Relapse prevention therapies in high-risk neuroblastoma

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For many years Solving Kids' Cancer UK has supported families to access maintenance therapy clinical trials in the United States aimed at relapse prevention following completion of standard frontline treatment. This is not a path for all parents; the financial, practical and logistical burdens are significant. Moreover, the prospect of appreciably extending an already intensive high-risk treatment regime by fundraising for unproven treatments abroad is deemed by many to be too much. It's important to be clear that in this there are no right or wrong answers. Parents must make whatever decisions they feel are in the best interests of their child and their family unit. A neuroblastoma diagnosis has profound impacts on all aspects of family life including on siblings, a fact that can be all too easily overlooked or minimised when the focus of attention is on a brother or sister who has cancer. The other side of this equation is that long-term survival for children with high-risk neuroblastoma, even among those whose disease responds completely to standard treatments, remains unsatisfactory and each of those current standard treatments began life as unproven and experimental until sufficient evidence of benefit was established through clinical trials. On the subject of clinical trials, this paper does not include any detailed commentary on the relative merits of single-arm versus randomised, nor single-institution versus multi-institution. That discussion is best left for another time and place.

There are currently two pathways that parents can elect to follow at the end of standard treatment in the UK - a Beat Childhood Cancer (Beat CC) research consortium clinical trial of DFMO or a clinical trial of a bivalent vaccine at Memorial Sloan Kettering Cancer Center (MSK) in New York. Solving Kids' Cancer UK has supported, and continues to support, families to access one or other of these therapies through enrolment on FDA regulated clinical trials.

While they are seeking to achieve the same outcome in preventing relapse, DFMO and bivalent vaccine are two very different treatments that work in two very different ways. It should also be remembered that neither DFMO nor bivalent vaccine represents a panacea in the fight against high-risk neuroblastoma. A significant proportion of children having primary refractory disease, early progressive disease, or persistent areas of disease at the end of standard treatment, never even reach a point where these maintenance therapies become a viable option.

DFMO

Maintenance trials using DFMO have been ongoing for nearly a decade and a number of UK children have been enrolled on such studies. The Principal Investigator is Dr. Giselle Sholler, currently at Levine Children's Hospital in North Carolina. Eligible patients must have either no evidence of disease by MIBG scan (or FDG-PET for MIBG non-avid disease), or no evidence of active disease by FDG-PET in the case of patients with persistent MIBG uptake at the end of standard treatment.

The scientific rationale for DFMO is that it's an inhibitor of ornithine decarboxylase (ODC) with the net effect of suppressing polyamine

uptake by neuroblastoma cells, a process implicated in tumour formation and growth. In BeatCC maintenance trials, DFMO is taken orally twice daily for a continuous two-year period. The current trial NCT02679144 has a number of strata and two different dose levels depending on which stratum patients are enrolled in.

There have been two publications reporting results from maintenance trials using DFMO. The first, from September 2018 in Nature Scientific Reports, provides outcomes for patients treated between June 2012 and September 2016 in two strata; (1) following completion of standard frontline therapy, and (2) after salvage therapy for relapsed or refractory disease. Whilst results themselves look promising, there are two major weaknesses to the paper. The first is the small number of patients in stratum 2 (relapsed/refractory), particularly in respect of subgroup analysis. The second is the comparison against unmatched historical controls and resultant overstatement of the impact of DFMO based on such analysis. A follow-up paper published in International Journal of Cancer (IJC) in May 2020 addresses the second of these weaknesses in respect of patients in first remission by performing a "matched" comparison between patients who received DFMO following completion of standard COG protocol (experimental arm) and patients who completed standard COG protocol at a BeatCC consortium hospital but who did not subsequently go on to receive DFMO (historical control arm). While still not as scientifically robust as conducting a prospective randomised clinical trial, this matched analysis is clearly the strongest evidence of benefit that currently exists for additional maintenance therapy following the end of standard treatment.

Bivalent vaccine

Solving Kids' Cancer UK has supported many families to access the bivalent vaccine at MSK over the last 5+ years, most in remission at the end of standard UK frontline treatment and a small number in remission after relapse. To date MSK is the only institution at which children can receive the bivalent vaccine.

