Summary and Recommendations of the 2023 Center Outcomes Forum Held on October 18, 2023

EXECUTIVE SUMMARY

The 2023 Center Outcomes Forum was held on October 18, 2023. The purpose is to review the current approach to the Center-Specific Survival Analysis (CSA) and to provide meaningful recommendations for future reports. CIBMTR® (Center for International Blood and Marrow Transplant Research) invited representatives of the hematopoietic cell transplantation (HCT) community, the American Society for Transplantation and Cellular Therapy (ASTCT) Committee on Quality Outcomes, Foundation for the Accreditation of Cellular Therapy (FACT), NMDP, governmental funding agencies, patients, private payers, and statisticians.

Discussion focused around 3 key topics involving center-specific outcomes reporting:

1. Updating processes to gather scientific input and communicate about the risk modeling,
2. Recommendations for revision to risk adjustment factors in AML, ALL and MDS, and
3. Handling participation in trials-based care for future analyses.

The main discussion and recommendations are briefly summarized in the following pages.

Final Recommendations include:

- CIBMTR should continue to leverage its Working Committees and other existing forums and processes, such as the ASTCT Committee on Quality Outcomes and ASTCT Center Administrative Directors SIG, to solicit recommendations to update information collection used for risk adjustment. These should occur on a scheduled basis through formal processes.
- CIBMTR should publish a simplified 1-page summary of the CSA report that highlights changes in the risk adjustment model and provides overall center results. This summary could serve as a cover page to the full report.
- CIBMTR should maintain current educational tools that explain the CSA risk-adjustment model, address common misunderstandings about the analysis and consider providing additional tools such as a recorded webinar(s) on the CIBMTR website.
- CIBMTR should consider hosting an information/education session during the Tandem Meetings to provide key updates about the CSA, including updated risk adjustment, analysis findings and future plans. Invitees could include center medical and administrative directors, FACT, ASTCT Committee on Quality Outcomes, payers, and data professionals. The primary purpose of this session would be educational but would also generate feedback from the HCT community.
    - This session could be recorded and made available on the CIBMTR website.
    - Questions could be solicited in advance to facilitate broad engagement.
- CIBMTR should take opportunities to remind centers about quality improvement tools available on the CIBMTR Portal, including the 1-year survival calculator and individual center datasets.
- CIBMTR should test the feasibility of adding the individual patient-level "predicted OS" generated from the risk adjustment model to individual center datasets (available on the CIBMTR Portal). This tool could support centers' quality improvement efforts and increase the visibility of predicted survival across clinical risk scenarios.

- Data collection should continue to reflect modern classification and risk assignment of hematologic malignancies as published by WHO and other international consensus groups. The work group strongly recommended updating to the WHO 2022 classification as well as updating the cytogenetic, FISH and molecular data that is used to assign the correct classification as soon as possible.
- CIBMTR data collection tools should continue to be updated to reflect modern disease response criteria (i.e., incorporating MRD status for AML and ALL and updated response criteria for MDS). Specific recommendations were provided for several disease-related factors, including genetic mutations and treatment-related variables.
- CIBMTR should continue to collect MRD data while also addressing several practical challenges to collecting and interpreting these complex data. When FDA-approved tests for MRD become available, these tests should be incorporated as discrete response options for MRD. As testing capabilities for MRD continue to evolve and become standardized, the work group recommended that CIBMTR continue to evaluate how best to capture these data.
- Refinement of information collected by CIBMTR should include the removal of information that has become obsolete or no longer used for the CSA or other research.
- CIBMTR should continue to collect essential information about recipients' participation in clinical trials, including trial sponsor, study number (for national/cooperative group studies), and ClinicalTrials.gov identification number (NCT #) to facilitate data linking as appropriate and to support future research proposals about impacts of trials participation on outcomes.
- CIBMTR should complete calibration plot analyses using individual patient observed and predicted OS to better describe the 'performance characteristics' of the risk adjustment model across the full range of outcomes.

INTRODUCTION

To increase transparency and understanding of center outcomes reporting in HCT, CIBMTR began in 2008 to hold Center Outcomes Forums at least biannually. CIBMTR invites representatives of the HCT community, including transplant physicians and center directors, the ASTCT, FACT, governmental funding agencies, patients, private payers, and statisticians. The purpose is to review the current approach to the Center-Specific Survival Analysis (CSA) and to provide meaningful recommendations for future reports. Summaries of these meetings and presentations are available on the CIBMTR website.

Participants included a broad range of invited stakeholder participants (Appendix A) and work group members (Appendix B) who presented recommendations. A summary of the group discussion and recommendations from this meeting follows.

BACKGROUND AND INITIATIVE UPDATES

Brief overview CSA 2023

An important function of the Center Outcomes Forum is to review the CSA and provide recommendations for improvement. It is essential that CIBMTR continue to collect relevant and updated patient, disease and transplant characteristics for use in the risk-adjustment models. Additionally, because this publicly available report has a high impact for the HCT community, it is important to periodically review the statistical modeling methodology to maintain accountability and transparency.

Details about the report methodology, including modeling to test for COVID impacts in previous reports, can be found on the CIBMTR website. The 2023 CSA Report was reviewed.

The 2023 analysis and report included more than 25,532 patients at 178 US centers who received a first allogeneic HCT between January 1, 2019, and December 31, 2021; 4 centers (~553 pts) were removed from the report because of quality concerns identified during audits.

The 2023 multivariate risk adjustment model is similar to 2022, except for the following:

- Variable additions:
    - Previous solid organ transplant
    - Categorization of AML using ELN 2022[1]
    - ALL cytogenetic/molecular risk stratification updated and based on Lazaryan[2]
    - Updated "other acute leukemia" categories and disease status
    - Distinct disease category for bone marrow failure syndrome
- Variables removed:
    - Therapy-related AML and MDS were not statistically significant and, therefore, not included
    - Ph+ ALL was included in the updated ALL risk stratification, rather than as an individual variable

The full list of variables tested in the 2023 CSA, and the variables included can be found in the 2023 report, and the 2023 methodology.

Like previous years, among the 178 US centers included in the report, 154 (86%) centers were performing as expected, while 12 (7%) centers performed above expected, and 12 (7%) performed below expected.

