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ORIGINAL RESEARCH

Clinician Concepts of Cure in Adult Relapsed and Refractory Philadelphia-Negative B Cell Precursor Acute Lymphoblastic Leukemia: A Delphi Study

Renato Bassan · Dieter Hoelzer · Xavier Thomas · Pau Montesinos · Jiri Pavlu · Jan McKendrick · Amber Kudlac · Arie Barlev · Beth Barber · Ze Cong

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ABSTRACT

Introduction: Despite the poor prognosis for adults with relapsed or refractory (RR) Philadelphia chromosome (Ph)-negative B cell precursor acute lymphoblastic leukemia (ALL), long-term survival is possible and may even be considered as "cure".

Methods: This study used a Delphi panel approach to explore concepts of cure in RR Ph-negative B cell precursor ALL. Ten European experts in this disease area participated in a survey and face-to-face panel meeting.

Results: Findings showed that clinicians conceptualize "cure" as a combination of three broad treatment outcomes that vary depending on the treatment stage: complete remission early in treatment (1–3 months) indicates initial success; eradicating cancer cells (minimal residual disease negative status) consolidates the early clinical response; leukemia-free survival is required in the long term.

Conclusions: Although such terminology remains contested, clinicians would begin considering "cure" as early as 2 years provided the patient is off therapy, with most considering the term applicable by the third year.

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R. Bassan
UOC Ematologia, Ospedale dell'Angelo e Ospedale SS Giovanni e Paolo, Mestre, Venice, Italy

D. Hoelzer
University Hospital, Frankfurt, Germany

X. Thomas
Lyon-Sud Hospital, Pierre-Bénite, France

P. Montesinos
Hospital Universitari i Politècnic La Fe, Valencia, Spain

J. Pavlu
Centre for Haematology, Faculty of Medicine, Imperial College London, Hammersmith Hospital, London, UK

J. McKendrick (✉) · A. Kudlac
PRMA Consulting Ltd, Fleet, UK
e-mail: jmckendrick@prmaconsulting.com

J. McKendrick
Faculty of Health, University of Technology Sydney, Sydney, NSW, Australia

A. Barlev · B. Barber · Z. Cong
Amgen Inc., Thousand Oaks, CA, USA

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INTRODUCTION

The prognosis is poor for adults with Philadelphia chromosome (Ph)-negative B cell precursor acute lymphoblastic leukemia (ALL) that is refractory to treatment or has relapsed. In this setting, more than 90% of patients die from the disease, typically within a few months of diagnosis [1–4].

There is no universally accepted treatment protocol for adults with relapsed or refractory (RR) Ph-negative B cell precursor ALL in Europe. Guidelines and recommendations for the treatment of adults with ALL generally do not recommend particular treatments specifically for patients with RR disease [1, 4–9]. The approach to treatment is thus heterogeneous, with a wide variety of therapies used and no clearly superior chemotherapeutic option. Currently, a common treatment option following complete remission achieved with chemotherapy is allogeneic hematopoietic stem cell transplant (HSCT), which may be offered as a curative approach. However, in the population with RR disease, even after HSCT, approximately 30% of patients may experience relapse [10].

Despite the poor prognosis in RR-ALL, long-term survival is possible and may even be considered as "cure". Published guidance and descriptions of what constitutes cure can vary, and the term "cure" itself can be used in a number of ways regarding outcomes in oncology [11]. Treatment outcomes in clinical trials are often reported as median overall survival and/or progression- and response-related endpoints, but these metrics may not completely describe the full benefit of treatments that can lead to long-term survival or "cure" [11]. In a recent literature review of how different groups (such as clinicians, academics, patient groups, and payers) describe cure in oncology, Johnson and colleagues found that "cure" itself can be understood as three broad categories: lack of disease progression, eradication of cancerous cells, and long-term survival [11].

The disease setting of RR-ALL is particularly appropriate for exploring concepts of "cure" as a result of a number of factors. This disease is generally associated with a poor prognosis and substantial heterogeneity in treatment approaches. Furthermore, the rarity of the disease means that some concepts and definitions of "cure" and outcomes used in other areas of oncology, such as eradication of cancerous cells, are less well established. As such, the aim of this study was to investigate clinician perceptions of what constitutes successful treatment outcomes and "cure" for adults with RR-ALL.