The bivalent vaccine builds upon MSK's long-established expertise in anti-GD2 immunotherapy with 3F8 and, more recently, hu3F8. For many years consolidation and maintenance at MSK consisted of many rounds of 3F8/hu3F8. The mechanism of action of the bivalent vaccine is that it induces the patient's immune system to produce its own anti-GD2 antibodies — that can find and attach to residual neuroblastoma cells so they are marked for killing. The development builds on the hypothesis that long-term survival was improved in patients who developed their own so-called idiotype network following treatment with anti-GD2 antibody therapy using 3F8. The vaccine does not have such a potent effect as administering manufactured antibodies e.g., hu3F8, so it is only given to patients in complete remission at the end of all other treatment including normal anti-GD2 immunotherapy using dinutuximab (Unituxin), dinutuximab beta (Qarziba) or naxitamab (Danyelza/hu3F8).

The first bivalent vaccine clinical trial opened in 2009 for patients in 2nd or greater remission i.e. patients in remission again after relapse. Phase I results were published in Clinical Cancer Research in 2014 and Phase II

results in Journal of Clinical Oncology (JCO) in 2020. Progression-free survival at 5 years from trial enrolment of 32.2% represents a highly promising finding in a patient group that would historically be expected to have very unfavourable outcomes. Perhaps unsurprisingly the best results were seen in patients who received the bivalent vaccine in 2nd remission i.e. having only experienced a single relapse. Further analysis found a correlation between antibody titers (the amount of anti-GD2 antibodies in the blood i.e., having been produced by the immune response to treatment with the bivalent vaccine) and outcomes. If a similar relationship were to hold in patients receiving the bivalent vaccine in first remission when results become available this would be an indication that it was indeed doing "something" to promote an effect against neuroblastoma cells.

Until mid-2021, the treatment schedule used in clinical trials of the bivalent vaccine (see NCT00911560) comprised a series of seven injections administered over the course of one year with children also receiving oral β-glucan to help stimulate an immune response. In August 2021 a new clinical trial NCT04936529 opened with a revised treatment schedule. While children still receive seven injections over the course of year one, the trial has been extended so that they now receive a total of seven additional injections over the course of years two to five. A new experimental arm has also been added to the trial that means some children are randomised to receive GM-CSF injections as well as the bivalent vaccine and oral β-glucan.

There are currently no published results relating to the use of the bivalent vaccine for children in first remission. Now that the NCT00911560 clinical trial has completed accrual it is a matter of waiting for the data to mature such that the median follow-up period for patients enrolled after frontline is long enough for results to be meaningful. One might reasonably expect initial results to be presented at some point during the next year with a publication to follow at some point thereafter.

Pharmaceutical company involvement

In 2021 it was announced in a press release that US WorldMeds had entered into an agreement with Norgine, headquartered in the Netherlands, for the latter to register and commercialise DFMO in Europe, Commonwealth of Independent States, Australia and New Zealand. The clear message from this being that DFMO will be taken forward for regulatory approvals. Norgine will be responsible for any clinical trials required to gain approval in the relevant areas. US WorldMeds remains responsible for DFMO elsewhere, and is actively seeking approval from the FDA in the United States.

Commercial rights for the bivalent vaccine were licensed to MabVax Therapeutics by MSK in 2008 and sub-licensed to Y-mAbs Therapeutics in 2018. There have been no further clinical developments since Y-mAbs acquired the rights.

Which maintenance option is better?

This is a question that many parents wrestle with when trying to decide which maintenance trial option, if any, to pursue. The first extremely important point is that both DFMO and bivalent vaccine have been

shown to be safe and well-tolerated with limited acute toxicity. While hearing loss is a known adverse effect of treatment with DFMO, at the lower of the dosages (750 ± 250 mg/m^2) used in BeatCC maintenance trials, incidence of moderate increased hearing loss was very low and reversible in all cases, and there were no reports of severe hearing loss. Regarding bivalent vaccine in the Phase II trial of one hundred and two patients in 2nd or greater remission there were no serious adverse events. Localised pain at injections sites was common.