Discussion

There were a few questions about the lack of inclusion of Measurable Residual Disease (MRD) for AML and ALL in the multivariate models. CIBMTR did use information collected about MRD pre-transplant to calculate MRD for AML and ALL for evaluation in the risk-adjusted model. However, these variables, based on the best available information collected from centers, were not statistically significant and were not included. This may be related to limitations in the level of detail about MRD currently collected by CIBMTR (see Work Group 2 topic, below). CIBMTR will continue to make relevant adjustments in information collected about MRD and continue to test MRD in subsequent Center-Specific Survival Analyses.

Initiatives to evaluate impacts of public reporting of Center-Specific Survival

Discussion at the 2018 Center Outcomes Forum regarding the consequences of public outcomes reporting led to a recommendation CIBMTR collaborate with ASTCT, FACT and interested investigators to conduct research to better understand the impacts of public reporting of center-specific survival on the practice of HCT. A broad range of research questions of interest were outlined[3].

> *Research could better define groups of patients at high risk of poor outcomes after HCT and variability in outcomes across US HCT centers. For centers that implement FACT corrective action plans, the impacts on short-term and long-term outcomes can be described. There was interest in exploring whether public reporting of center-specific survival has adversely influenced access or the types of patients undergoing HCT in the US. Analysis of enhanced datasets on selected cohorts of HCT recipients, perhaps derived from clinical trials or PRO*

studies, could lead to a better understanding of unexplained/unmeasured sources of variability in center outcomes modeling to improve future data collection.

Although public reporting of outcomes in healthcare are intended to promote quality improvement, in general, studies in various settings have demonstrated mixed results. Public reporting of survival at US HCT centers may have implications for patients, centers, and payers and may impact how centers select patients for HCT, transplant volumes, and HCT outcomes. Several studies have been proposed since the 2018 Center Outcomes Forum and two studies have been completed through CIBMTR Working Committees. One study has been published[4], and one study was presented at ASH 2023[5].

Impact of public reporting of CSA on patient volumes[4]

The central hypothesis of this study was a change in CSA score (performance below expected, as expected, or above expected) is associated with a change in patient volume at the index center in the same direction (i.e., negative score decreases volume, positive score increases the volume or has no change) while changing volumes at surrounding centers in the opposite direction. A few mechanisms for changes in volumes were proposed. In response to public reporting of survival below expected, such a center may be reluctant to select patients recognized to be at greater risk of worse outcomes, believing avoidance of these patients may improve outcomes at the center. Centers with performance below expected may note reduced patient volumes in subsequent years because of adverse insurance contract changes or because some patients may choose alternate centers with better performance. Changes in insurance contracts with centers performing below expected may lead to smaller patient volumes, financial losses, and loss of clinical expertise.

The study included 91 centers included in public reporting of survival in the US between 2012 and 2018; 68 of these centers experienced a change in performance at least once during the interval. Centers with newly reported under-performance experienced an 8-9% reduction in the mean volume of HCT patients in the subsequent year after adjusting for the previous year's volume. The effect persisted for up to 2 years after being classified as underperforming. Being a neighbor to a center with performance below expected was associated with a 3.5% increase in mean patient volume in the subsequent year. The study did not have the information necessary to identify the cause of volume changes.

Impact of public reporting of CSA on patient selection[5]

This study hypothesizes US centers with a new report of performance below expected in the CSA will systematically transplant fewer patients with a high risk of mortality in the subsequent years compared to other US centers performing as expected or above expected. It addresses a potentially important question regarding access to HCT. Some centers may be concerned that performing transplants for patients at high risk of adverse outcomes leads to performance below expected in the CSA report, despite risk adjustment. In response to performance below expected, these centers may intentionally avoid patients with adverse risk characteristics, effectively reducing access to HCT.

Patient risk characteristics in the 3 years following a 'new' performance rating below expected at a total of 24 centers over five 1-year cohorts were compared to 35-43 control centers where performance was as predicted for a similar 6-year period. Baseline patient risk characteristics were compared to behavior in response to under performance in these centers, where risk characteristic trends among centers with no change in performance across an entire 6-year period represented the control group. Risk characteristics included predicted 1-year survival, age >60, race, HCT CI and comorbidity, advanced disease, preparative regimen intensity, and use of mismatched grafts. Centers were the unit of comparison.

Results suggest centers with new performance below expected do not significantly change their patient selection practices in ways that differ from the control centers whose performance did not change

during the cohort period. There were no significant differences in the changes in predicted 1-year OS from the risk adjustment model at newly underperforming centers in the subsequent 3-year time period compared to the control centers. Similarly, there were no significant differences in changes in risk characteristics outlined above between newly underperforming centers in the subsequent 3 years and the control centers. These findings suggest newly underperforming centers do not selectively avoid patients with high-risk characteristics following achieving below expected performance compared to control centers. Further, overall survival improved in both groups of centers, suggesting underperforming centers may have taken action to improve processes and practices.

Discussion

Participants were enthusiastic that CIBMTR is researching the impacts of public reporting and generally encouraged by the results regarding patient selection.

UPDATING PROCESSES FOR SCIENTIFIC INPUT TO SUPPORT RISK ADJUSTMENT AND COMMUNICATION ABOUT RISK MODELING (WORK GROUP 1)

Background

This work group was formed to make recommendations to address two key questions:

1. *What revisions should CIBMTR consider making to current processes to collect recommendations about data (especially disease-specific) to be used in risk adjustment for the CSA? This is essential to maintain up-to-date and relevant risk adjustment.*
2. *What (if any) additional approaches to communication should be made by CIBMTR to inform relevant stakeholders about the CSA and ongoing changes to risk adjustment?*

Current processes were presented; they are available on the CIBMTR website. CIBMTR uses several venues to collect suggested revisions to the data collection to support the risk adjustment used in the CSA. CIBMTR has a formal process to revise the information collected on a regular basis. All "essential" information collection is reviewed and potentially revised on a regular basis with participation by physicians and subject matter experts from Working Committees, statisticians, clinical research professionals, and CIBMTR staff. Clinical research professionals from participating centers are purposefully included to address issues of data attainability and burden. Aside from the standard revision process, other venues include ad hoc engagement of Working Committee leadership, annual polling of CIBMTR Scientific Directors associated with the review of the CSA report, public discussion and feedback during the Center Outcomes Forum, formal input from the ASTCT Committee on Quality Outcomes, and ad hoc suggestions from transplant center physicians and data professionals. Guiding principles about data collection were reviewed. Data elements must be discrete, unambiguous, readily obtained to achieve completeness and high quality without undue burden, and universally used in clinical care across centers.

