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Personalised Cancers Treatment for Children, Teenagers, and Young Adults (CTYA)

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Abstract: Cancer treatment has gone through several decades of treatment strategies of phase I, phase II and randomized controlled trials until reaching the current phase of successful treatment that approaches >95% cure rates in some paediatric based chemotherapy protocols. However some diseased are still not curable despite the use of combinations of surgery, chemotherapy, radiotherapy, immunotherapy, hormonal treatments, biological modifiers, novel agents and stem cell transplants (autologous and allogeneic). Such diseases are demanding alternative approaches and hence the oncology community is heading towards personalised management approaches. Here we present an overview of the precise medications approaches that have been tried by different teams. The near future would include a combinations of these approaches to gain better understanding of the disease and achieve better outcomes.

Keywords: Personalised medicine, Genomic profiling, Live kinetic cytotoxicity assay, Xenografts

1 Background

With a global incidence of millions of cases and a disease related mortality/morbidity of cancers in children, adolescents and young adults and accumulated translational research knowledge, a new paradigm of superior management strategies of cancer is anticipated. For despite of the establishment of well-designed chemotherapy regimens, high dose chemotherapy/stem cell rescue (HDSCR) and novel biological drugs, the overall progress had fallen short of finding an absolute cure for cancer in general and for dismal malignancies such as Neuroblastoma (NBL), High Grade Glioma, Anaplastic Ependymoma, Colorectal Carcinoma, Metastatic Non-Small Cell Lung Cancer. (Zacharouli*set al* 2007, Segal *et al* 2009, Rossi *et al* 2014) in particular.

This suboptimal success, together with other observations such as diverse treatment outcome, treatment failure and limited efficacy of novel agents, imposed switching the notion of uniform clonality of cancer to a more personalised polymorphic heterogeneous disease. The scientific community is currently addressing this individualistic nature of genomically driven heterogenic cancer via personalising patient's management (Morelli *et al* 2012).

However, the small number of patients included in clinical trials keeps the practical implementation of this concept difficult in children, teenagers and adults. So far, cancer treatment personalisation is focused on finding the right patient for a particular drug based on biomarkers predictive drug activity (Hidalgo *et al* 2011). This drug-centered rather than patient focused approach has several issues that are illustrated in Figure 1.

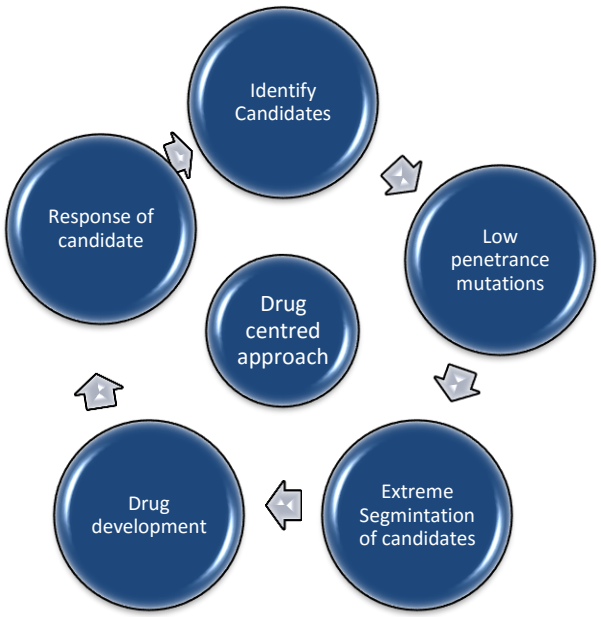

Figure 1: The challenges facing personalised cancer management due to drug centred approach. a) Its main goal

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is to identify good candidates for an agent that often predicts resistance of the tumour rather than its susceptibility to specific regimens (Hidalgo *et al* 2011). b) It usually fails to provide a solution for most patients due to the low frequency of such biomarkers within a given patients population and the lack of approved drugs, for which biomarkers are known (Arneddo*set al* 2012). c) Drug discovery is usually restricted to a certain cancer in which the drug is approved, for treatment. However, the application of such approved drug in other disease types is limited (Hidalgo *et al* 2011). d) The prediction tools for patient's response are not accurate even in the presence of appropriate biomarkers and patients might respond transiently, fail to respond at all or even progress (Stebbing*et al* 2013).

