PERSPECTIVE

Understanding Refusal and Abandonment in the Treatment of Childhood Cancer

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Treatment refusal and abandonment is the principal cause of therapy failure in children with cancer in the developing world. A complex interplay of biological, socio-economic and treatment-related factors underlies this problem. Interventions are likely to succeed when they try and address all of these issues simultaneously, as exemplified by the success of twinning programs linking resource-rich and resource-limited countries. Hitherto, there has been no systematic attempt to understand and address this problem in India. Based on the knowledge gained from research in other parts of the developing world, we offer suggestions for dealing with this problem.

Key words: *Childhood cancer, Treatment refusal, Treatment abandonment, Developing countries, India.*

With early aggressive treatment and robust supportive care, more than 7 out of 10 children with cancer in the developed world are cured(1). In such a setting, toxicity-related death and relapse, although less common, nevertheless are the main causes of treatment failure(2). However, 80% of the approximately 200,000 new cases of childhood cancer each year worldwide live in resource-limited countries(3). In contrast to what is seen in the developed world, failure of treatment of childhood cancer is still a common occurrence worldwide with refusal (non-initiation) and abandonment (non-completion) of treatment often exceeding all other causes of failure(2,4,5). In the developed world, any refusal or abandonment is likely to lead to health and social services intervening and they may even take court action to ensure that the child receives treatment. Such state support and intervention is non-existent in large parts of the world, including in India, so that treatment refusal and abandonment remain common events. In a recent study from a tertiary healthcare establishment in India, of 762 children with acute lymphoblastic leukemia, 30% refused and another 15% abandoned treatment(6). As progress is being made to reduce infection-related childhood deaths in India, it should no longer be acceptable to allow children with cancer who have the potential for cure with appropriate treatment, to be ignored when treatment abandonment occurs.

In our efforts to improve the outlook of this chronic but largely curable childhood disease, it is essential that we understand and address the problem of treatment refusal and abandonment. It was previously reported that this problem was wide-spread across the developing world(7). The magnitude of refusal/abandonment was difficult to estimate reliably as it varied between countries, the type of healthcare system and type of cancer. In India, available data from tertiary centers shows abandonment rates varying from 17- 62%(7). Even this figure is likely to be an under-estimate as the

bulk of the childhood cancer patients are provided care by smaller healthcare establishments scattered across the country. This would imply that, of the estimated 40,000-50,000 annual new cases of childhood cancer in India(8,9), the majority would not be adequately treated and consequently die of their disease.

Even lesser has been our understanding of the causes of treatment refusal and abandonment, and of the possible solutions. In 2003, Metzger, *et al.*(4) had shown that abandonment of treatment in children with acute lymphocytic leukemia (ALL) in Honduras was associated with prolonged travel time to the treatment facility (>5 hr) and age younger than 4.5 years but not with patient sex or ALL risk group(4). Following this, Howard, *et al*.(2), in their seminal paper in 2004(2) showed that a multi-pronged and sustained approach involving training of doctors and nurses, transfer of diagnostic and therapeutic protocols, improving supportive care, financial aid, and involvement in research projects resulted in impressive reductions in abandonment (besides decrease in relapse and mortality rates and improvement in five-year survival). In the last four years, more evidence of the mechanism and interplay of different factors has begun to emerge from across the world and herein we summarize these findings. Research from India on this topic is still conspicuous by its absence.

UNDERSTANDING THE CAUSES

Age - Metzger, *et al*.(4) first reported an association of abandonment with age less than 4.5 years in a cohort of children with ALL(4). However, they could not explain this finding and suggested that it was a confounder for some other association e.g family size or lack of extended family support. Other studies have subsequently not found such a relation between age and treatment refusal/abandonment(10,11).

Gender - Gender of the child was also not found to be associated with differences in abandonment rates in Central America(4,10) and Indonesia(11). However, in a follow-up survey from North India of those who abandoned treatment, 28% of parents reported that the patient being a female influenced their decision(12). Gender, like age, is a demographic variable, but any variation in behaviour based on gender can also be a reflection of societal prejudices. Gender bias by parents when seeking healthcare for children or for cancer registration is well documented(13,14). Thus, it would not be unexpected to find a similar bias when analyzing refusal/abandonment rates. Further investigation of the extent of this bias is required.