Initial Work Group Recommendations and Discussion

Question 1: **What revisions should CIBMTR consider making to current processes to collect recommendations about data (especially disease-specific) to be used in risk adjustment for the CSA? This is essential to maintain up-to-date and relevant risk adjustment.**

To maintain up-to-date and relevant risk adjustments for the CSA, the work group made suggestions for CIBMTR to consider about its current processes for collecting recommendations about data, especially disease-specific data.

1. Stakeholder Engagement: Continue to interact proactively with essential stakeholders such as clinicians, researchers, statisticians, data professionals, and center administrators using established channels like the ASTCT Committee on Quality Outcomes and CIBMTR's Working Committees. Consistent dialogue with participants from these groups can yield suggestions about additional information to collect that may enhance the model and provide valuable feedback about attainability. It may be beneficial to systematically request this input on an annual basis. This could be coordinated through the Committee on Quality Outcomes.
2. Open Forum to Solicit Feedback – In-Person Session at Tandem: Establish an active mechanism to elicit feedback directly in person at Tandem. Such a session could include a focused review of the current CSA report and address questions (solicited in advance and/or from in-person attendees). The audience for this session should, where practical, include a range of stakeholders including transplant center directors.

   Discussion:

   There was an acknowledgment that CIBMTR already has several effective venues to systematically collect suggestions about information collection from a range of stakeholders. The work group initially proposed the use of a web-based tool/online "suggestion box." Several challenges were raised, including the administrative burden of collecting and responding to requests, the likelihood of repetitive suggestions, and concerns about effective communication about ideas in this format. Following discussion, the group advised against the use of an open feedback tool on the CIBMTR website, favoring use of existing forums with adjustments to ensure regular review and to provide a venue at Tandem that includes center directors.

Question 2: What (if any) additional approaches to communication should be made by CIBMTR to inform relevant stakeholders about the CSA and ongoing changes to risk adjustment?

The work group presented communication approaches CIBMTR can consider to better inform relevant stakeholders about the CSA and ongoing changes to risk adjustment. These suggestions will help foster collaboration, promote transparency, and further ensure that all stakeholders can be well-informed and engaged in the process.

The work group presented several approaches to consider:

1. Simplified communication: CIBMTR can improve its communication strategy by introducing a streamlined summary of CSA report updates, including risk adjustment variables and methodology. The proposed "Key Highlights" section could comprise a limited number of succinct bullets that outline the essential changes from previous versions or important new information. This section should also direct readers to further details, ensuring they have access to comprehensive information as needed.
2. Brief Newsletter about the CSA Released at the End of the Calendar Year: This newsletter should be published prior to the release of the CSA. The newsletter could include the "Key Highlights," summarizing essential findings from the CSA, highlighting changes to risk adjustment models, and sharing important updates for the next year's analysis cycle. These newsletters could be distributed to all stakeholders, including participating centers, clinicians, administrators, payers, and researchers.
3. Webinars and Sessions at Tandem: CIBMTR may consider hosting/recording an annual webinar to discuss updates to the CSA before the release of the report. Additionally, as outlined previously, an interactive education session about the CSA report at the Tandem Meetings would provide stakeholders with the opportunity to pose questions and interact directly with CIBMTR.

4. Online Portals and Resources: CIBMTR has developed several tools for centers hosted on its secure portal that are updated annually concurrent with the publication of the CSA report. However, many centers may not know about them, and they may be under-utilized. There may be opportunities to increase awareness of the CIBMTR online portal/website and collect feedback from users about ease of use or suggested revisions.
5. Inclusion of Patients and Families: There may be an opportunity to expand the CIBMTR CSA newsletter to include a section designed for patients and their families. By doing so, CIBMTR can transparently communicate the steps undertaken to maintain data integrity, underscoring our commitment to the accuracy and security of the information we manage. This initiative will also recognize and engage patients as essential stakeholders in our data-sharing efforts.
6. Misconceptions regarding the CSA: There may be misunderstandings among center physicians about how "high-risk" patient and disease characteristics are handled in the risk adjustment model. These misunderstandings might adversely affect patient selection decisions. To address this, CIBMTR could consider creating an educational presentation like its summary slides. This resource could be made accessible on the CIBMTR website, allowing individuals to download it and use it as a tool to educate their colleagues about the CSA's methodology, the latest updates and the model specifics for the current year.

Other Suggestions

1. Surveys and Feedback Mechanisms: CIBMTR could conduct periodic surveys to gather feedback from stakeholders about their communication preferences and the effectiveness of current communication strategies. The feedback can be used to refine communication strategies.
2. Communication with payers relevant to the report, which may influence their policies: Several individuals expressed the importance of bilateral communication between CIBMTR and payers, health plans, etc. This could be accomplished through the ASTCT Carrier Advisory Committee.

Discussion

Attendees generally agreed the current CSA report is a thorough, clear, and detailed foundation for communication. CIBMTR currently provides educational tools that are readily accessible to the HCT community through its public website, including a detailed description of the analytic methodology, included variables and an FAQ that are updated annually. However, stakeholders' understanding of the report, including risk factors analyzed, analytic methodology, and meaning of results remains variable. There was strong agreement about additional opportunities to provide simplified tools to educate various stakeholder groups on these basic topics, and several of the suggestions of the work group were strongly endorsed, including the introduction of "Key Highlights," recorded webinars and other educational materials. There was also support to provide an in-person session at the Tandem Meetings, recognizing the practical challenge of finding an appropriate time/venue within the meeting footprint essential stakeholders can attend.

