Abstract:

Modern paediatric oncology practice has rapidly evolved from a fatal condition at diagnosis in the 1940s to modern survival rates over 80%. With the advent of the “omics” era and modern diagnostics platforms, we can now determine many of the molecular driving mechanisms of malignancy. Current molecular diagnostics trials PRISM and AIM/MNP, open in Australia, allow accurate diagnosis and determination of the molecular drivers of many cancers leading to new targeted opportunities for treatment. Unfortunately, clinical trial support, development and drug access for children has lagged behind. This is leaving clinicians and their institutions with increasingly difficult medical and ethical decisions, further complicating an already demanding profession.

Key words:

Oncology, clinical trials, personalised medicines

Modern paediatric medicine is undergoing a renaissance with increasing reliance on molecular testing and diagnostics to inform clinical decision-making processes. In paediatric oncology, we have made many historic advances over the last twenty years to improve our overall survival to ~80% for all paediatric malignancies(1). With such success, comes much pressure to succeed with all children though. Unfortunately, one child in five still succumbs to their disease despite our best cares(1) .

With scientific advances, many commercial opportunities have arisen to help “assist” the family and physician to inform their treatments and decisions. Organizations such as Foundation One™ and Caris™ offer families and clinicians rapid tumour evaluation with possible targeted therapies for their child’s specific malignancy. They promise a sized report about the tumour and suggested therapeutics available for this malignancy. However, many of these drugs are either completely untested, unavailable for paediatric use or not open to children on clinical trials.

Compounding the commercial input to patient management is “doctors” Google™ and Facebook™ and the wonders of the World Wide Web. While we all revel in the opportunity to learn and share information including medical advances rapidly, it can also give families an amazing array of bad information and mismanagement. Often it offers misinformation and false hope to families who are grieving and looking for any possible benefit for their child.

Parents see constant reports in print or on television of the latest breakthrough or the newest drugs. We are a fad driven culture and we all want what is biggest and brightest toy, but it does not mean it is the right or safest toy. Unfortunately research relies on media for exposure to increase awareness and improve philanthropy and donations to continue this work.

Much publicity and supports from government and philanthropy in Australia has been thrust behind several personalised medicine trials in paediatric cancer to inform the clinician about the unique nature of individual paediatric tumours. Millions of dollars has been invested to personalise our diagnostics platforms through the national trials AIM/MNP and PRISM. Unfortunately, funding for diagnostics platforms is currently outstripping access to novel agents or the funding for them.

The PRISM trial through the Zero Childhood Cancer Project brings hope to all children with high-risk malignancy in children where previously no hope existed. The study utilizes multiple platforms

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including whole genome sequencing, panel sequencing and RNA sequencing looking for novel and previously underappreciated genetic and chromosomal fusion events. In the pilot TARGET program, nearly 67% of children were found to have actionable tumour changes (Ziegler unpublished). The AIM/MNP trial seeks to validate methylation profiling of all brain tumours in children. This technique has been the crux of much of the advances in the understanding of brain tumour biology and can be used to classify brain tumours with excellent reliability (2). Through simple improved diagnosis and classification of brain tumours, many previously misdiagnosed, we suspect improved outcomes for all children enrolled. As well, the AIM/MNP trials, in conjunction with PRISM, utilize targeted sequencing of tumour, seeking specific mutational events in common cancer genes. Both studies have contributed to improved diagnosis and identification of possible targeted and personalised treatments for individuals. These studies are promising in their assistance to diagnosis and therapeutic targeting, of cancer driving events. However, clinicians are increasingly being placed in ethical dilemmas predicted by the outcomes of these studies .

A critical question is whether traditional drug development and trial models work for rare tumours (and all paediatric tumours are considered such)(3). Traditional models of drug development and design are slow and tedious. If applied to rare diseases, good evidence is often completely lacking. Thus in the setting of rare cancers we must improve our systems of testing new drugs or regimens. Traditionally we have sought to enrol children on phase 1/2/3 studies to show toxicity, efficacy and improvement over standard care. This model is increasingly failing in modern paediatrics. Current phase 3 Children's Oncology Group study ACNS0831 was opened for accrual in 2010.. The study aimed to definitively answer whether children with ependymoma derive benefit from adjuvant chemotherapy with radiation.

Since this time, multiple therapeutic advances have resulted in a complete explosion of biologic data about this disease. What was traditionally called classic or anaplastic ependymoma is now clearly one of four sub-groups described as YAP-fused, Rel-fused, GroupA/CIMP+ or GroupB/CIMP- (4). If clinicians are to follow our creed of 'do no harm', we will be determining the Sub-groups of ependymoma treating and making informed treatment decisions based on this data. This might mean that we skew the enrolments on 0831 such that only those with high risk (Rel-fused and CIMP+) ependymoma have adjuvant chemotherapy. Indeed enrolments have dramatically declined since this evidence began to emerge.

