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SIE, SIES, GITMO updated clinical recommendations for the management of chronic lymphocytic leukemia

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ABSTRACT

By using GRADE system we updated the guidelines for management of CLL issued in 2006 from SIE, SIES and GITMO group. We recommended fludarabine, cyclophosphamide, rituximab (FCR) in younger and selected older patients with a good fitness status, no unfavourable genetics (deletion 17p and/or p53 mutations), and a less toxic treatment in nonfit and elderly patients. In patients without unfavourable genetics, relapsed after 24 months the same initial treatment including rituximab can be considered. In patients with unfavourable genetics, refractory or relapsed within 24 months from a prior fludarabine-based treatment, allogeneic SCT or experimental treatments should be given.

1. Introduction

In its mandate to promote the best hematological care, the Italian Society of Hematology (SIE) and the affiliate societies SIES (Società Italiana di Ematologia Sperimentale) and GITMO (Gruppo Italiano Trapianto di Midollo Osseo) issued in 2006 the guidelines for the management of patients with CLL [1]. As recommended by the AGREE group [2], and due to the new available knowledge on this disorder, we projected to update the original guidelines. In areas covered by the evidence, the production of recommendations was performed according GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system [3], a method that has been proposed to overcome shortcomings of previous approaches used for developing guidelines.

2. Methods

2.1. Guidelines development process

A 3-member Advisory Council (AC) with expertise in clinical epidemiology, hematology, critical appraisal and research synthesis oversaw the process. An expert panel (EP) was selected according to the conceptual framework elements of the NIH Consensus Development Program [4]. The steps in the process are shown in Table 1. During a first meeting the panel decided which of the original clinical issues needed an update and the issues for which there was the need for a critical evidence appraisal. On this basis, we identified and produced recommendations about 6 clinical issues.

2.2. Producing consensus-based recommendations

The consensus methodology was applied by the EP for 4 of the 6 identified issues. During three consecutive consensus conferences, the four issues were analyzed and discussed according to the nominal group technique [5] as previously described [1].

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Table 1
Definition of project's objectives.

Presentation to panel members of the GRADE system
Definition of the clinical issues and key questions
Discussion of all the relevant outcomes and individual rating of the importance (relevance) of each outcome
Systematic literature search and preparation of the evidence and summary of findings tables for each relevant outcome
Individual rating of the quality of evidence for each relevant outcome and overall individual rating of the balance of benefits and harms for each relevant outcome and overall
Drafting of recommendations by individual panel's members, and individual rating of the strength of the recommendation(s)
Meetings to reach the final version of the recommendations by group discussion

2.3. Producing and grading evidence-based recommendations

The two issues selected for updated recommendations got through evidence analysis and GRADE methodology. The AC systematically retrieved pertinent literature. Search was performed on December 2009 and limited to English-language publications edited after 2005. Conference proceedings were manually retrieved. The following proceedings were examined: American Society of Hematology, 2008 and 2009; European Hematology Association, 2009; American Society of Clinical Oncology, 2008, 2009. Ongoing or finished but yet unpublished trials registered at the NCI web site and addressing patients with CLL were selected and protocol description was downloaded. Even though the recommendations were issued on the basis of systematic review of literature published up to December 2009, analysis of data published since that date up to March 2011 was performed before publication of the present paper.

For the issues deserving evidence-based recommendations, the outcomes of interest relevant for deciding whether a given treatment is worth recommending were preliminarily chosen after discussion by the EP. The AC prepared for each relevant outcome "evidence tables," with evaluation of all the predefined dimensions of quality (i.e. study design, consistency, directness, precision and publication bias) along with the corresponding quantitative summary of finding tables (copies of this material are available from the authors).