Final Recommendations

Getting input about the data collection

- CIBMTR should continue to leverage its Working Committees and other existing forums and processes, such as the ASTCT Committee on Quality Outcomes and ASTCT Center Administrative Directors SIG, to solicit recommendations to update information collection used for risk adjustment. These should occur on a scheduled basis through formal processes.

- An information/education session at the Tandem Meetings, as outlined in "Communication about the analysis and risk adjustment model" section, will likely generate suggestions about data collection from stakeholder groups.

Communication about the analysis and risk-adjustment model

- CIBMTR should publish a simplified 1-page summary of the CSA report that highlights changes in the risk adjustment model and provides overall center results. This summary could serve as a cover page to the full report.
- CIBMTR should maintain current educational tools that explain the CSA risk-adjustment model, address common misunderstandings about the analysis and consider providing additional tools such as a recorded webinar(s) on the CIBMTR website.
- CIBMTR should consider hosting an information/education session during the Tandem Meetings to provide key updates about the CSA, including updated risk adjustment, analysis findings, and future plans. Invitees could include center medical and administrative directors, FACT, ASTCT Committee on Quality Outcomes, payers, and data professionals. The primary purpose of this session would be educational but would also generate feedback from the HCT community.
    - This session could be recorded and made available on the CIBMTR website.
    - Questions could be solicited in advance to facilitate broad engagement.
- CIBMTR should take opportunities to remind centers about quality improvement tools available on the CIBMTR Portal, including the 1-year survival calculator and individual center datasets.
- CIBMTR should test the feasibility of adding the individual patient-level "predicted OS" generated from the risk adjustment model to individual center datasets.

RISK ADJUSTMENT IN AML, ALL AND MDS (WORK GROUP 2)

Background

A second work group was asked to recommend ways to optimize current risk adjustment by disease based on currently collected data and ways to update data collection to inform near-term future risk adjustment. They addressed these key questions:

1. *What additional information already collected by CIBMTR should be used for disease-based risk adjustment for AML, ALL, and MDS?*
2. *Should CIBMTR begin to use MRD as a risk adjustment in AML and ALL, and if so, what criteria should be used to define MRD?*
3. *What changes in data collection are recommended soon to improve risk adjustment for AML, ALL, and MDS while being respectful of practical issues related to data collection at centers?*

The group reviewed what CIBMTR currently collects for the various indications; details can be found in Appendix C.

Approach to Disease Classification

The process of adjusting risk is based on the patient's disease and subtype (per WHO 2016 Classification) and supporting data collected on the 2402 form. Laboratory data includes cytogenetic (karyotyping and FISH) and molecular information collected at diagnosis, directly before transplantation and at a time point in between. Assignment to a risk category in the 2023 CSA report used algorithms based on the European Leukemia Net (ELN) 2022 guidelines for AML[1], Lazaryan et al. for ALL[2], and the IPSS-R for MDS[6]. The work group generally agreed with the approach used for disease-based risk adjustment for the 2023 CSA.

In 2022, the classification of these diseases and subtypes was updated by the WHO[7,8]. Additionally, the International Consensus Classification (ICC; [9]) released classification guidelines in 2022 that, while similar, do not completely align with the WHO 2022 classification. A preferred classification schema has not emerged from the AML community. Compared to previous versions, the new WHO schema stresses the importance of genetic and molecular data for disease classification. Most, but not all, of the information necessary to assign WHO classification is available on the current 2402 form. For data not requested as a discrete field, data professionals can enter additional information in "Specify, other" fields, acknowledging this approach may lead to under-reporting of mutations not specifically requested.

The work group strongly emphasized the critical importance of maintaining data collection that is current with contemporary scientific standards. This becomes more important as the pace of scientific discovery continues to accelerate, and standards are frequently updated.

Recommendations included the following:

1. Disease classification using the WHO 2022 system is highly recommended. When possible, it is recommended that data needed to assign ICC classification is also collected.
2. The cytogenetic and molecular mutation information collection should be updated to include discrete fields that reflect the data required for WHO and, where possible, ICC classification. Specific attention should be paid to collecting TP53 mutation status for all relevant diseases.
3. CIBMTR should collect data necessary to calculate the IPSS-M for MDS. While this new scoring system represents ongoing evolution in defining risk for patients with MDS, a few challenges were noted. This system is currently designed to assign prognosis at diagnosis and may not account for dynamic changes that occur between diagnosis and HCT. Further, data to be provided by centers to support IPSS-M is more complex. This topic will be discussed further with the Chronic Leukemia Working Committee leadership.

Other Disease-Related Factors

In addition to the disease-based risk classification recommendations described above, there were recommendations for several variables included as risk adjustment in recent CSA reports:

1. **ALL, AML, and MDS: Disease status**
   Recommendation: Currently, disease status for ALL or AML is categorized as primary induction failure, 1st complete remission (CR), 2nd CR, ≥3rd CR, 1st relapse, 2nd relapse, ≥3rd relapse, or no treatment. Disease status for MDS is categorized as CR, hematologic improvement, No response/stable disease, Progression from hematologic improvement, Relapse from CR, or Not assessed. With newer AML therapies, it is likely CR with partial hematologic recovery will be reported more often. Therefore, it is recommended that options for disease status be expanded to reflect the ELN 2022 response criteria for AML[1], the International Working Group for High-risk MDS 2023 response criteria (when finalized)[10], and the Pediatric International Consortium for ALL[11].
2. **AML: Transformation from MDS/MPN**
   Recommendation: The updated WHO 2022 classification now considers "AML transformed from MDS" in the category of "Acute myeloid leukemia, myelodysplasia-related," with a defined list of genetic abnormalities or cytogenetic changes commonly found. It is likely that "AML, transformed from MDS" will not be needed as an independent factor in future analyses. CIBMTR should update its information collection systems to reflect these changes.
3. **AML: Number of induction cycles for AML in the first complete remission**

Recommendation: New lower toxicity treatment strategies for AML induction have changed definitions of treatment cycles and their duration. It is recommended that time from diagnosis to first complete remission be captured and evaluated as a significant risk factor in future analyses. The date that first complete remission is achieved should be added to the data collection to facilitate this analysis.

