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A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process

Hydroxycarbamide (HC; hydroxyurea) is a non alkylating antineoplastic agent widely used for the treatment of myeloproliferative neoplasms (MPNs) polycythaemia vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (PMF). Variable numbers of patients treated with HC do not achieve the desired response with the recommended dose of the drug, thus exhibiting clinical resistance, while others may develop unacceptable side-effects, demonstrating clinical intolerance (Tefferi *et al*, 1995; Barbui & Finazzi, 2005; Dingli & Tefferi, 2005; Harrison *et al*, 2005; Randi *et al*, 2005; Kiladjian *et al*, 2006; Christoforidou *et al*, 2008). The development of a standardized definition of resistance/intolerance to HC in MPNs is necessary for appropriately moving patients to second line therapy in clinical practice. However, molecularly targeted therapies have opened a new era in the management of patients with MPNs, and ethical considerations indicate patients refractory to first line therapy as the most appropriate population for testing. Thus, the need for a definition of resistance/intolerance to HC in MPNs has been urged for the provision of criteria for enrolling patients into clinical trials aimed at assessing the efficacy of new molecularly targeted therapies. Bearing this in mind, a group of European investigators has recently collaborated to produce a definition of resistance/intolerance to HC in patients receiving the drug for ET (Barosi *et al*, 2007).

In this present work, an international working group (WG), sponsored by an European Community Network of Excellence (LeukemiaNet) grant, produced a definition of resistance/intolerance to HC in patients receiving the drug for PV and PMF. In an attempt to consider all the factors that may affect the definition of resistance/intolerance to HC, formal methods for consensus attainment were employed. A WG was constituted in December 2008, composed of fourteen experts in MPNs, and was chaired by a clinician with expertise in clinical epidemiology (GB). The WG agreed that resistance and intolerance to HC are interrelated constructs, so the goal was to produce a unified definition.

We first aimed at selecting the criteria in their conceptual terms, worded without any numerical or quantitative attributes. To achieve this, a questionnaire was mailed to each member of the WG asking them to propose candidate conceptual criteria that were further refined in a Delphi process with a second questionnaire that asked to rank the top choices among candidate criteria. The candidate conceptual criteria were, then ranked according to their priority votes, with the criteria that ranked highest and that received at least 80% consensus to be included in the list. We then aimed at selecting the criteria in their operational terms, populating the conceptual criteria with quantitative or numerical attributes. A third questionnaire requested that the WG should propose candidate operational criteria for each conceptual one. Selecting the best operational criterion for each conceptual criterion was exploited in a consensus meeting using the nominal group technique. This process clarified the expert's judgments regarding which considerations were pertinent and their relative importance, facilitating an open discussion during the consensus process.

The six conceptual criteria for the definition of resistance/intolerance to HC in PV with the highest preference rate (>80% consensus) were: (i) Not achieving the desired reduction of haematocrit with the addition of HC in patients who do not tolerate enough frequent venesections after a critical period of time and at the maximum tolerated dose of the drug, (ii) Progression on HC after a critical period of time and at the maximum tolerated dose, (iii) Not achieving the desired stable reduction of leucocyte count when

leucocytesare a target of therapy, after a critical period of time and at the maximum tolerated dose of HC, (iv) Not achieving the desired reduction of spleen size in patients treated for massive or symptomatic splenomegaly after a critical period of time, and at the maximum tolerated dose of HC, (v) Not achieving the desired stable reduction of platelet count when platelet count is a target of therapy, after a critical period of time and at the maximum tolerated dose of HC, (vi) Persistence of splenic symptoms after a critical time period at the maximum tolerated dose of HC. The seven conceptual criteria with the highest preference rate (>80% consensus) for PMF were: (i) Not achieving the desired reduction of spleen size in patients treated for massive or symptomatic splenomegaly after a critical period of time and at the maximum tolerated dose of the drug, (ii) Not achieving the desired stable reduction of leucocyte count when leucocytes are a target of therapy, after a critical period of time and at the maximum tolerated dose of HC, (iii) Progression on HC after a critical period of time and at the maximum tolerated dose, (iv) Not achieving the desired stable reduction of platelet count when platelets are a target of therapy after a critical period of time and at the maximum tolerated dose of HC, (v) Persistence of splenic symptoms after a critical time period at the maximum tolerated dose of HC, (vi) Not controlling hepatomegaly after a critical period of time and at the maximum tolerated dose in patients treated for hepatomegaly after splenectomy, (vii) Not controlling extra hematopoietic deposits at the maximum tolerated dose in patients treated for extramedullary haematopoiesis.