There is no information available through which to attempt to make any comparison between the effectiveness of DFMO and bivalent vaccine. It is also not possible as yet with the available published information to make any definitive determination regarding whether each of them makes a difference in their own right.

The best available evidence for DFMO at the end of standard frontline treatment is the 2020 matched subset analysis published in IJC. These results look very promising but they are still not in and of themselves clear and unequivocal scientific evidence that DFMO works to prevent relapse. It remains to be seen whether the existing evidence is sufficient to obtain regulatory approvals from the FDA and EMA.

There is a prevailing view in some quarters that DFMO works better in MYCN amplified patients compared to patients without MYCN amplification. While there is scientific rationale for the inhibition of polyamines in MYCN-driven oncogenesis there also remains much that is unknown regarding neuroblastoma formation and development. In the IJC paper there was a greater absolute difference in event-free survival (EFS) and overall survival (OS) for DFMO versus non-DFMO patients among those with MYCN amplification compared to those without MYCN amplification. However, caution needs to be applied in respect of reading too much into this result. Firstly, beyond three years the proportion of patients receiving DFMO who are censored rises sharply. Censored refers to the longest point of follow-up. For example, if a patient first received DFMO 3.5 years ago they are censored at 3.5 years – because we cannot yet know what happens with this patient beyond that time point. Their full effect on results at, say, 5 years is not included in the survival estimate – if they were to relapse during the next 1.5 years that would affect the result. Secondly, it is a well-understood feature of MYCN amplified neuroblastoma that patients tend to relapse earlier and with more aggressive disease progression. It's not unreasonable, therefore, to think that results for children without MYCN amplification will take longer to fully mature and for the true extent of any effect of DFMO to materialise. In the IJC article one can see that survival curves begin to separate earlier for MYCN-amplified patients relative to MYCN non-amplified patients. Lastly, these are small sub-cohorts of (30-40) patients and as such any results need to be interpreted with a degree of caution. The devil is always in the details of confidence intervals, p values, statistical methodologies and power.

There is no published evidence for the use of bivalent vaccine at the end of frontline as these results from the Phase II trial that started in 2015 are not yet available. The best evidence is survival impact among patients in remission following relapse as published in JCO in 2020. Though one might logically

reason that evidence of effectiveness in post-relapse patients suggests there will also be benefit for patients in remission at the end of frontline treatment there is currently no scientific evidence to support this supposition.

In so far as existing published information is concerned there is currently greater evidence for DFMO. However, there are clinical trials of both agents ongoing and so this is most definitely not the same as saying DFMO is better than bivalent vaccine. The take home should be that nobody knows which is better, it is currently impossible to know. People may have their own opinions, but they will not be based upon any objective assessment. The very purpose of running clinical trials is to gather evidence about safety, tolerability, and effectiveness – and for both DFMO and bivalent vaccine that process is continuing. That there are published results for DFMO but not yet for bivalent vaccine is simply a function of when the respective clinical trials commenced for children in first complete remission.

Why do parents travel abroad?

Although the introduction of immunotherapy using anti-GD2 monoclonal antibodies has improved survival for patients with high-risk neuroblastoma there remains a clear unmet need for more effective therapies. It is widely acknowledged that maintenance therapy using dinutuximab (Unituxin) and dinutuximab beta (Qarziba) cures some children and extends time to relapse for others. Incidence of relapse after completion of standard therapy, however, remains too high and more effective therapies are still needed.

In 2019 an expert group of UK clinicians produced an extremely important piece of information and guidance for parents considering whether or not to pursue DFMO or bivalent vaccine upon completion of standard frontline treatment. It rightly points out the uncertainties parents experience at the end of their child's treatment. Transitioning from more than a year of intensive multimodal therapy to being off-treatment, attending infrequent follow-up appointments, and living with the fear of relapse is an extremely difficult time.