METHODS

Design

This study used a Delphi design to achieve consensus on perceptions of "cure" and treatment success in adult patients with RR-ALL. The Delphi approach uses a system of iterative questioning on an issue that leads to consensus [12]. The iterative process combines the benefits of obtaining insights from subject matter experts with the structure and detail of a survey. It has long been recognized that when a subject cannot be quantitatively determined or measured, the Delphi approach allows experts to contribute subjective assessments [13]. It is a well-accepted methodology that has been increasingly used in health care over time [13], where it is beneficial for a range of activities such as grappling with clinical problems and clinical guidelines, forecasting disease patterns and funding requirements [14], and gaining consensus on specific questions, such as establishing biomarkers in certain diseases [15]. Although the traditional Delphi technique uses a series of surveys to gain consensus, it is increasingly common to adapt the Delphi process by including a face-to-face meeting component while maintaining the essential Delphi features of consensus on a specific topic from a group of experts [15]. The face-to-face aspect allows more immediate discussion between panelists than would otherwise be possible with surveys.

Compliance with Ethical Guidelines

All participants agreed to complete the survey and attend the panel meeting, thereby consenting to participate in the project. The study and consent procedure were approved by the Human Research Ethics Committee of the University of Technology Sydney, Australia (reference number PRMA3477_2015_04).

Setting and Participants

International clinical experts with backgrounds in hemato-oncology were invited to join the study via email. The clinicians were invited on the basis of their background and were required to be board-certified or a specialist in clinical or medical oncology. Experience requirements included a minimum of 5 years in their role post-training and treating a minimum of 10 patients with ALL per year.

Data Collection

Data collection for the Delphi process in this study included two phases (Fig. 1). In phase 1, the clinicians completed an interactive PDF survey via email, comprising categorical, numerical, and open-ended questions that related to a clinician's background, treatment practices, and definitions of relevant terms and concepts (Table 1). Phase 2 consisted of a face-to-face expert panel meeting with a survey component.

In recognition of the sometimes contested terminology of cure in relation to ALL, the adopted survey terminology was designed to be broad, to facilitate discussion among respondents. The survey used the following terminology to categorize cure: "complete remission", "eradication of cancerous cells (i.e., molecular minimal residual disease (MRD) negative)", and "prolongation of survival". Although there was no established definition of "complete remission" specific to RR-ALL at the time of the study, the definition used in acute myeloid leukemia after the first line of treatment was adopted for this survey. This definition included a number of different aspects of remission, such as morphologic complete remission with incomplete blood count recovery, neutrophil count, molecular complete remission, and the absence of extramedullary leukemia (e.g., central nervous system or soft tissue involvement) [16]. The term "eradication of cancerous cells" was used in the survey with an explanatory note that it should be considered to refer to molecular MRD negativity, which indicates the lack of residual leukemic cells as determined by thresholds for conventional morphologic methods [17]. MRD is important in ALL because