Moreover, oncologists globally have reached a blockade in trying to manage poorly prognostic diseases after discovering that HDSCR is not a superior strategy to combined chemotherapy in certain diseases (Zacharoulis*et al* 2007, Agarwal *et al* 2009).

In CTYA, a number of CNS and Non-CNS tumours have such a dire outcome with no satisfying treatment options. These include CNS tumours such as High Grade Gliomas (HGG), Medulloblastomas (metastatic and anaplastic), Supratentorial PNET, ATRT, and Ependymomas. Non-CNS solid tumours include metastatic Sarcomas, Neuroblastomas and patients diagnosed with Desmoplastic Small Round Cell Tumour.

CNS- High Grade Gliomas (HGG) (Sposto*et al*, 1989, Finlay *et al* 1995, Dufour*et al* 2006, Parajuli*et al* 2007 and Elaimy*et al* 2013)

Glioblastoma Multiforme (GBM) and Anaplastic Astrocytoma (AA) have a better survival rate (albeit very small) if the tumour is totally resected. The standard treatment following resection is focal irradiation ± chemotherapy drugs such as Temozolamide, Procarbazine, CCNU and Vincristine.

Stupp*et al* in 2005 reported a 26% survival in adult patients treated with Temozolomide and Radio Therapy (RT) simultaneously vs 10% for those treated with radiotherapy alone. However this result could not be reproduced in children. Nevertheless, Temozolomide is now the standard upfront treatment of HGG in children and adults due to its relatively lower toxicity profile.

Diffuse Intrinsic Pontine Gliomas (DIPGs) on the other hand are aggressive highly infiltrative un-operable malignancies with universal dismal clinical outcome. Patients have a median survival of 9-12 months with no effective chemotherapy or targeted modifiers. Recently a recurring ACVR1 mutation, which activates the BMP–TGF-β signalling pathway and represents a potential target has been reported (Taylor *et al* 2014)

Novel biological modifiers and targeted drugs are currently the focus of attention of several groups trying to improve the outcome of aggressive HGGs. Of note, an EGFR inhibitor containing regimen (Radiotherapy, Nimtozumab and Vinorelbine) showed promising results in subset of children patients. Several other EGFR inhibitors have been used including Cetuximub, Gefitinib and Elrotinib with only low responses (Daw*et al* 2005).

The VEGF monoclonal antibody, Bevacizumab, despite showing impressive response rates in adults with relapsed GBM (30-60%) did not alter the overall survival significantly and to date there is no data to predict patients who are likely to respond. Several other antiangiogenic agents have been used with varying degrees of success, such as Sorafenib, Sunitinib, Pazopanib and Cilengitide. These and other agents are under investigation with no evidence of significant improvement so far (Kreis*et al* 2013, Robert *et al* 2013). One of the major limitations of these studies is the examination of these agents in a very gnomically heterogeneous population of HGG.

Medulloblastoma/ PNET/ ATRT (Pearson *et al* 1982, Hamilton *et al* 1995, Morland and Parkes 1995, Gilbertson and Gajjar 2005, and Packer 2005)

As the second most common childhood brain tumour, Medulloblastoma peaks at 4 years of age. Children are either average-risk (3 years old and >1.5 cm3 residual tumour) or High-risk group. Currently, stratification of treatment is guided by the molecular subgrouping of Medulloblastoma according to cytogenitics, immunohistochemistry and genomic signatures of the disease (Ramaswamy*et al* 2013).

Treatment includes surgical resection, CNS irradiation (craniospinal RT and local boost RT) and chemotherapy (cyclophosphamide or CCNU with vincristine and cisplatin / HDSCR). The 5-year event-free survival ranged between 67% -78% and a 2 year progression-free survival between 74 - 94% (Chi *et al* 2004).