Using data gathered from the SIOPEN/HR-NBL1 clinical trial this guidance includes the best available estimate of survival for children who complete all elements of high-risk neuroblastoma treatment and are in remission at both the beginning and end of immunotherapy. Among such children 79% remain alive and disease-free five years after the completion of immunotherapy. To enrol on the bivalent vaccine trial children need to be in remission before and after immunotherapy. For DFMO the situation is slightly different; children must have no evidence of disease or no evidence of active disease at the end of treatment. In the ongoing trial (NCT02679144) children receive a different dose of DFMO depending on whether remission was achieved before or after stem cell transplant.

The figure of 79% represents the best achievable outcome for any group of patients following current standard of care treatment in Europe, including the UK. That is, children disease-free before and after the end of immunotherapy have the greatest chance of being cured. However, this still means that even among the group of children with the very best outcomes one out of every five children will suffer a relapse. Options for children who relapse in the UK remain limited and long-term survival is widely acknowledged to

be poor. Putting the numbers into a different context if this were a class of 30 children then 24 would be disease free after five years, but 6 would not.

For some parents, if there's a possibility that DFMO or bivalent vaccine might increase their child's chances of long-term survival, and they are willing and able to contend with all the challenges that come with pursuing treatment abroad, then that's what they resolve to do. Their decision for their child, and for their family, is therefore to fundraise in order to access an additional maintenance option. Parents do understand that there are no guarantees, for them it's about doing absolutely everything possible that might benefit their child.

For other parents, weighing the unknowns in terms of potential benefit, the knowns in terms of burden of treatment to date and future challenges, and the risks from more treatment and additional exposure to ionising radiation during scans, it is time to stop. It must further be acknowledged that fundraising and accessing treatment abroad is beyond the reach of some families due to a variety of different factors such as socioeconomic disparities, language barriers, lack of fundraising networks, logistical difficulties, and family circumstances.

Why are these options not available in the UK?

Over the years there have been various discussions regarding potential options for making DFMO and/or bivalent vaccine available in the UK within the context of a clinical trial. The single biggest issue has been a difference of opinion regarding the level of scientific evidence that can be obtained through a non-randomised trial. Maintenance trials are among the most challenging to conduct effectively because a child in remission receives an intervention and they either remain in remission or they don't. Of course, they could have stayed in remission even if they had been given nothing at all. There is no directly observable effect as there is with having detectable disease, administering a treatment and being able to measure a response in terms of the amount of disease still present afterwards.

The teams at BeatCC and MSK have their own views and reasons for conducting single-arm trials, one clearly being that every child is able to receive a therapy that they might benefit from. In a much wider setting, however, giving a treatment to every child effectively makes it standard of care even though it is unproven. The experience of gaining approval for dinutuximab beta in the UK demonstrated the high levels of evidence that are required for drugs to become approved and available on the National Health Service.

In terms of conducting a randomised trial of DFMO this has also been discussed over the years, but there are inherent problems. The first being that it would require a large number of patients to generate the necessary statistical power to produce a compelling result (to the earlier point about maintenance trials being the most difficult to conduct). Moreover, the better the outcomes to begin with the harder it becomes to obtain sufficient evidence to demonstrate further benefit. Therefore to be scientifically meaningful such a trial would realistically need to be conducted within a cooperative research network e.g. SIOPEN. At which point the scale of the necessary buy-in, commitment, prioritisation and planning increases substantially.

Another major problem relates to the design of any potential randomised trial. If one group of children receives DFMO (the 'experimental' arm) and another group of children do not (the 'control' arm) what should happen with the group who do not? Would conducting a placebo trial be feasible? Would it be ethical, considering the young age of these patients and the fact that for some even taking oral medication is a major challenge? Why would parents enrol their children on a trial where they could receive nothing at all and therefore have zero chance of benefit? The option of fundraising to receive DFMO in America would still exist in case of randomisation to the control arm, potentially resulting in poor protocol compliance that undermines the validity of any trial. Parents may simply elect to withdraw and go off-trial once they discover their child has been randomised to not receive DFMO.

The lack of belief in what a single-arm DFMO study would be able to show and significant challenges in designing and conducting a randomised trial have ultimately meant that discussions have remained just that, and nothing has developed further. Even if an individual clinician believed published results were promising enough for them to want to open the BeatCC DFMO maintenance trial in their own institution, the practical implications of that would be very significant. The principle of fair and equitable access that applies in the UK would essentially mean such a clinical trial would be open and available to all children and families right across the country.

