9863 (no information about cytogenetic), 9875 (BCR/ABL positive CML) and 9876 (BCR/ABL negative CML).

Statistical methods

Initially we will consider all the EUROCARE-5 database. From those CRs that provided continuous incidence and good quality data from 1995 to 2007, we will select appropriate CRs for analyzing CML data.

We will apply a complete approach to estimate age-standardised and age-specific (in principle, <50, 50 to 59, 60 to 69, 70 to 79, and >79 years) 1-, 3-, 5-, and 10-year RS for CML, overall and by European region or country, and gender.

The ratios (conditional survival) between the age-standardised 3-year to 1-year RS; 5-year to 1-year RS; 10-year to 1-year RS; 5-year to 3-year RS and 10-year to 5-year RS will be analysed.

The RS is defined as observed survival in the patient group (where all deaths are considered as events) divided by the expected survival of a comparable group from the

general population, which is assumed to be free from the cancer under study. Expected survival will be estimated using the Ederer II method.[17] However, the unbiased Pohar-Perme will be also considered.

Poisson regression or flexible parametric models will be used to model the excess mortality rate ratio[18] adjusting for age, gender, country or European region.

All analyses will be performed using Stata statistical software.

Timing

The data analysis will start approximately in December 2015. A draft of the paper will circulate among the EUROCARE Working Group within May 2016. The Italian team, at the Fondazione IRCCS Istituto Nazionale dei Tumori, will carry out the main statistical analyses, and will collaborate with the interested members of the EUROCARE Working Group in order to interpret results and write the relevant article(s).

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