If Medulloblastoma relapses, the event free survival and progression free survival drops dramatically with only limited palliative options for the majority of patients. The molecular Hedgehog–Patched signalling pathway is being targeted in Medulloblastoma as mutations in several components of the pathway occur in approximately 30% of cases.

On the other hand, patients with Supratentorial PNETs although treated as Medulloblastoma, carry poor prognosis indicating different biological behaviour and the diagnosis of Atypical TeratoidRhadoidTumours (ATRT) hold an extremely poor prognosis with long-term survival less than 20%.

For these two diseases, patients who relapse, very limited options are available with long-term cure being achieved in less than 10% of the patients and the survivors are primarily

amenable to further local therapy. The chemotherapeutic options include the combination of Temozolomide with Irinotecan with 40% response rate (Gottardo and Gajjar 2008) .Similar response rates are observed using oral etoposide with a median response duration of 6 months (Chamberlain *et al* 1995). Unfortunately the vast majority of these patients will relapse further. Bevacizumab is currently being investigated in a randomized trial at Children Oncology Group (COG). In ATRTs on the other hand, the main targeting therapies are Aurora A, Cyclin D1, IGF-1 and PLK-1.

Ependymomas (Kun *et al*, 1988, Gilbertson *et al* 2002, Merchant and Fouladi 2006, Tabori*et al* 2006, Zacharoulis*et al* 2008)

Ependymoma represents 8 – 10% of all childhood CNS tumours. 40% of patients are less than 3 years of age and all are high risk. Surgery is the most important prognostic factor; complete resection followed by RT might result in 67–80% event free survival (EFS). However incompletely resected tumours show 0 – 26% Progress Free Survival (PFS) even if RT is used. For children < 3 years, RT must be delayed and chemotherapy is used to keep the tumour at bay until RT can be used, however treatment outcome for these children continues to be poor.

The molecular pathophysiology of Ependymomas is poorly understood. Recently the RelA fusion status has been reported to define two major molecular subgroups of supratentorialEpendymoma with the paediatric group being aggressive, invasive, recurrent and metastatic with poor survival (Wani*et al* 2014). Despite of this recent finding and the known activity of telomerases and ERbB receptor, targeted therapies have not been examined prospectively in multi-institutional trials and have not been translated into therapeutic strategies yet. However, possible targets include Notch, EPHB2 and PDGFRs for which the use of novel agents is still in its infancy.

Sarcomas (Wagner *et al* 2007, Loeb *et al* 2008, Amankwah*et al* 2013)

Sacomas account for 1% of tumours in adults and 7% of childhood solid tumours. The most common paediatric sarcomas include Rhabdmyosarcomas, Ewings Sarcomas, Osteosarcomas and Non Rhabdomyosarcomatous Soft Tissue (Desmoplastic round small cell tumour (DSRT). Alveolar Rhabdomyosarcomas, DSRT and metastatic sarcomas have poor prognosis (20-30% survival). Treatment includes local control with maximal surgical resection ± radiation and systemic chemotherapy with Vincristine, Actinomycin-D, Ifosfamide/Cyclophosphamide, Doxorubicin and Etoposide. For patients with metastatic disease at diagnosis and patients who relapse new agents are being investigated such as VEGF/VEGFR inhibitors (Bevacizumab, Pazopanib and Sunitinib) IGF1R inhibitors or mTOR inhibitors (Temsirolimus and Everolimus). They are being investigated in clinical trials based on their preclinical activities. Currently there are no established predictive biomarkers in paediatric sarcomas and new approaches are needed for metastatic and relapsing patients (Amankwah*et al* 2013).

