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WHEN TO SAY WHEN: HOW AGGRESSIVELY TO CARE FOR CHILDREN WITH MULTIPLY RELAPSED CANCER?

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Over the last 50 years, we have seen a consistent decline in mortality in children with cancer, with five-year relative survival now approaching 85% [1]. New chemotherapeutics, combined modality treatment, collaborative clinical trials, and improved methods of local control and supportive care all play a role in this incredible accomplishment. And the future is brighter still, with advances such as cancer vaccines, immunotherapy, and personalized cancer medicine all providing hope that one day no child will die of cancer.

We are clearly not yet to that point, however, as some cancers are still infrequently cured. In a recent edition of *Pediatric Blood & Cancer*, Tamamyan and colleagues reported the case of a child with one such diagnosis, multiply recurrent osteosarcoma, who achieved a prolonged remission following five separate relapses [2]. Such a success story would not have been possible a few decades ago, as the treatments employed were not previously available. The authors' perseverance enabled the child to achieve an improbable sixth remission, a commendable accomplishment in the face of a disease generally thought to have a dismal prognosis [3].

Yet one can readily imagine an alternate scenario in which the outcome is not so rosy, and the collateral damage much more significant. We all have cared for children whose families wished to "do everything," even in the face of incurable disease. Many of us have been kept up at night by the gnawing fear that we were violating the ancient medical dictum, *primum non nocere*, by causing pain and suffering via morbid surgeries and side effect-laden chemotherapy. The incredible advances of the past few decades have brought us to a point where there is almost always another surgery, another round of chemotherapy, another phase 1 trial available to our patients...but at what cost? In light of these advances, should we be pushing for cure in even the bleakest of scenarios? We would argue that the ultimate decision should lie not with the medical team but with the patient and his/her family.

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A growing body of literature describes the goals and preferences of oncology patients and their families in the setting of grim prognoses, and the field of palliative care has arisen from the understanding that for some, relief from symptoms and suffering is a more appropriate (and more attainable) goal than “cure at all costs.” Patients’ and parents’ preferences vary greatly, and these preferences are sometimes quite discordant with those of the treating oncologist [4-6]. Though this discordance is notable in its own right, its importance is further highlighted by the fact that 34% of parents who recognize that their child has no realistic chance of cure but still opt for cancer-directed therapy report at least some suffering and little to no benefit from this therapy [4]. It is likely that these concerning findings are magnified further when parents and oncologists disagree regarding a child’s prognosis. Wolfe et al. demonstrated that parents of children who died of their cancer recognized that their children had no realistic chance of cure 100 days later than did their physicians [7]. These discrepancies in understanding and preferences at the end of life can greatly impact the care that is provided during this important time period. In order to provide the best care to our patients, the care most in line with patients’ and families’ values and beliefs, we must take care to understand those values and beliefs, even if they are not perfectly in line with our own. The challenge is finding the appropriate balance between pushing ahead toward a cure at all costs and deciding when instead to direct focus toward symptom management and minimization of suffering.

Luckily, providing our patients the best and most technologically advanced therapy need not come at the expense of providing excellent end-of-life care. Levine et al. reported that the quality of end-of-life care received by pediatric oncology patients who died and were enrolled on phase 1 clinical trials was no different than that of those who were not on such trials [8]. This finding reassuringly indicates that a balance can be found between the provision of cancer-directed care and quality end-of-life care. While some might consider these two approaches contradictory or even incompatible, parents often report having simultaneous “primary” goals of lessening suffering and extending life [7]. Furthermore, we now know that the early integration of palliative care for adults is associated with improved quality of life, less depressive symptoms, and longer survival than those who receive standard care [9]. Providers must have access to the tools and support to elicit the preferences of patients and families and not lose sight of the fact that families may not always have the same values as the medical team. A recent study demonstrated that nearly 50% of pediatric oncology providers would not support the refusal of standard chemotherapy by a family whose young child had a likelihood of survival of less than 33% [10]. This highlights the need for further exploration of family preferences and perhaps a shift in how we decide what is an acceptable or appropriate course of action.

So when to say when? When should we provide aggressive cure-directed care and when should we aim primarily for comfort? Some families want everything done – every available clinical trial, surgery, and chemotherapeutic that might provide even one additional day of life, no matter the risks that each might incur. Others focus much more on quality of life, preferring to minimize interventions that might cause additional side effects, even when said interventions might prolong their child’s life. And this is not an all-or-nothing proposition, as many will desire some amount of cancer-directed therapy while still focusing on symptom control. The key is the development of open lines of communication to enable parents to

accurately understand their child's prognosis and thereby empower them to make treatment decisions that are best for them and their family. As providers, we have an ethical obligation to provide the best information at our disposal to families, even when that information is difficult or uncomfortable to communicate, involves discussions about poor prognoses, and/or involves the uncertainty that often is inherent in such prognostications. Only such forthcoming discussions will enable families to make fully informed decisions about their child's care that are in line with their own values, not just those of their medical team. For some, this will involve every new drug, trial, and second opinion that we can provide; for others, it will entail a focus on symptom control and minimization of suffering.

We cannot predict with 100% certainty the outcome of a given case. Diseases thought to be incurable sometimes are cured, and some that are expected to be curable progress and lead to a patient's death. As a result, the latest technological advance or a good outcome in yesterday's patient should not push us toward cure-directed care for every child with a poor prognosis. Tamamyan and colleagues achieved the goal we all have for our patients, but for some families, a more measured approach would be preferable. As pediatric oncologists, we must work with families to make the best treatment choices for them, rather than unilaterally opting to aspire for cure at all costs simply because science allows us to do so.

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