13th CML Community Advisory Board (CML-CAB) / 24th session
2nd Academic CML-CAB – 11 June 2023, 14:00-19:00 CET
Title: A cure for CML beyond TFR: is it possible?

Executive Summary

Introduction

CML Community Advisory Board (CML-CAB) is a working group of the CML Advocates Network operating since 2016. It is a global panel of 19 leading patient advocates from all world regions ("CML-CAB members") who all speak from the unique perspective of a CML patient or relative. CML-CAB members work together to address issues of strategic importance to the community and advocate for the best possible research and equal access to the most innovative treatment & care for CML patients around the world. CML-CAB monitors pharmaceutical developments and research in CML through active and targeted interaction, long-term cooperation and continued dialogue with pharmaceutical partners, regulators, medical experts, and the scientific CML-community. With that, CML-CAB is a key strategic tool to have a dialogue of experienced advocates and decision makers about the advocacy community´s priorities and concerns. CML-CAB meetings are based on two key strategic pillars: research and access, with "cure" being a key priority addressed within the area of „research".

This 2nd Academic CML-CAB meeting was a continuation of the 1st Academic CML-CAB meeting held virtually in October 2020 under the motto "Mechanisms to cure CML – beyond TFR" (TFR = treatment free remission) and to which we had invited 8 researchers (all of them working on novel areas of CML research) and 16 CML-CAB members. The main objectives of that first meeting were to build a dialogue with academic researchers, reach consensus on what the key issues are in CML (status quo), establish a vision of where we want to be and what a cure could look like (beyond TFR), look at different approaches to cure and learn which of these are most promising to cure CML, and – last but not least – identify what we as a community can contribute to achieve the vision of a cure for CML, and define a "roadmap to cure". A series of enablers and barriers were identified during said meeting. Parts of these barriers were further discussed during the recent follow-on session, the 2nd Academic CML-CAB, which was held as a hybrid panel meeting and entitled: **A cure for CML beyond TFR: is it possible?** The aims of this latest Academic CML-CAB were to develop a mutual understanding, to learn from scientists who are involved in CML research and innovation, to see what is possible in terms of a cure for CML, and to try to get an answer to the following key questions:

- What is the researchers' approach and contribution towards CML cure beyond TFR?
- Do they understand the needs and expectations of patients?
- What are the barriers to move research forward?
- How can the patient community and researchers support each other and collaborate?

Historically, there has been more focus on eradicating the disease than there is today. Currently there seems to be a trend to focus on prevention of resistance and improving TFR rates. The pharmaceutical industry has little or even no interest in research into the eradication of the disease whereas the research community and the clinical community have. Thus, the need to come together and see how both communities can best work together.

Setting the scene: CML worldwide in the year 2023 and the role of the CML Advocates Network

As an umbrella organisation governed by CML patients and caregivers from all over the world, for 20 years the CML Advocates Network has laboured to represent, strengthen, and unify the voice of the CML patient community. During that time, the community has thankfully witnessed the transformation of the patient journey from an often-devastating prognosis to outcomes which are often now that of a survivable chronic disease. The community is acutely aware of the decades of scientific ingenuity and perseverance that took place, often behind the scenes, to get to this point. Indeed, the community is often reminded of how the CML patient journey is somehow a victim of its own success. It's not unusual at the time of diagnosis to hear CML referred to as "The Lucky Cancer".

Sadly, today young clinicians or researchers are attracted by the challenges or career opportunities offered by choosing specialities in other disease areas. This is because the continuing unmet medical needs of many CML patients go unnoticed or solutions to such are seen differently than two decades ago. However: **in 2023 patients still die from CML**, especially in low-and-middle-income countries (LMICs). Quality of life for all who live with CML and TKI treatments is still less than optimal. Despite having several lines of therapies approved, they are not always accessible to patients, nor is adequate monitoring or expert follow-up, all of which leads to suboptimal treatments.