4. **AML: Time from diagnosis to transplant for AML in relapse or in CR2 or higher.**
   Recommendation: This variable was identified as a potential surrogate for the duration of CR. No specific recommendations were made.
5. **ALL: Number of induction cycles for ALL in first complete remission**
   Recommendation: This has been retained in the 2023 CSA model due to clinical but not statistical significance and should continue to be evaluated in future models.
6. **ALL: Time from diagnosis to transplant for ALL in relapse or in CR2 or higher**
   Recommendation: This has been included in recent CSA models. No specific recommendations were made.
7. **MDS: MDS with a predisposing condition**
   Recommendation: The WHO 2022 classification has categorized these diseases as myeloid neoplasms associated with germline predisposition. CIBMTR should update its data collection to reflect this change and future analyses incorporate this disease classification when appropriate.
8. **MDS: MDS, therapy-related**
   Recommendation: The WHO 2022 classification states that these neoplasms should be classified based on the most specific pathologic diagnosis available. A designation of "post cytotoxic therapy" should be made based on clinical history. Although this variable is already evaluated in the CSA, it is recommended that the data collection be updated to reflect this change.

Measurable Residual Disease (MRD)

The importance of MRD is well established in ALL and its role in AML is becoming more defined[12]. The work group recommended collecting the date when MRD negativity was first achieved following the initial diagnosis. Testing options for MRD continue to expand, and with that, it becomes more challenging for centers to accurately report complex MRD results. Members voiced concerns that data professionals have difficulty distinguishing routine clinical test results from purpose-specific MRD testing (e.g., flow cytometry results). Some methods of MRD testing (e.g., NGS myeloid panels) require advanced knowledge to appropriately interpret results. Misunderstandings between routine disease testing and genuine MRD testing or misinterpretation of results could lead to inaccurate reporting of clinical remission status or MRD status.

A prior Center Outcomes Forum work group developed questions to assess MRD, which were reviewed by this work group. The consensus was that, in the short term, questions should be directed towards acquiring the MRD status for an individual patient based on the determination of the treating physician and the testing method used. That assessment is commonly reported in patient notes.

Recommendation:

1. Consider adding: "Was the patient considered to be MRD positive, MRD negative or was it not assessed?
2. ClonoSEQ is currently the only FDA-approved test for MRD in ALL. Consider adding a question asking whether ClonoSEQ was performed and, if so, the result.

Discussion

Participants expressed strong agreement maintaining data collection current with international consensus organizations and the scientific literature is essential to appropriate risk adjustment for these diseases. This includes disease classification systems, disease- and risk-defining genetic mutations, methods of disease detection (MRD) and other evolving prognostic factors. The CIBMTR risk adjustment approach using currently available data is appropriate. There was considerable discussion about the best approach to disease risk adjustment for patients with MDS. CIBMTR is currently using the IPSS-R status at transplant for risk adjustment; specifically, blood and blast counts at HCT and cytogenetics at diagnosis are used to calculate the IPSS-R at HCT. Several CIBMTR studies demonstrate the prognostic significance of this approach. Some members acknowledged this may "under-estimate" disease status since intercurrent treatment between diagnosis and transplant may modify the disease status and IPSS-R score at HCT. One possible future approach is to use the raw data for each element of the IPSS-R to calculate a "dynamic" variable for the worst disease status between diagnosis and HCT. However, elements to calculate IPSS-R are only collected at diagnosis and HCT on the current 2402 form. There was interest in beginning to use IPSS-M once the data are available in future CSA cohorts. As expected, there was strong support for critically reviewing the information collection to remove any obsolete data elements or those not used by CIBMTR.

The limitations of current data about MRD and challenges to collecting complete and accurate MRD data in the future were highlighted. There was strong agreement about the prognostic value of MRD in ALL, and acknowledgement that its value in AML is still being proven and unknown for MDS. Nonetheless, participants agreed that CIBMTR should continue to collect MRD status as best as possible and continue evaluating MRD as a risk factor in the CSA. Cytogenetic or FISH methods of detecting MRD, as currently collected by CIBMTR, are likely representative of gross/morphologic disease rather than CR with MRD. The debate centered on the importance of collecting relevant MRD information from centers while recognizing the burden and limitations. There is considerable heterogeneity of testing methods and sensitivity in use, utilization across centers, incorporation of discrete data in EMRs, and expertise of data professionals to interpret and report results accurately. CIBMTR should continue to revise information collection to include MRD status at HCT for patients in morphologic remission at HCT, including the level of sensitivity of testing methods, particularly for flow cytometry. The education of data professionals is important to improving data completeness and quality, and efforts to capture such data directly from EMR or lab information systems should continue in the future.

Participants expressed universal agreement maintaining data collection current with international consensus organizations and the medical literature is essential to appropriate risk adjustment for these diseases. This includes disease classification systems, disease- and risk-defining genetic mutations, methods of disease detection (MRD) and other evolving prognostic factors. CIBMTR should integrate recent (2022 and 2023) changes to disease classification as soon as possible and make frequent adjustments as disease classification evolves. Further, it should keep response options for genetic mutation risk factors like TP53 updated as close to real-time as possible. It is important to capture genomic data with clear, discrete response options to avoid ambiguity and set the stage for future automated data capture using data standards. A pragmatic approach to data collection and robust training tools for data professionals must also acknowledge the difficulties of capturing these complex and sometimes nuanced data.

The pace of scientific discovery of risk factors, particularly genetic risk factors, continues to accelerate, and CIBMTR will need to expedite its data revision process and streamline, where possible, the review and approval process required by the US Government to keep pace.

Final Recommendations

- Data collection should continue to reflect modern classification and risk assignment of hematologic malignancies as published by WHO and other international consensus groups. The work group strongly recommended updating to the WHO 2022 classification as well as updating the cytogenetic, FISH and molecular data that is used to assign the correct classification as soon as possible.
- CIBMTR data collection tools should continue to be updated to reflect modern disease response criteria (i.e., incorporating MRD status for AML and ALL, recently updated response criteria for MDS). Specific recommendations were provided for several disease-related factors, including genetic mutations and treatment-related variables.
- CIBMTR should continue to collect MRD data while continuing to address several practical challenges to collecting and interpreting these complex data. When FDA-approved tests for MRD become available, these tests should be incorporated as discrete response options for MRD. As testing capabilities for MRD continue to evolve and become standardized, the work group recommended CIBMTR continue to evaluate how best to capture these data.
- Refinement of information collected by CIBMTR should include the removal of information that has become obsolete or no longer used for the CSA or other research.