How can we possibly complete a randomized controlled trial for a tumour such as embryonal tumour with multilayered rosettes that would be seen only once or twice a year in all of Australia? While using informed biologic studies, we must find a mechanism to balance the risk of unknown therapeutic effect against possible therapeutic advances.

With the explosion of new drugs, we are confronted by further problems of cost. New drugs are expensive and with little evidence for their use, how do we access novel therapeutics for rare conditions such as paediatric malignancy? How can drugs committees and hospital executives approve expensive drugs with very little evidence of benefit beyond biologic rationale? Should parents have to front the cost of novel therapeutics outside the context of clinical trials? If not, then who pays for expensive trials of n=1? This author suggests that no family should have to pay for their child's cancer therapy but is aware of instances that this has occurred.

Are families prepared to deal with unknown side effects or consequences of drugs or regimens because FoundationOne™ and web-based information from Google™ suggested it should work?

Are they prepared to accept

risk based on open molecular trials? Traditional medicine is based on an evidence-based practice. Is informed biology sufficient to make clinical decisions and make therapeutic choices outside the contexts of a clinical trial? Can a generic trial looking at therapy based on informed biology only with limited clinical trial data be an acceptable alternative structure? Is this ethically sound practice if a family is fully informed of the unknown evidence about a particular therapy? From experience around the country and internationally, the answer to all of these questions is unequivocally yes. The COG opened one such generic “basket” study, APEC1621, assigning attached drugs to the underlying genetic change of tumours, not the pathologic diagnosis. Enrolments have been swift with 234 patients screening for molecular targets and ~10% of children assigned matched targeted drugs since opening in July 2017 (COG unpublished). Unfortunately this study is not available to Australian children.

Clinical trial support has been sorely lacking in oncology units across the country for years. Much of the paediatric oncology units clinical trial groups across the country are funded on “soft” money generated from philanthropy. This has resulted in highly stressed and pressured units unable to open as many clinical trials as oncologists seek. This results in a lack of therapeutic options for the child. Unless there is a profound change in how clinical trials are viewed in paediatric oncology, our children’s access to drugs and novel therapies identified by such trials will lag. As such, while we now have the capacity to identify cancer driving events in many instances, clinicians are more commonly being confronted by an inability to offer treatment.

Evidence for paediatric indications has often lagged years behind adult cancers. For example, dabrafenib was approved for use in adult malignancy in 2013, but is yet to be given PBS approval despite excellent trial data in BRAF altered tumours in paediatrics over the last several years (5). While paediatric trials are ongoing for many drugs, can our children wait? A lack of evidence should and does not equate to a lack of efficacy in children. Our capacity to act on novel events or combinations of events remains the hold up in advancing outcomes. While some studies are open and afford enrolment for unique tumour drivers, what happens when we cannot offer a clinical trial? As mentioned above, oncology units around the country have encountered unique cases where evidence lacked for therapy for children with terrible outlooks and ethical dilemmas. Families, clinging to hope, enrolled on the cited molecular trials seeking something, anything that might assist their child. In many instances we have found the tumour driving events. Oncologists, keen to offer a chance have sought access to drugs that multiple layers of expertise advised a trial of, only to be knocked back by drug companies and hospital drug committees. I am not aware of any family, if afforded the opportunity, knowing there is a lack of toxicity or efficacy data, would not accept this risk. Acceptance of risk with limited clinical evidence lies at the heart of challenge in paediatric oncology practice over the next 25 years if we do not act soon.

How do we tackle this expensive issue financially and ethically? The answer lies in global support of informed and rational therapeutic trials at the national and international levels. As mentioned above, trial support has lacked in Australia. Much of the cancer clinical trials capacity in children is driven by charity groups, most founded in grief for deceased children. In the last 2 years clinical trial

support has been bolstered by the government since the impassioned public plea from Mr. Dustin Perry to then Prime Minister Turnbull as his daughter was dying of brain cancer. The Department of Health via Cancer Australia have funded the AIM/MNP, PRISM and a low grade glioma study, now open nationally for children. They have also launched the Australian Brain Cancer Mission seeking to improve survival for all sufferers of brain cancer. While this is a great start, novel agent access continues to concern paediatric oncologists and the children they treat.

We must find a way to access novel therapy and drugs for children with cancer. Much of all paediatric malignancy is rare, but if we are truly going to aim for “Zero” childhood cancer, we need buy in from all levels of government and hospital administration to make this happen. While expensive, I would argue childhood cancer and its treatment should work outside “normal” hospital budget frameworks and would implore all hospitals, states, territories and governments to invest in clinical trials so we can start legitimately offering hope where previously we had none.

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Personalised Medicine in Paediatric Oncology: Ethical practice outside the clinical trial framework?

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