The EP members received the material by mail and they were asked to individually drafting recommendation by individually agreeing on benefit/risk ratio profile for each intervention. Using a modified Delphi process [6], the list of produced statements was circulated electronically to all participants through 2 iterations. Participants voted on which statements they felt warranted discussion, and provided comments on the wording of the statements which were progressively finalized. Final adjudication of the recommendation (s) was made through the three face-to-face meetings held in Bologna, Italy. Recommendations were both classified into four mutually exclusive categories: do it, probably do it, probably don't do it, don't do it, according to GRADE suggestions, and were also provided in conversational form following the comments derived from the discussion of the EP.

3. Results

3.1. Issue 1: patient evaluation at diagnosis, indication for treatment initiation, and patient monitoring (consensus-based recommendations)

The recommendations produced in the 2006 SIE, SIES, GITMO guidelines were revised according to new knowledge on this issue.

3.1.1. Recommendations

In order to plan an optimal clinical management, the EP recommended that the following information should be obtained at the time of CLL diagnosis: serum lactate dehydrogenase and β2-microglobulin level; imaging of adenomegalies as assessed either by total body computed tomography or by the combination of chest X-ray and abdomen ultrasound; direct Coombs' test in patients with anemia.

Del [11q], del [17p] and the IgVH mutational profile should be investigated, especially in patients who are eligible for more intensive treatments. In patients with no del [17p], testing of p53 deletions or mutations is recommended.

The indication for treatment initiation includes the presence of at least one of the following features: B symptoms (i.e. fever, sweats, fatigue or weight loss), rapid lymphocyte doubling time, progressive enlargement of lymph nodes or hepatosplenomegaly, obstructive adenopathy, development or worsening of thrombocytopenia or anemia, immune hemolysis or thrombocytopenia not responsive to steroids.

In the clinical practice, the presence of an unfavourable biologic profile is not a reason to start treatment when the disease is in an early stage and clinically stable.

In patients with no treatment indication, a disease monitoring should be made at least every 6 months and should include: physical examination, hematologic evaluation and biochemistry, including serum lactate dehydrogenasis and β2-microglobulin. Patients with a poor prognostic biologic profile or clinical signs of a more aggressive disease should be evaluated more frequently, at least every 3 months. An abdominal ultrasound should be monitored every 6–12 months. Chest X-ray should be evaluated when informative at diagnosis.

3.2. Issue 2: information required at the time of treatment initiation (consensus-based recommendations)

3.2.1. Recommendations

Before starting treatment, the following information should be obtained in order to evaluate the more appropriate treatment approach: physical examination, performance status, co-morbidity assessment, peripheral blood count with morphologic examination, when required, bone marrow evaluation, serum biochemistry including serum lactate dehydrogenasis and β2-microglobulin, Coombs' test, imaging of adenomegalies, assessed either by CT scan or by the combination of chest X-ray and abdomen ultrasound.

3.3. Issue 3: first line therapy (evidence-based recommendations)

In 2006, SIE-SIES-GITMO group recommended that low-risk younger patients and selected elderly patients, should receive a first-line therapy with fludarabine plus cyclophosphamide [1]. In order to update these recommendations, we searched for evidence questioning whether novel single agents or new treatment combinations should be preferable in the clinical practice. Following the GRADE method, the results of trials were evaluated taking into account selected relevant outcomes, that for this issue were PFS and OS. The rate of patients with treatment-related adverse events (AEs), including myelotoxicity and infections, were also considered an important outcome.

The evidence related to this issue was divided into 4 sections. The assessments described herein led to the recommendations reported in Table 2.

3.3.1. Single agents

Three RCTs addressed the comparison between fludarabine and chlorambucil monotherapy in the first line therapy. Catovsky et al. [7] allocated 777 previously untreated patients of all ages (median age, 65 years) in three treatment arms: fludarabine monotherapy, fludarabine cyclophosphamide combination, and chlorambucil monotherapy. Survival at 5 years was the primary endpoint. Complete remission (CR) rates were significantly higher with fludarabine as compared to chlorambucil (15% vs. 7%). However, there was no significant difference in the PFS and OS between the two arms. Serious AEs were more frequent in patients treated with fludarabine (7% vs. 4%).