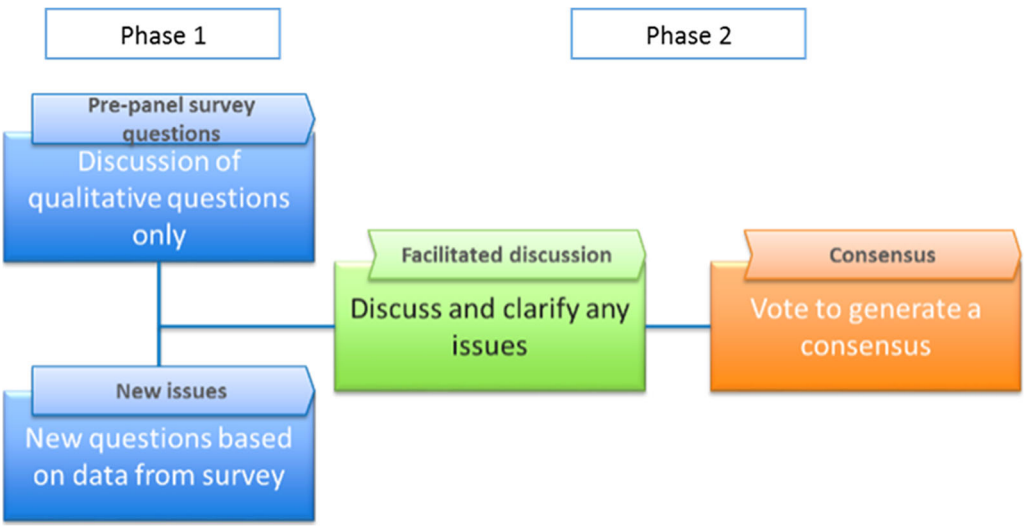

Fig. 1 Delphi process data collection schema

Table 1 Phase 1 survey topics

Main topics covered in phase 1 survey	Content
Clinicians' demographic characteristics and experiences in treating ALL	Establish each clinician's experience and caseload
Treatment intent, treatment outcomes, and definitions of treatment success	Identify any definitions of cure used in clinical practice; describe and define successful treatment outcomes that could be surrogate endpoints for cure; establish the parameters used when defining treatment with curative intent; establish the importance/role of HSCT in the decision-making process for defining cure
Disease that is particularly difficult to treat (described in the survey as primary resistance to first-line therapy, early relapse in less than 12 months, or undergoing second salvage therapy/third-line therapy)	Establish the parameters used when defining disease that is particularly difficult to treat; establish whether curative treatment outcomes and the approach to treatment differ for this subset of patients from those for the general population of patients with relapsed or refractory Ph− precursor B cell ALL
Successful treatment outcomes in relation to the treatment pathway	Identify the earliest step in the treatment pathway where a clinician would consider a patient to be cured, how long after this point they would measure cure, and, if a patient is considered to be cured, how this affects monitoring

ALL acute lymphoblastic leukemia, *HSCT* hematopoietic stem cell transplant, *Ph−* Philadelphia chromosome negative

it can be evaluated in approximately 95% of patients with all types of this disease [17]. Although the panel responses in this study were specific to the definition "eradication of cancerous cells (molecular MRD negativity)", it is acknowledged that MRD response must be durable, and that defining MRD itself can be complicated and open to dispute given the different technologies available with varying specificity and sensitivity [17–19].

Following the survey, individual responses were entered into a spreadsheet and anonymized. The analysis involved determining frequencies for descriptive (categorical) responses and reviewing qualitative data in preparation for the face-to-face meeting.

In phase 2, the question set featured in the phase 1 survey was not expected to change beyond the initial version; however, as a result of the nature of the Delphi technique, further questions which would benefit from a consensus vote during the panel meeting evolved through this process. At the face-to-face panel meeting, the aim was to achieve consensus on answers to the questions in the phase 1 survey and to address any new questions that were developed for phase 2. The panel was moderated by members of the research team experienced in the consensus technique, and involved presenting each question and a summary of anonymized responses from phase 1. The discussion around the responses sought to achieve consensus by collecting responses confidentially, with televoting "clickers", that showed anonymized summaries of results immediately for live review.

In published Delphi studies, definitions of consensus vary widely from 50% to 100% [15]. In this study, consensus was defined as 80% agreement for categorical questions; numeric responses were displayed in pre-specified categorical ranges, and consensus was defined as responses within two consecutive ranges. Where no consensus was achieved after two rounds, and where discussion suggested further voting would not achieve consensus, this

outcome was noted and no further iterations took place.

RESULTS

Participants

Ten clinicians from France, Germany, Italy, Spain, and the UK participated in the survey and expert panel. Nine were hematologists and one was a hemato-oncologist. Most worked in the hospital setting (university hospitals, $n = 8$; community/urban/general hospital, $n = 1$), and one worked in a specialist hematology center.