At the end of the consensus process, the members of the WG proposed that the definition of resistance/intolerance should require the fulfilment of at least one of the operational criteria reported in Tables I and II. The performing characteristics of the resulting definition should be interpreted acknowledging the uncertainty inherent both to the consensus process and to the panelists' preferences and attitudes, reflecting the absence of scientific evidence upon which to base the definition. To focus the problem, the panel of experts used group techniques with the assumption that such acknowledged experts have an implicit and comprehensive mastery of scientific and practical information that would yield the most appropriate definition.

Table I. Definition of resistance/intolerance to Hydroxycarbamide in patients with polycythaemia vera.

1. Need for phlebotomy to keep haematocrit <45% after 3 months of at least 2 g/day of Hydroxycarbamide, OR
2. Uncontrolled myeloproliferation, i.e. platelet count $>400 \times 10^9$/l AND white blood cell count $>10 \times 10^9$/l after 3 months of at least 2 g/day of Hydroxycarbamide, OR
3. Failure to reduce massive* splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of Hydroxycarbamide, OR
4. Absolute neutrophil count $<1{\cdot}0 \times 10^9$/l OR platelet count $<100 \times 10^9$/l or haemoglobin <100 g/l at the lowest dose of Hydroxycarbamide required to achieve a complete or partial clinico-haematological response†, OR
5. Presence of leg ulcers or other unacceptable Hydroxycarbamide-related non-haematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of Hydroxycarbamide

*Organ extending by more than 10 cm from the costal margin.
†Complete response was defined as: haematocrit <45% without phlebotomy, platelet count $\leq 400 \times 10^9$/l, white blood cell count $\leq 10 \times 10^9$/l, and no disease related symptoms. Partial response was defined as: haematocrit <45% without phlebotomy, or response in three or more of the other criteria (Barosi *et al*, 2009).

Table II. Definition of resistance/intolerance to Hydroxycarbamide in patients with Primary Myelofibrosis.

1. Failure to: (i) reduce massive*, or progressive† splenomegaly, or hepatomegaly in splenectomized patients, by more than 50% as measured by palpation, OR, (ii) completely relieve symptoms of splenomegaly, or hepatomegaly in splenectomized patients, after 3 months of at least 2 g/day of Hydroxycarbamide
2. Uncontrolled myeloproliferation, i.e. platelet count $>400 \times 10^9$/l AND white blood cell count $>10 \times 10^9$/l after 3 months of at least 2 g/day of Hydroxycarbamide, OR
3. Absolute neutrophil count $<1{\cdot}0 \times 10^9$/l, or platelet count $<50 \times 10^9$/l at the lowest dose of Hydroxycarbamide required to achieve a complete or major clinico-haematological response‡, OR
4. Presence of leg ulcers or other unacceptable Hydroxycarbamide-related non-haematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of Hydroxycarbamide

*Organ extending by more than 10 cm from the costal margin.
†Organ increasing by more than 3 cm in the last 3 months.
‡Complete response was defined as complete response in anaemia, splenomegaly and constitutional symptoms; major response was defined as any response in anaemia and splenomegaly without progression in constitutional symptoms, OR complete response in anaemia (or partial response in anaemia that was transfusion-dependent), and response in constitutional symptoms without progression in splenomegaly, OR any response in splenomegaly and response in constitutional symptoms without progression in anaemia (Barosi *et al*, 2005).

Authors' contribution

G. Barosi designed the research, chaired the consensus meetings and wrote the paper. T. Barbui designed the research, was in the expert panel and reviewed the paper. G. Birgegard, G. Finazzi, M. Griesshammer, C. Harrison, H. Hasselbalch, J-J. Kiladijan, E. Lengfelder, R. Mesa, M.F. Mc Mullin, F. Passamonti, J.T. Reilly, A.M. Vannucchi were in the Expert Panel and reviewed the paper.

Conflict of interest disclosure

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