HANDLING SUBJECTS CLINICAL TRIALS PARTICIPATION TO INFORM FUTURE ANALYSES INVOLVING TRIALS-BASED CARE (WORK GROUP 3)

Background

A third work group was formed to recommend relevant information CIBMTR can collect about clinical trials participation, types of trials and other relevant information to be used to test hypotheses about participation in trials and impacts on outcomes. They addressed these key questions:

1. *Should CIBMTR collect specific information about patients' participation in transplant-related clinical trials to inform future analyses about the impact of trials-based care on clinical outcomes?*
2. *What specific types of information should be collected by CIBMTR for this objective? What barriers must be overcome?*
    a. *Phase of trial development?*
    b. *Type of intervention (e.g., directly related to transplant procedure (prep regimen, graft source/manipulation, GVHD prophylaxis), supportive care, treatment of early complications, or other)?*
    c. *Identify discrete, unambiguous, and readily available data that can provided by centers to achieve this objective*
3. *Beyond traditional patient-, disease-, and transplant- characteristics, should CIBMTR test information related to clinical trial participation for inclusion in future center-specific risk adjustment models?*
    a. *Are there potential negative consequences that can be anticipated?*

i. *Could this introduce patient participation bias or bias related to unequal distribution of center participation in certain types of trials?*

Since the expansion of the Center-Specific Survival Report to include all first allogeneic HCT in 2010, there have been intermittent concerns expressed by the HCT community that publicly reporting outcomes could cause reluctance of some centers to offer innovative clinical trials to patients with "high risk" of poor outcomes. Such trials may be intended to expand the benefits of HCT to patients with aggressive diseases who might not otherwise receive a transplant. Because there are negative consequences to centers who perform below expected in the CSA, centers may avoid performing HCT in "high-risk" patients, particularly on an early phase trial, because of concerns the predicted survival of these patients will not be accurately represented in the risk adjustment model. This topic is important as the HCT community and other major stakeholders (payers, HRSA) increasingly focus on improving access to HCT. Further, there is substantial academic interest in advancing scientific discovery in HCT, and perceived negative consequences of the CSA could constrain development and accrual to innovative clinical trials. These considerations are further confounded because the approach to modeling center outcomes intentionally avoids adjusting for center-based decisions about HCT since those decisions are inherent to a center's quality.

Previous discussions at the Center Outcomes Forum, with input from the ASTCT Committee on Quality Outcomes and other groups did not reach actionable recommendations to fairly represent or define appropriate early-phase trials for "high-risk" patients for special consideration.

Discussion

Participants debated whether care delivered in clinical trials impacts quality or outcomes compared to patients who receive standard care. A few members suggested that trials-based care may even negatively affect outcomes, though the consensus was trials-based care had no impact or minimal positive impact on outcomes [13].

CIBMTR collects limited information about patients' participation in clinical trials for the observational database, particularly focused on intervention trials and those with a ClinicalTrials.gov number.

Centers' concerns the CSA risk adjustment model may not adequately account for the full spectrum of expected outcomes emerged as the fundamental issue underlying requests to adjust for clinical trial participation. Centers are most concerned the risk adjustment model may not adequately capture patients at risk for poor survival, and if their predicted survival is over-estimated, the centers will be disadvantaged in the CSA report. Suggestions were made to capture information about patients receiving HCT on clinical trials "who would not otherwise receive a transplant" if such a trial were not available. Unfortunately, this concept is very difficult to capture in a discrete and consistent way across centers and was considered not practical.

There is no clear reference standard by which CIBMTR can benchmark the expected outcomes derived from its analytic methodology for the range of patients who receive transplantation. However, some tools were discussed to better describe the performance of the risk adjustment model, including calibration plots of predicted and observed survival. Including the predicted OS for each patient included in the analysis as part of individual centers' datasets made available on the CIBMTR Portal could be an important quality improvement tool for centers and increase transparency. Centers could use patient-level comparisons of actual and predicted survival for quality improvement, and the predicted survival for patients across the risk spectrum would be more apparent.

Subsequent conversations focused on other purposes and practical challenges of collecting additional information about trial exposure for HCT recipients. Patients may participate in trials whose

experimental focus is not the transplant or transplant-related complications–these trials are less likely to influence survival outcomes. There was agreement the most essential information to collect about study participation is the study sponsor, trial number and ClinicalTrials.gov study identifier. This information can be used, as appropriate, for linking observational data with data collected for the trial and to categorize subjects' study participation for future research objectives that could include the impacts of trial participation.

Most participants agreed that CIBMTR should continue its focus on maintaining an updated collection of risk factors to support the risk adjustment model (see Work Group 2 recommendations). Increased communication about these efforts, and how they are integrated in the CSA (see Work Group 1 recommendations) can help increase the confidence of centers in the process and the results. Sharing model calibration and results of CIBMTR research about the impact of public reporting of center outcomes will also be valuable to increase transparency.

Recommendations

- CIBMTR should maintain its consistent focus on updating patient, disease, and transplant risk factors necessary to support high-quality risk adjustment in the CSA, including recommendations outlined in Work Group 2.
- CIBMTR should continue to collect essential information about recipients' participation in clinical trials, including trial sponsor, study number (for national/cooperative group studies), and ClinicalTrials.gov identification number (NCT #) to facilitate data linking as appropriate and to support future research proposals about impacts of trials participation on outcomes.
- CIBMTR should complete calibration plot analyses using individual patient observed and predicted OS to better describe the 'performance characteristics' of the risk adjustment model across the full range of outcomes.
- CIBMTR should incorporate individual patient's predicted OS estimate in the dataset shared with centers on the CIBMTR Portal as another tool to support centers' quality improvement efforts and increase the visibility of predicted survival across clinical risk scenarios.