Clinicians were asked about their patients in the clinic; trial patients were excluded. The clinicians had between 6 and 35 years of experience treating adults with RR-ALL. Before participating in the survey, clinicians answered a screening question to ensure they treated at least ten patients with ALL per year. In the survey, clinicians were asked how many patients they treated with specific subtypes of ALL. Survey responses showed that, in the preceding 12 months, clinicians had treated a mean of 14 patients with B cell precursor ALL (range 3–30), a mean of 9 patients with Ph-negative B cell precursor ALL (range 2–20), and a mean of 6 patients with RR-ALL (range 2–15).

Definitions of "Cure"

Clinicians agreed that three outcome elements of "cure" are important in ALL: complete remission, eradication of cancerous cells (i.e., molecular MRD negative), and prolongation of survival. The most common priority outcome (i.e., ranked first), according to those who responded to the question, was complete remission; eradication of cancer cells was frequently ranked second; and prolongation of survival was ranked third by four of the five clinicians who ranked all three options. Responses in phase 1 suggested that prolongation of survival may be a consequence of one (or both) of the other two outcomes (complete remission and eradication of cancerous cells). Responses relating to timing indicated that these three outcomes are not considered separately, and may be closely linked.

After further discussion at the panel meeting, clinicians agreed that aims of treatment changed with time, and that the outcomes were difficult to consider individually. Clinicians noted that in the 1–3 months following the start of treatment, complete remission is a key aim of therapy because it is the best indicator of response in this time frame (as it may not yet be possible to see or measure cell changes). After 3–6 months, clinicians look for the eradication of cancerous cells as reflected by persistent MRD negativity. Beyond 6 months, survival is the key outcome if the other two outcomes have been achieved (Fig. 2).

The curative outcomes are therefore considered as a package or stepwise approach. Survival is the prerequisite to measuring either complete remission or MRD negativity (the patient must be alive to measure complete remission and MRD status; physicians acknowledged the current lack of consensus around measuring MRD itself, in terms of heterogeneity of testing and the appropriate cutoff for determining negativity). Complete remission was agreed to be essential in keeping the patient alive.

Clinicians indicated that their treatment priorities change for their patients with disease that is particularly difficult to treat; such

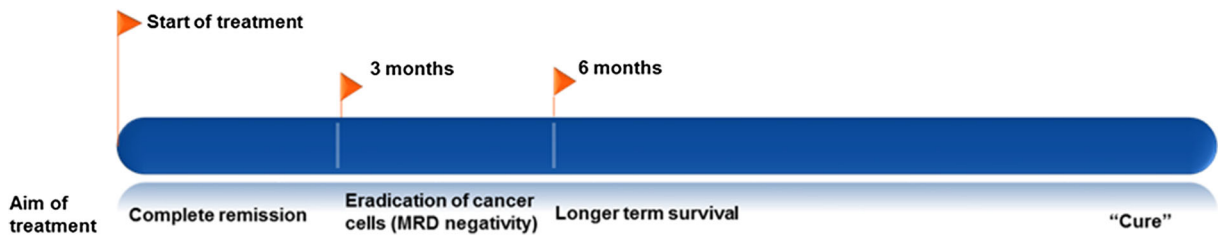

Fig. 2 Aim of treatment over time. MRD, minimal residual disease

patients are more advanced along the treatment line and therefore the focus becomes eradicating cancerous cells, but no consensus was reached for the priority of curative outcomes for this subgroup.

HSCT

Clinicians also noted that a number of factors influence their decision to treat a patient with curative intent, including whether or not that patient was eligible for HSCT (Table 2). Clinicians were also asked for their opinion about the role of HSCT in cure, specifically, whether a patient should only be considered "cured" if the patient has undergone HSCT or is eligible for HSCT. There was consensus that HSCT is an essential step on the treatment pathway (80% agreed that HSCT is an essential step on the pathway to cure), but not that HSCT necessarily determines cure. A patient may be considered cured without HSCT when reaching the stated time points in complete remission without relapse. However, it was also noted by clinicians that the proportion of patients who may be cured without HSCT is extremely small with currently available chemotherapy treatments. For most other HSCT-eligible patients, transplant is currently considered the best therapy option for achieving cure after complete remission is achieved.

