The value of reporting on end-of-treatment outcome of patients in low-income settings

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The value of reporting on end-of-treatment outcome of patients in low-income settings

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LIC Low-income country

HIC High-income country

GICC Global Initiative for Childhood Cancer

EFS Event-free survival

OS Overall survival

TRM Treatment related mortality

DRM Disease related mortality

CANCaRe Africa Collaborative African Network for Childhood Cancer Care and Research

Commentary

Progress has been made over the past decades in childhood cancer care in low-income countries (LIC) and there has been a steadily increasing focus on trained staff, medication availability and locally-adapted treatment protocols.[1,2,3] With the launch of the World Health Organization (WHO) Global Initiative for

Childhood Cancer (GICC) in 2018, there has been a much-needed increment of resources and efforts. The target of the GICC is to increase survival worldwide to 60% by 2030, with an initial focus on six common and curable ('index') childhood cancer types for which survival is currently over 85- 95% in high income countries (HIC).

In contrast, estimated overall childhood cancer survival in LICs including many countries in sub-Saharan Africa is still below 20%.[2,4] Local data on outcomes of children with cancer and impact of interventions to increase survival in LIC settings are lacking. There is an urgent need to close this survival and research gap. End points that are relevant, feasible and provide an estimate within a short time-frame may be desirable. They can serve as proxies and compliment established end points such as overall survival (OS) and event free survival (EFS) while data collection mechanisms such as cancer registries and resources for follow up are strengthened in LIC.

To identify such end points, we need to distinguish three different types of treatment failure: treatment related mortality (TRM), disease related mortality and treatment abandonment.[5] The frequency distribution and relative importance of these differ by setting In HIC settings, most treatment failure is disease related mortality (progression or relapse of disease), while TRM is less common and treatment abandonment almost non-existent.[2] In LIC settings, treatment abandonment is often common and in sub-Saharan Africa, it is frequently the most common cause of treatment failure.[2,6,7] TRM is frequently prominent as well.[8]

These different causes of treatment failure require specific and different interventions. To decrease disease related mortality, required interventions include early diagnosis and optimisation of the treatment protocol, which often translates to intensifying the treatment. To decrease TRM, required interventions may include reducing treatment intensity or improving supportive care. To decrease and prevent treatment abandonment, required interventions may include adequate counselling on the need to complete treatment, introduction of health insurance, active tracking of patients and financial support with out-of-pocket costs of families during treatment. Since these required interventions are so different, it is key to distinguish between the different causes of treatment failure. This is often challenging, especially in LIC.

Traditionally, cancer outcomes in HIC are reported as EFS, progression-free survival, relapse-free survival and OS depending on the specific cancer type, often summarised as 2- and 5-year survival estimates. These survival methods account for different lengths of follow-up and censoring.[9] They also can consider competing events. Typically, the probability of survival, or the cumulative incidence of disease relapse are reported as some time point. That time point will depend on the prognosis and natural history of a specific cancer cohort. For example, if events are expected to occur late, reporting survival at an early time point will be less useful.[10] Reporting of these statistics require the ability to identify when a patient was last seen in the healthcare system (to inform censoring) as well as the ability to monitor for events such as relapse or death during the window in which these events are relevant (for example, 5 years).

The Collaborative African Network of Childhood Cancer Care and Research (CANCaRe Africa) have reported on the end-of-treatment outcome of patients.[11,12] This approach describes outcomes at the end of the planned first line treatment protocol. This time point is usually not included in traditional reporting of cancer outcomes in HIC. It can also indicate the moment of switch from first line treatment protocol to either a rescue protocol or palliative care. End of treatment outcomes in abovementioned studies were categorised as follows: (1) Alive, no evidence of disease; (2) Treatment abandonment; (3) Persistent disease (evidence of disease), including relapse or progression of disease during treatment; (4) Death before the start of treatment and (5) Death during treatment.[11,12] Death during treatment can be divided into treatment related mortality (TRM) and disease related mortality (DRM) if the required information is available.[8] Death before treatment is DRM. A misdiagnosis becoming apparent during treatment needs to be classified if relevant for the study and managed accordingly, e.g. by excluding the patient.

This approach can be used as a starting point to create a feasible and uniform way to categorise the outcomes at the end of treatment in LIC. We will need a system in which the different different domains at the end of treatment are sliced according to causes of treatment failure and are mutually exclusive. It may be useful

to have the preferred categorisation and terminology decided upon by consensus and a modified Delphi approach by a group of representative stakeholders to create uniformity in reporting. This has recently been done for similar topics in relation to the Global Initiative for Childhood Cancer (GICC).[13]

The advantage of reporting outcomes at the end of treatment is that it requires no follow up and is thus easier to collect. Follow up is often challenging in LIC due to limited resources to obtain patient status at regular intervals following treatment completion. Families have other priorities than to return with a well child to clinic for follow up. Active follow-up, initiated by the health team, is challenged by long distances, bad roads, lack of addresses, lack of phones and lack of funding.

End-of-treatment outcome provides complete information on the proportion of patients with treatment abandonment. It also captures most patients with TRM, although will miss patients who die from late toxicities such as cardiotoxicity.

As an illustration of the potential value of reporting on end-of-treatment outcome, a retrospective study described end-of-treatment outcomes of children with newly diagnosed common and curable childhood cancer types in Malawi. The study found 53% of patients alive without evidence of disease, 19% with treatment abandonment and 23% with death during treatment.[12]The study concluded that interventions to enable patients to complete treatment and improve supportive care require prioritization to improve survival. These data justified a pilot study to prevent treatment abandonment by supporting families with out-of-pocket costs. Using the abovementioned study as a baseline, the intervention was associated with a decrease in treatment abandonment from 19% (49 of 264) to 7% (10 of 150) ($p<0.001$). The proportion of patients alive and without evidence of disease at the end of treatment non-significantly increased from 53% (139 of 264) to 61% (91 of 150) ($p = 0.1$).[14]

Documenting end of treatment outcome has limitations. It does not allow us to properly consider when events occur or incorporate competing events (such as death due to malaria). Comparisons across centres using protocols of different lengths for a given disease are more challenging, even for treatment abandonment and death during treatment. For example, if a protocol for acute lymphoblastic leukaemia is 1 year in one centre and 3 years in a second centre, the abandonment rates will almost certainly be higher in the latter scenario, but may not translate into differences in OS. End-of-treatment outcomes can only estimate the maximum EFS and OS – but these estimates may decline considerably with follow-up depending on the disease.

In conclusion, local evidence is key to prioritise and evaluate impact of interventions to increase care and survival of children with cancer in low-income countries. Information on outcome of patients and causes of treatment failure is essential. Documentation of end-of-treatment outcome is a relatively simple method providing data most relevant to the LIC setting while LIC capacity improves to enable reporting of traditional survival metrics.

Conflict of interest Statement None declared.

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