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APPENDIX A: ATTENDEES OF 2023 CENTER OUTCOMES FORUM

Full Name	Organization	Representation	Registered	Attended
Andre Williams	ASTCT	ASTCT	X	
Navneet Majhail, MD, MS	Sarah Cannon Transplant and Cellular Therapy Program at TriStar Centennial Medical Center	ASTCT QOC/Adult	X	X
Dianna Howard, MD	Wake Forest Baptist Health	ASTCT QOC/HCT Ctr-Adult	X	X
Christopher Dandoy, MD, MS	Cincinnati Children's Hospital Medical Center	ASTCT QOC/HCT Ctr-Peds	X	X
Jeffery Auletta, MD	NMDP	CIBMTR ScD	X	X
Steven Devine, MD	NMDP	CIBMTR ScD	X	X
Kristin Page, MD	CIBMTR - Milwaukee	CIBMTR ScD	X	X
J. Douglas Rizzo, MD, MS	CIBMTR - Milwaukee	CIBMTR ScD	X	X
Stephen Spellman, MBS	CIBMTR - Minneapolis	CIBMTR ScD	X	X
Patricia Steinert, PhD, MBA	CIBMTR - Milwaukee	CIBMTR ScD	X	X
Leslie Lehmann, MD	Dana-Farber Cancer Institute - Peds	CSA Research TF	X	X
Akshay Sharma, MBBS	St. Jude Children's Research Hospital	CSA Research TF	X	X
Mark Juckett, MD	University of Minnesota Blood and Marrow Transplant Program - Adults	CSA Research TF, HCT Ctr-Adult	X	
Tonya Cox	Sarah Cannon Transplant and Cellular Therapy Program at TriStar Centennial Medical Center	Ctr Admin	X	X
Gary Goldstein	Stanford Health Care	Ctr Admin	X	
Stephanie Lee, MD, MPH	Fred Hutchinson Cancer Center	HCT Ctr-Adult	X	
John Levine, MD, MS	Mount Sinai Medical Center	HCT Ctr-Adult	X	X
Richard Maziarz, MD	Oregon Health and Science University	HCT Ctr-Adult	X	X
Joseph McGuirk, DO	University of Kansas	HCT Ctr-Adult	X	X
Michael Rabin	City of Hope	HCT Ctr-Adult	X	X
Amelia Scheck	Stanford Health Care	HCT Ctr-Adult		X

Full Name	Organization	Representation	Registered	Attended
Bart Scott, MD	Fred Hutchinson Cancer Center	HCT Ctr-Adult	X	X
Brian Shaffer, MD, MS	Memorial Sloan Kettering Cancer Center - Adults	HCT Ctr-Adult	X	X
Robert Soiffer, MD	Dana-Farber Cancer Institute - Adults	HCT Ctr-Adult	X	X
Amir Steinberg, MD	Westchester Medical Center	HCT Ctr-Adult	X	X
Keith Stockerl-Goldstein, MD	Barnes Jewish Hospital	HCT Ctr-Adult	X	X
Christopher Strouse, MD	University of Iowa Hospitals & Clinics	HCT Ctr-Adult	X	X
Geoffrey Uy, MD	Barnes Jewish Hospital	HCT Ctr-Adult		X
Edmund Waller, MD, PhD	Emory University Hospital	HCT Ctr-Adult	X	X
John Wingard, MD	Shands HealthCare & University of Florida	HCT Ctr-Adult	X	X
Joycelynne Palmer, PhD	City of Hope	HCT Ctr-Adult, PhD Stats	X	
Firas El Chaer, MD	University of Virginia Health System	HCT Ctr-Adult, WC	X	X
Selina Luger, MD	Abramson Cancer Center University of Pennsylvania Medical Center	HCT Ctr-Adult, WC	X	X
Stella Davies, MBBS, PhD, MD, BS	Cincinnati Children's Hospital Medical Center	HCT Ctr-Peds	X	X
Leslie Kean, PhD	Boston Children's Hospital	HCT Ctr-Peds	X	X
Michael Verneris, MD	Children's Hospital Colorado	HCT Ctr-Peds	X	X
Michael Grunwald, MD	Levine Cancer Institute	Med Dir	X	
Robert Lisac, MD	Organization/Center information not available	Patient Advocate	X	X
Alberto Santos III, DO, MBA, MS	Aetna	Payer	X	
Julie Walz	Humana	Payer	X	X
Kristy Warren	Humana	Payer	X	X
Michelle Williams	BCBSA	Payer	X	X
James Bowman, MD	Health Resources & Services Administration	Gov't staff (HRSA)	X	X
Marilyn Levi, MD	Health Resources & Services Administration	Gov't staff (HRSA)	X	

Full Name	Organization	Representation	Registered	Attended
Nawraz Shawir, MBBS	Health Resources & Services Administration	Gov't staff (HRSA)	X	X
Shannon Taitt, MPA	Health Resources & Services Administration	Gov't staff (HRSA)	X	
Nancy DiFronzo, PhD	NIH - NHLBI Government agency partners	Gov't staff (NIH)	X	
Kwang Woo Ahn, PhD	CIBMTR - Milwaukee	CIBMTR PhD Stats	X	X
Brent Logan, PhD	CIBMTR - Milwaukee	CIBMTR PhD Stats	X	X
Michael Martens, PhD	CIBMTR - Milwaukee	CIBMTR PhD Stats	X	X
Mei-Jie Zhang, PhD	CIBMTR - Milwaukee	CIBMTR PhD Stats	X	X
Jesse Troy, PhD, MPH	Duke University Medical Center; Pediatric Blood and Marrow Transplant	PhD Stats	X	
Jenni Bloomquist, BA, MS	CIBMTR - Minneapolis	MSP Staff	X	X
Sue Logan, BS	CIBMTR - Minneapolis	MSP Staff	X	X
Meggan McCann, MPH	CIBMTR - Minneapolis	MSP Staff	X	
Jaime Preussler, MS	CIBMTR - Minneapolis	MSP Staff	X	X
Mandi Proue, MPH	CIBMTR - Minneapolis	MSP staff	X	X
Mary Senneka	NMDP	MSP Staff	X	X
Gregory Sides, BS	CIBMTR - Minneapolis	MSP Staff	X	X
Mariam Allbee-Johnson, MPH	CIBMTR - Milwaukee	MKE Staff	X	X
Sharniece Covill, BS	CIBMTR - Milwaukee	MKE Staff	X	X
Carol Doleysh	CIBMTR - Milwaukee	MKE Staff	X	X
Alicia Halfmann	CIBMTR - Milwaukee	MKE Staff	X	X
Waleska Pérez, MPH	CIBMTR - Milwaukee	MKE Staff	X	X
Charimar Santiago Parrilla, MPH	CIBMTR - Milwaukee	MKE staff	X	X