Table 2 Factors that influence treatment with curative intent

Question	Response options	Phase 1
What factors and/or patient characteristics would prompt you to treat a patient with relapsed or refractory Ph− precursor B cell ALL with curative intent?	Age	9 (90%)
	Number of prior relapses	9 (90%)
	Length of time between the start of salvage therapy and achieving remission	5 (50%)
	Length of time in remission (i.e., time from start of remission to relapse)	9 (90%)
	Number of salvage cycles	6 (60%)
	Eligibility for HSCT	10 (100%)
	ECOG performance status	10 (100%)
	Other	8 (80%)

Respondents could select multiple options
ALL acute lymphoblastic leukemia, *ECOG* Eastern Cooperative Oncology Group, *HSCT* hematopoietic stem cell transplant, *Ph*− Philadelphia chromosome negative

Timing of "Cure"

All clinicians who responded in the survey stated that a patient could be considered to be cured from either 3 or 5 years from the start of salvage therapy; however, some comments from the survey suggested that "cure" may be possible after 2 years. These time frames were not dependent on how clinicians defined cure (complete remission, eradication of cancerous cells, or prolongation of survival). In the phase 2 voting, the consensus was that "cure" would be considered at 2–3 years, since the combination of these two consecutive responses exceeds the 80% threshold for consensus (Table 3); one further clinician noted that cure would be established at 5 years.

Clinicians noted that if they consider the survival curve for the overall natural history of the disease, the curve flattens from around 3 years, which aligns with the time frame for thinking of cure; some clinicians felt that they might start to think a patient may be cured after 2 years, but do not say so with complete confidence until after 5 years.

This approach to the timing of "cure" did not vary between patient populations (overall population versus patients with disease that is particularly difficult to treat).

Rates of "Cure"

Clinicians were asked to estimate the percentage of their patients (in their current caseload)

Table 3 Time period for assessing "cure"

Question	Response options (years after salvage therapy)	Phase 1	Phase 2
For the overall group of patients who have RR-ALL, what is the minimum period from the start of salvage therapy that you would consider a patient to be "cured"?	1	0	0
	2	0	2 (20%)
	3	2 (20%)	7 (70%)
	4	0	0
	5	7 (70%)	1 (10%)
	No response	1 (10%)	0

Respondents were asked this question specifically in relation to each of a three criteria (complete remission, eradication of cancerous cells, and prolongation of survival) but responses were given only once

ALL acute lymphoblastic leukemia, *RR* relapsed or refractory

whom they considered to be treated with curative intent. When estimating this, clinicians reported in the phase 1 surveys that between zero and 40% of patients might be considered "cured"; no consensus was reached in the face-to-face panel, and the panelists noted that the original upper limit of the range of 40% was somewhat high for patients seen in clinical practice.

Responses to the clinician survey suggested that no more than 10% of patients with particularly difficult-to-treat disease would be considered cured, but no consensus was reached by the panel on the percentage range for these patients. Clinicians noted that 10% is a realistic upper limit of the range of patients who can be considered cured.

DISCUSSION

This study shows that clinicians conceptualize "cure" as a combination of three key treatment outcomes for patients being treated for RR-ALL: complete remission, eradication of cancerous cells (i.e., prolonged molecular MRD negativity), and prolonged survival. Moreover, they see these outcomes as interlinked, with prolongation of survival as a consequence of one (or both) of the other two outcomes. The consensus was that "cure" would be considered at 2–3 years (80% of the respondents selected these two consecutive time periods). Clinicians noted that if they consider the survival curve for the overall natural history of the disease, the curve flattens from around 3 years, aligning with the time frame for thinking of cure. The published literature also suggests that many patients who survive for 2 years will also reach 3-year survival, with studies indicating that survival curves for patients with MRD negative status generally begin to plateau from around the 2-year mark [20, 21].