Neuroblastoma (Brodeur*et al* 1984, Kushner *et al* 2006, Johnson *et al* 2007, Park *et al* 2008, Castel *et al* 2010 and Modak& Cheung 2010)

Neuroblastoma (NBL) is the most common non- CNS solid tumour in children, its risk stratification (low – Intermediate – high risk) depends on disease stage (International Neuroblastoma Staging System (INSS)), MYCN status, International Neuroblastoma Pathologic Classification (INPC) Score and DNA index. Low-risk NBL can be observed or cured with surgery only. Intermediate-risk NBL requires surgery and chemotherapy whereas high-risk NBL have a 30% chance of 5 year overall survival with the current multimodal treatment strategy (pre surgical chemo, surgery, radiation therapy, HDSCR, biologic modification with 13-cis-retinoic acid and Anti GD2 immunotherapy). Relapse or refractory high-risk patients have extremely poor prognosis and are treated with oral Etoposide, Topotecan, Vincristine Doxorubicin, Temozolomide Irinotecan, Cycophosphamide and MIBG therapy. These different strategies have approximate transient response rates of 15 to 40%. New identified targets include VEGF/VEGFR2, AKT, PI3K, mTOR, EGFR, Aurora Kinase, ALK. All of which have ongoing Phase I/II trials.

2 The Need to supplement Randomised Controlled Trials (RCT) with Novel Approaches

However despite of advancement in clinical oncology, the above mentioned poor prognostic diseases are still no closer to optimal management even with multiple RCT investigating targeted modifiers. With 10's of new targeted drugs appearing regularly, their translation into useful regimens via the traditional RCT will take 10's of years and might not produce the desired answer in view of the inherent segmentation of patients into very small heterogenic populations (Arnedos*et al* 2012). The need for supplementation with other approaches is a hot discussion topic among oncologist scientists. (Chin *et al* 2011, Vaidyanathan 2012).

2.1 Personalised Treatment Approaches

Currently several approaches for personalising treatment do exist and possibly in the future they will compromise a matrix that combines simple techniques with high throughput and complex techniques that require longer periods to produce high content information.

2.1.1 Cancer Stem Cell Isolation, Culture, and Cytotoxicity Assays

The *in vitro* isolation of patients specific cancer stem cells is being used to produce quick personalised data to guide management options of patients with dire diseases. Using live kinetic cell imaging systems, the sensitivity of expanding patient specific cancer stem cells to a wide panel of drugs could be screened (Pollard *et al* 2014). This approaches produces a quick patient specific drug sensitivity for panels of drugs that can be further tested in a xenograft model (See below).

2.1.2 Genomic profiling

Tumour tissue genomic profiling makes use of pathway-specific therapeutics to identify and suggest alternative therapies for those patients at high risk of disease recurrence and resistance to standard cytotoxic therapies (Garman *et al* 2007). This approach is useful for testing the efficacy of novel agents in randomized controlled trials.

2.1.3 Xenograft sensitivity testing

Xenografts that produce patient specific models of implants are being proposed by some researchers as a way of *in vivo* testing of tumour sensitivity and prediction of response (Hewit*et al* 2012, Ruggeri *et al* 2014). This approach is useful to address the inherit segmentation of patients undergoing personalised management approach (Arnedos et al 2012).

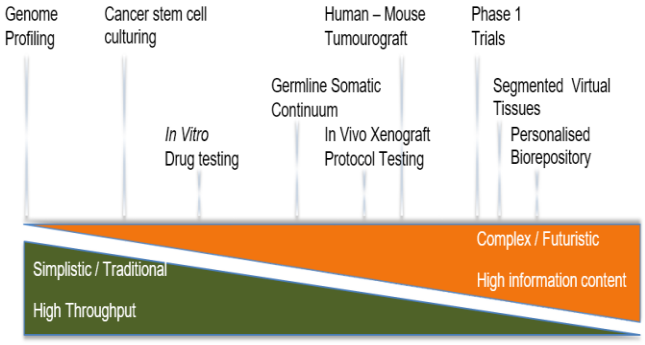

Figure 2: Schematic representation of the personalised approach for management of refractory cancers in CTYA. Note on the extreme right hand side the potential futuristic continuation of the approach in addressing extreme segmentation of small number of patients through virtual networks and personalised biorepository. With enough recruited number of patients a Germline Somatic mutation continuum could also be established.

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