APPENDIX B: WORK GROUP MEMBERS

Updating processes for scientific input to support risk adjustment and communication about risk modeling (Work Group 1)

Full Name	Organization	Representation
Christopher Dandoy, MD, MS (chair)	Cincinnati Children's Hospital Medical Center	ASTCT QOC/Adult
Dianna Howard, MD	Wake Forest Baptist Health	HCT Ctr-Adult
Mark Juckett, MD	University of Minnesota Blood and Marrow Transplant Program - Adults	CSA Research TF
Michael Rabin,	City of Hope	HCT Ctr-Adult
Alberto Santos III, DO, MBA, MS	Aetna	Payer
Robert Soiffer, MD	Dana-Farber Cancer Institute - Adults	HCT Ctr-Adult
Amir Steinberg, MD	Westchester Medical Center	HCT Ctr-Adult

Risk adjustment in AML, ALL and MDS (Work Group 2)

Full Name	Organization	Representation
Kristin Page, MD (chair)	CIBMTR - Milwaukee	CIBMTR MD
Kwang Woo Ahn, PhD	CIBMTR - Milwaukee	CIBMTR PhD
Yi-Bin Chen, MD	Massachusetts General Hospital	HCT Ctr-Adult
Stella Davies, MBBS, PhD, MD, BS	Cincinnati Children's Hospital Medical Center	HCT Ctr-Peds
Firas El Chaer, MD	University of Virginia Health System	HCT Ctr-Adult
Selina Luger, MD	Abramson Cancer Center University of Pennsylvania Medical Center	HCT Ctr-Adult
Wael Saber, MD, MS	CIBMTR - Milwaukee	CIBMTR MD
Bart Scott, MD	Fred Hutchinson Cancer Center	HCT Ctr-Adult

Handling Subjects Clinical Trials participation to inform future analyses involving trials-based care (Work Group 3)

Full Name	Organization	Representation
Michael Verneris, MD (chair)	Children's Hospital Colorado	HCT Ctr-Peds
Anthony Bonagura, MD	Optum Health Services	Payer
Steven Devine, MD	NMDP	CIBMTR MD
Leslie Kean, PhD	Boston Children's Hospital	HCT Ctr-Peds
Stephanie Lee, MD, MPH	Fred Hutchinson Cancer Center	HCT Ctr-Adult
John Levine, MD, MS	Mount Sinai Medical Center	HCT Ctr-Adult
Michael Martens, PhD	CIBMTR - Milwaukee	CIBMTR PhD
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David Porter, MD	Abramson Cancer Center University of Pennsylvania Medical Center	HCT Ctr-Adult
Brian Shaffer, MD, MS	Memorial Sloan Kettering Cancer Center - Adults	HCT Ctr-Adult

APPENDIX C

CIBMTR TED-level data collected by indication (** indicates this is currently in the CSA model)

AML

- Disease subtype based on WHO (2016) ** ELN risk category (2017)
- Transform from MDS (Y/N) **
- Therapy related (Y/N) **
- Predisposing conditions (Bloom/Down/Fanconi/DKC/Other)
- Disease-specific cytogenetic and molecular markers (FISH, Karyotyping, Flow, PCR)
    - Three time points: diagnosis, in between, before prep
    - Used to confirm disease classification and MRD status
- CNS leukemia (Y/N)
- Disease status (PIF, CR1, CR2, CR3+, in relapse (#)) **
- How many induction cycles were required to achieve 1st CR? **
    - Time from CR1 to HCT for patients in CR2+ or relapse (AML/ALL) ** (surrogate for time in CR1)
- Measurable Residual Disease (MRD) questions for patients in CR at time of HCT
    - Presence of MRD and method of detection (see below)

ALL

- Disease subtype based on WHO 2016 ** Risk stratification (Lazaryan) T-cell and Ph+ status
- Predisposing conditions (SAA, Bloom, Down, Fanconi, Other)
- Prior TKI use (Y/N)
- Disease-specific cytogenetic and molecular markers (FISH, Karyotyping, Flow, PCR)
    - Three time points: diagnosis, in between, before prep
    - Used to confirm disease classification and MRD status
- CNS leukemia (Y/N)
- Disease status (PIF, CR1, CR2, CR3+, in relapse (#)) **
- How many induction cycles were required to achieve 1st CR? **
    - Time from CR1 to HCT (if AML/ALL and in CR2+ or relapse) **
- Measurable Residual Disease (MRD) questions for patients in CR at time of HCT
    - Presence of MRD and method of detection (see below)

MDS

- Disease subtype at diagnosis based on WHO 2016 **
    - Therapy related (Y/N)
    - Predisposing condition
        - SAA/DDX41/Diamond Blackfan/ Fanconi/ GATA2/ Li-Fraumeni/ PNH/ RUNX1/ SAMD9/ Shwachman/ Telomere/Other
- CBC, blasts in PB and BM and whether Hgb and Platelet counts supported by transfusion at diagnosis and HCT
- Disease specific cytogenetic (FISH, Karyotyping):
    - Two time points at diagnosis and at HCT
- Did the recipient transform to a different subtype or AML?
- Information necessary to support calculation of IPSS-R risk score at diagnosis and HCT

MRD

- Specify method(s) that was used to assess measurable residual disease status (check all that apply)
    - FISH/Karyotyping/Flow/PCR/NGS/Not assessed
- Was measurable residual disease detected by…
    - FISH (Y/N)
    - Karyotyping (Y/N)
    - Flow (Y/N)
    - NGS (Y/N)