"The Lucky Cancer" is further complicated by the phenomenon of Treatment Free Remission (TFR), a milestone in the progress toward a cure. For those not fortunate enough to benefit from such a deep response to treatment, and despite the psychological and physical burdens, this is the closest to the meaning of the word "cure" that one can currently hope for, for a significant cohort of CML patients living in countries with advanced healthcare systems. It is a goal to which many aspire. Yet, for more than 85% globally, the TFR journey is laden with frustration and disappointment as they relapse and hope to try again or perhaps give up in despair. The CML Advocates Network follows with keen interest the scientific work at the genetic level which continues to add tools to further support clinicians in their assessment of the possibility of a successful TFR journey. Currently though, TFR alone is just one option for a small percentage of patients living with CML. The key question is: what more can be done? Therefore, the 2nd Academic CML-CAB meeting was focused on the question: **A Cure for CML beyond TFR, is it possible?**

2nd Academic CML-CAB: Meeting format

The 2nd Academic CML-CAB meeting was attended by 11 CML-CAB members for all world regions (one attending virtually, the rest attending in person), 9 researchers working in novel areas of CML (one attending virtually, the rest attending in person), two research funding representatives (both attending virtually), the CML Advocates Network's (CMLAN) Director and Scientific Project Manager, CML-CAB officer, besides other staff. Two moderators guided the discussions and established the tenor. The meeting started with a patients' panel discussion which was followed by a researchers' panel discussion. Then, there was a presentation on research funding strategies, followed by a joint round table discussion that included all panellists. The meeting closed with a wrap up focused on next steps.

Patients' Panel: The patients' view on CML cure beyond TFR – Moderation: Denis Costello

To set the scene for the panel discussion, Jan Geissler, CML-CAB member and outgoing CML-CAB chair, started out by stating that from the patient perspective, TFR is clearly not a cure for everyone. He presented a model developed by CML Advocates Network that reflects different approaches to look at cure, taking into consideration different target groups, intended outcomes and potential treatment burden/long-term burden of the respective approaches. The CML community is particularly interested in discussing ways towards a cure with eradication of the disease for all CML patients, including those who do not have access to tyrosine kinase inhibitors (TKIs) or polymerase chain reaction (PCR) testing, who are not candidates for TFR, or who do not achieve sustained Deep Molecular Remission (DMR). These patients represent the great majority of the patient community worldwide and need to be treated life-long. But although successful TFR is only feasible for at best 35% of patients who have access to TKIs, research & current treatment approaches seem to be focused on improving TFR instead of finding a cure.

In the following discussion, patient panellists represented the perspectives of patients from the global CML community. Patients' needs and expectations on cure differ largely depending on access to treatment in the region where they come from. Researchers were urged to address the following questions:

- Is there anything we can do to eradicate the disease?
- Is there a way to prevent the onset of CML?
- Is there a way to stop monitoring?

In a lively discussion, researchers provided feedback and insights before the next panel was introduced.

Researchers' Panel – Moderation: Jan Geissler

In this session, potential approaches were addressed to find a cure outside of the current treatment pathways. Given that most patients do not achieve cure or sustained TFR, the patient community wanted to understand from researchers what can be done to find a real cure for those patients, what approaches researchers are currently working on, how the patient community can support research efforts, and if we are setting the right priorities in research.

The discussion was focused around the following main areas:

- The different patient populations for research and cure
- Candidates for new drug targets and mechanisms
- Clinical trials, basket trials, platform trials
- Data sharing/ data protection
- Basic research approach and its translation from bench to bedside
- Funding/funders
- Priorities in research efforts – free treatment for everyone or treatment-free for everyone?

The following **barriers** towards a search for a cure were identified:

- Dysfunctional research/translation of findings from bench to bedside: preclinical and clinical research are misaligned, findings in cell models are not taken to the next level.
- Lack of support/funding from pharmaceutical companies and philanthropic funders. As well as funders lacking understanding of TFR and seeing CML as a "done deal".