Biology of the disease - One might expect that childhood tumors requiring less intensive therapy (e.g. low risk ALL, Hodgkin lymphoma, Wilms tumor) would have lower abandonment rates compared with those cancers needing more intensive treatment with consequent higher toxicity (e.g. high risk ALL, AML, high risk neuroblastoma) and cost. There was a suggestion to this effect in our previous review(7). However, nearly 90% of children with Wilms' tumor in Sudan refused or abandoned treatment, thus illustrating that overall economic, social and political factors are probably more significant than type of treatment itself(15). In a recent study from El Salvador, abandonment rates were not different between leukemias/lymphomas, CNS tumors and other solid tumors(10). Abandonment rates were not found to be associated with the risk grouping of children with ALL(4,11) or with length of protocol(10). Additional research is needed before definitive conclusions can be drawn on the impact of tumor type/biology of the disease on abandonment.

Treatment-related factors - While there is no clear association between type of tumor and abandonment, it has been shown in several studies that abandonment rates for ALL are highest during the early phase induction(4,5,11). This may be related to multiple factors acting singly or in combination. These include treatment-related toxicity, painful procedures performed with inadequate analgesia and sedation, inadequate communication provided by health care providers, predetermined health beliefs of parents, and lack of finances. Although these factors are relevant during the entire treatment, their role is amplified during the initial intense phase of therapy. Studies have consistently shown that adverse effects of treatment including painful procedures are of major concern to parents, often contributing to abandonment(5,11,12,16). The

standard practice of using short-acting general anesthesia for bone marrow aspirations/biopsies and lumbar punctures is uncommon in the developing world. The unease of parents is also reflected in their health seeking behaviour after they abandon treatment. The majority of them seek complementary and alternative medical treatment, often citing lack of adverse effects as a reason compared with modern chemotherapy(11,16,17).

Communication issues and attitude of health care providers - Closely linked to the treatment related toxicity, is the ability of the healthcare provider to communicate effectively with the parents and the child. Clear and detailed information given repeatedly to the parents is vital for them to understand the disease, its treatment and the effects (beneficial and adverse) of treatment. This is particularly important during the initial part of treatment and in a setting where a majority of parents may believe in the inevitable "fatality" of cancer(11,18). This belief is often based on a parent's experience of witnessing a close adult family member or friend who had succumbed to cancer. Only through repeated counseling can parents understand the necessity of continuing and completing treatment after the cancer has apparently long "disappeared". Resources and staff are often stretched in providing care in developing countries. In such a setting, doctors can come across as impatient, busy or irritated, which makes parents hesitant in asking for information(16,18,19). In children with ALL, Mostert, *et al*.(5,20) partly attributed the variation in abandonment rates between children of prosperous parents (2%) and poor parents (47%) to the differences in the quality and quantity of communication given and individualized attention offered by healthcare providers.

Financial burden - Perhaps the single most important factor that underpins all others is the financial resource of the family. In developing countries, social and economic support from the state is either non-existent or inadequate, and medical insurance mostly absent(21). The burden of the cost of treatment falls mostly, if not entirely, on the family of the child. Parents consistently report financial burden as the main reason for abandonment and there is variation in abandonment rates between children of prosperous parents and poor parents(5,12). Not surprisingly, monthly income of the family has been shown to be significantly related to abandonment rates(10). As shown in ***Fig.* 1**, the cost of therapy is more than simply the sum of the cost of investigations and treatment. Cost of transport is also a major concern for parents and contributes to abandonment(11,12). Travel time to treatment center has been shown to be significantly associated with abandonment rates in Honduras(4). An indirect impact is also in the form of loss of employment and income as well as incurring debts for the family as a relative (and a key income generator) has to stay with the child(11,18,19).

Other factors - Abandonment rates are suggested to be related to lower educational status of parents but it may actually be a confounder for financial status(5). In a multivariate analysis, educational status of mother was not significant once monthly income had been taken into account(10).

WHAT ARE THE SOLUTIONS?