Although "cure" is understood to comprise complete remission, eradication of cancerous cells, and prolonged survival, the particular clinical focus on each element changes over time. As the findings show, early in treatment (1–3 months), clinicians look for complete remission to indicate initial success; eradicating cancer cells (achieving MRD negative status) and maintaining this status will then strengthen clinicians' view of the initial success. Finally, after treatment is completed, if the patient continues to remain MRD negative over a prolonged period of time, then clinicians begin to consider cure.

In theory, HSCT is not necessary for patients to be considered cured, although complete remission and MRD negative status may make patients better candidates for HSCT, if eligible. However, although it is possible for patients to achieve "cure" without having received HSCT, it is very rare for this to be the case with currently available chemotherapy treatments. This may change as new treatment options become more widely available, but historically, HSCT has been considered the best option for achieving "cure" for those patients eligible for the treatment. The published literature shows that the majority of patients with long survival have received HSCT, while other factors also play a part in survival, such as a younger age, time to complete remission, duration of complete response, and late relapse [3, 22–25]. Some

clinicians would start to consider "cure" as early as 2 years in this setting, with the consensus being that "cure" would be considered by the third year. It is important that these findings are understood in the context of treatment: these time frames may be considered for "cure" but only if the patient is no longer receiving treatment; that is, a patient must have ceased therapy at these time points for them to be considered in any way "cured".

It should also be emphasized that the terminology used to conceptualize "cure" and outcomes, and specifically the term "eradication of cancerous cells", is yet to be fully established in this particular disease setting. Thus, although the broad categories of cure described by Johnson and colleagues [11] are useful as starting points for discussions of "cure" in cancer, a degree of caution is needed in interpreting these findings, as intrapractice definitions of MRD and thresholds for MRD negativity can be unclear, given the different techniques available and their respective advantages and disadvantages [18, 19].

This study had several strengths and limitations. The findings contribute knowledge to an under-researched area; using the Delphi technique to generate this knowledge is a further strength, because this is an established method to elicit critical thinking on complex issues from a group of experts who may be geographically scattered [13], and it is an appropriate choice for an area such as this, where there is little published evidence or consensus available [14]. As with all studies, there are some limitations. Although the panel involved expert members in the field, potential limitations of the Delphi approach include the comparatively small sample of experts. However, given the rarity of the disease, there are relatively fewer experts in this field than in other disease areas. Additionally, the experts included in the study were from France, Germany, Italy, Spain, and the UK, and thus the findings may not be generalizable in other geographical regions and oncological contexts outside the scope of this study. This study also modified the traditional Delphi approach by using a face-to-face expert panel in the second phase, rather than a further survey; therefore, it was not possible to maintain anonymity for the participants, nor to avoid the potential for group dynamics to play a role in establishing a consensus for a given item [12]. However, the electronic "clickers" ensured individual responses were unknown to others within the panel, and anonymity in their responses was maintained [14, 15].

Future research could examine perceptions of "cure" in other settings, and extend this research to involve more clinicians across countries. A registry and database study could also be established to verify these results, particularly in the context of new treatments that may affect perceptions of "cure" in the future.

CONCLUSIONS

This study shows that clinicians do have a concept of "cure" when treating patients for RR-ALL. Although exact definitions may vary, and the terminology may remain contested, there is agreement that clinicians could consider patients cured after a period of 2 years off therapy, and most agreed that a patient would be considered cured after a third year.

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Authors' contributions. JM and AK designed the study with input from AB and BB. JM and AK collected the data, including that provided by RB, DH, XT, PM, and JP. All authors (RB, DH, XT, PM, JP, KM, AK, AB, BB, and ZC) contributed to interpretation and analysis of the data and revision of the manuscript, and read and approved the final manuscript.

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Compliance with Ethical Guidelines. All participants agreed to complete the survey and attend the panel meeting, thereby consenting to participate in the project. The study and consent procedure were approved by the Human Research Ethics Committee of the University of Technology Sydney, Australia (reference number PRMA3477_2015_04).

Data Availability. The questionnaire that study participants were asked to complete before the Delphi panel has been provided in a supplementary file. Sharing of individual responses is not appropriate as the Delphi process is anonymous and focuses on generating consensus, rather than collecting data.

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