- Bureaucracy around data protection makes international collaboration in rare disease research difficult.
- Risk averse environment: most pharmaceutical companies are unwilling to conduct basket studies with combination agents, especially if drug is not yet approved.
- Overregulation and high costs of basket trials: simplification and more pragmatic approaches needed.

The following steps to **enable** searching for a cure beyond TFR were mentioned:

- Identifying candidates for targets and mechanisms/ looking more closely at translational research/ bench to bedside.
- Identifying the right patient populations for research and cure (e.g., multi-resistant or multi-intolerant patients; patients with needs in underserved countries with no clinical trials).
- Identifying funding/funders, perhaps get involved with philanthropic funders.
- Identifying and creating incentives: for researchers and for pharmaceutical companies.
- Building a research platform with pragmatic trials, basket trials, platform trials.
- Enabling data sharing whilst addressing data protection and drawing conclusions from data that are already available.
- Enabling discoveries in basic research by donating bone marrow/biosamples.

Research funding by The Leukemia & Lymphoma Society (LLS) – James Kasper

In this session, James Kasper, representing the Leukemia & Lymphoma Society (LLS), presented a model on how collaboration between patient communities and researchers can be enhanced. LLS is the largest non-profit funder of cutting-edge research to cure blood cancers. Since 2017, LLS has helped advance 85% of FDA-approved blood cancer treatment options. LLS provides funding mainly through two programs:

- **Research Grant Program** – includes core programs and special grants that cover blood cancer research from the earliest phase of discovery science to translational research directly benefiting patients. Project proposals are subject to a structured review process to ensure that the best proposals receive funding. Any revenues received from research programs supported by LLS go directly back into funding research.
- **Therapy Acceleration Program (TAP)** – advances innovative cures through LLS strategic venture philanthropy initiative. TAP goals & investment strategy focuses on high-value assets addressing high unmet needs or providing innovative, first-in-class therapies.

CML-CAB expressed interest in collaborating with LLS to see how they could advance the prospects of innovating CML.

Panel Discussion – Moderation: Jan Geissler

Following up on the points discussed earlier in the Researchers' Panel, the moderator encouraged all panellists to think about how the patient community/CML-CAB can support or facilitate current and future efforts in research towards a cure beyond TFR and how researchers can enable each other. Numerous ideas were discussed that can be grouped into the following areas of work:

- Involvement of CML-CAB members in trial design
- Support research projects not (yet) aiming towards cure
- Engage in academic research groups/projects more = more collaboration
- Overcome divide & conquer by pharma companies by aligning on interactions
- Submission for research proposals (for review and support by CMLAN)
- CML scientific community discussing most promising 2–3 ideas for therapeutic approach, then discussion with CML-CAB/CMLAN
- Joint CAB of CMLAN, Researchers and company
- HARMONY Foundation as a platform for joint research projects?
- Data sharing – find an approach beyond the European level
- Medical education to Health Care Providers (HCP) and patients
- CMLAN to support making biobanking more visible

Conclusion & Next Steps – Moderation: Jan Geissler

The 2nd Academic CML-CAB turned out to allow for a fruitful dialogue between the patient community and the academic research community. Researchers felt that openly discussing different perspectives helped them better understand patients' expectations and needs. It was agreed that there was a desire to work together on a path towards cure in CML and to continue collaboration with another Academic CML-CAB in the future.

The group agreed on the following next steps to enable searching for a cure beyond TFR:

- Identifying candidates for targets and mechanisms/ looking more closely at translational research/ bench to bedside.
- Identifying the right patient populations for research and cure, (e.g., multi-resistant or multi-intolerant patients; patients with needs in underserved countries with no clinical trials).
- Identifying funding/funders, perhaps get involved with philanthropic funders.
- Identifying and creating incentives: for researchers and for pharmaceutical companies.
- Building a research platform with pragmatic trials, basket trials, platform trials.
- Enabling data sharing whilst addressing data protection and drawing conclusions from data that are already available.
- There is a need for a bone marrow (CML and other blood cancers) global research biobank which does not exist today.

Executive Summary prepared by:
Nicole Schröter (CML-CAB officer)