There are models of successful interventions in certain parts of the developing world. Most notable among them have been the "twinning programs" between St Jude Children's Research Hospital in Memphis, USA and multiple countries in the developing world, and links established by Monza's International School of Pediatric Hematology/ Oncology and 14 Latin American countries(2,22). Twinning fosters interaction between public hospitals in developing countries and established cancer treatment centers in the developed world,

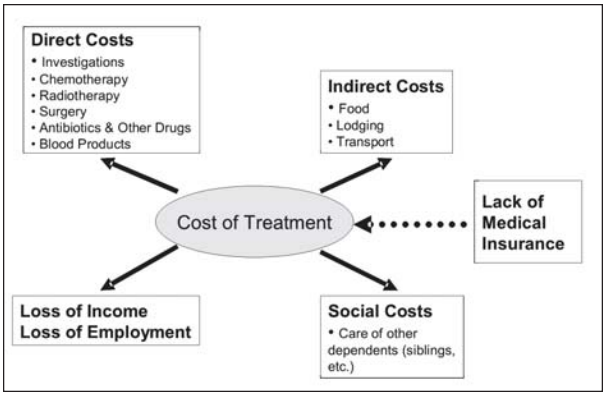

FIG. 1 *The true "cost" of therapy in childhood cancer.*

with the goal of improving survival rates among children with cancer.

As financial burden is the major cause of abandonment, it would seem an obvious target for intervention. However, giving money to patients for transport led to only a marginal improvement in abandonment rates in Bolivia(23) and providing free chemotherapy did not prevent abandonment in Indonesia(24). As ***Fig* 1** shows, the true cost of treatment is a complex interplay of multiple factors and interventions are likely to work when they take all factors into account. Only when poor, uneducated parents in Indonesia were given free chemotherapy and equipped with the knowledge of how to access this resource, did abandonment rates decrease(25). A multi-pronged approach of educating healthcare providers to facilitate early diagnosis, developing a treatment protocol, training ophthalmologists and donating essential equipment has led to similar success in reduction of treatment refusal and abandonment in those children treated with retinoblastoma in Central America(26).

Another area of focus to reduce abandonment has been in the adaptation of established treatment protocols used in the developed world to suit local needs. In the absence of robust supportive care, giving intensely myelosuppressive therapy can lead to more harm than benefit. This treatment-related toxicity is a major reason for abandonment during the initial intensive phases of treatment. When children in Malawi with Burkitt lymphoma were treated with a modified version of the French LMB 89 protocol, treatment related deaths and abandonment rates were high(27). Subsequently, the protocol was made short and less intense making it cheaper and leading to shorter hospitalization. This considerably reduced abandonment and decreased the number of treatment-related deaths, albeit with a higher relapse rate(28). It is important that treatment protocols are not only evidence-based but also locally appropriate. In recognition of this, treatment strategies of graduated intensity for ALL have been proposed for India as well as the rest of the developing world(29,30). These take into account availability of diagnostic, therapeutic and supportive care facilities as well as the financial resources.

THE WAY AHEAD

As clinicians providing care to children with cancer in India, our role should not be limited to providing diagnostic and therapeutic care. The onus is upon us to find strategies to deal with those who refuse or abandon treatment. First, we need to get a more accurate assessment of the size of the problem. Currently, hospital-based cancer registries using web-based technology (e.g. www.pond4kids.org internationally, and www.indiapod.org in the Indian context) are prospectively collecting data on children with cancer including information on refusal and abandonment rates. Centres in India providing care to children with cancer should consider utilizing these freely available resources.

Data collected from these registries can then be analyzed for the relation of treatment refusal and abandonment to various demographic, biologic, treatment-related and socio-economic variables. This can be used to identify factors common to other developing nations as well as those unique for India. This information will be useful to generate hypotheses and plan interventions.

Interventions which have shown to effectively reduce refusal and abandonment should be adopted by centres treating children with cancer. Some of these include twinning with tertiary centres within or outside the country; adapting established treatment protocols to local needs; providing adequate pain relief during diagnostic and therapeutic procedures; delivering clear and honest communication in a sensitive and a culturally appropriate manner; and providing assistance with direct medical costs as well as indirect ones like food, lodging and transport.

CONCLUSIONS

Refusal and abandonment is the leading cause of treatment failure in children with cancer in the developing world. Hitherto, there has been no systematic attempt to understand and address this problem in India, and is urgently needed. There is a growing body of research from other parts of the developing world which should serve as useful pointers.

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