Regarding bivalent vaccine, the only institution that has treated any children to date is MSK. They hold the Investigational New Drug (IND) for the product used in their studies and it is manufactured in their own facility. All of the same points made in respect of DFMO apply equally to the bivalent vaccine, only possibly more so given the only experience thus far has been within a single institution.

The decision by MSK to extend the bivalent vaccine study from one year to five years without as yet reporting any results or opening themselves up to external scrutiny is likely to draw more question marks from elsewhere in the scientific community. There is very little prospect that any UK clinician would countenance supporting an additional five years of active therapy beyond the end of existing frontline treatment. Some parents will undoubtedly feel that more is (must be) better, and receiving additional vaccine shots in years two to five will at the very least serve as some comfort that the point of being totally off-treatment and vulnerable to relapse has not yet arrived. However, the probability of this new trial producing the sort of evidence that will move the field forward more generally is very low – five years for the last patient enrolled to reach the end of treatment plus follow-up is a long elapsed period of time, likely over a decade before results are known. Clearly, experts at MSK have seen something during their experience of using the bivalent vaccine over one year that suggests to them there may be greater benefit gained by administering injections over a longer time period. There are freedoms afforded to experts working at MSK that do not exist elsewhere and that is definitely reflected in this move to go direct from a one year study to a five year study.

It remains to be seen what plans Y-mAbs may have for moving the bivalent vaccine forward. Their strategy with naxitamab was to sponsor a multi-institution study in Europe and North America leading to FDA approval

for treating patients with primary or secondary refractory disease limited to bone or bone marrow. For the bivalent vaccine, for reasons previously stated, obtaining evidence of benefit strong enough to support regulatory filings and commercialisation activities will be more challenging. All of the issues; shortcomings of single-arm study designs, difficulty conducting a randomised control trial with no active comparator arm, ethical considerations around use of placebo, will apply here too and require very careful thought and attention.

Conclusions

Things are seldom straightforward and simple and that is very much the case in respect of UK families accessing clinical trials of DFMO and bivalent vaccine in America. It is easy for some who are not parents to criticise the decision to fundraise to access clinical trials abroad, to criticise charities such as Solving Kids' Cancer UK for supporting families in such an endeavour, to downplay the potential benefit, and focus on the uncertainties and risks. Parents are thrown into a situation where they are faced with a life-threatening and unpredictable disease, limited and imperfect scientific evidence, anecdotal accounts from other families and information picked up in online support groups. Where a parent's only motivation is to do what they believe is in the best interests of their child and what's right for their family no one can criticise them for any of the difficult choices they make along the way.

Likewise, it is easy for some to criticise clinicians for not rushing to open clinical trials to make DFMO and/or bivalent vaccine directly available to children in the UK. Parents are very single-minded in respect of advocating for their child and doing what they believe is best for their child. Clinicians and researchers must do what they believe is in the best interests of all children including those who are not even diagnosed yet, as well as every individual child. Neuroblastoma, like all children's cancers, is under resourced and under funded. Navigating the complex systems and structures relating to health research and delivery in order to develop and run clinical trials is a massive undertaking. The number of children affected by neuroblastoma each year in the UK means that the most scientifically meaningful clinical research must be conducted through international collaboration, adding further complexity. What studies can be conducted where, when, and how with any particular drug is ultimately the purview of the pharmaceutical company who holds the license for it. Importing a clinical trial from abroad and running it in the UK may sound simple, but for all the considerations previously discussed it is not. At the same time, fundraising for and then accessing treatments abroad is not a viable option for all families. If medical professionals were to endorse an unproven – or even a promising but unproven – therapy that is not accessible to all patients they would risk placing themselves and others in a very difficult position. All of these factors, to varying degrees in different circumstances and in respect of different individuals and personalities, parent and professional alike, come into play. There are no right or wrong answers and there are no easy solutions. In these circumstances, understanding and respecting the complexities and different perspectives; being honest, open and transparent; is truthfully the best that any of us can strive for.