

# Immunotherapy and High Risk Neuroblastoma

## Consensus document on the current UK/SIOPEN position July 2011

These comments represent a consensus of UK expert opinion, they do not necessarily represent individual views and will need regularly updating as and when new information arises.

### Survival of patients with high risk neuroblastoma

Survival of patients around the world in developed countries with high risk neuroblastoma is gradually improving due to improved treatments targeting the tumour from different angles. US data from their most recent high risk neuroblastoma trial demonstrate an event free survival at 2 years (taken from study enrolment which was after high dose chemotherapy) with immunotherapy of 66%±5% and without immunotherapy of 46%±5% (Yu et al, 2010).

Recent data on UK and European survival have not been published due to the ongoing European high risk neuroblastoma trial (HR-NBL-1). However one of the aims of this trial which was to determine which of two high dose chemotherapies produced a better event free survival has now been answered. High dose busulphan and melphalan is associated with a 3 year event free survival of 49%±3% from the time point of randomisation prior to high dose. This is comparable with patients in the US who were not randomised to receive immunotherapy who had a 2 year event free survival of 46%±5% from the time point of entry into the study after high dose. The European result above does not include any additional benefit that patients will now have as a result of the introduction of immunotherapy to all eligible patients since December 2009 in the UK and Europe. This means there is no evidence that patients with high risk neuroblastoma in the UK and Europe treated on the current SIOPEN HR neuroblastoma trial fare worse than their US counterparts.

### UK/European antibody trial versus US treatments

The US immunotherapy trial published by Dr Alice Yu and colleagues in the New England Journal of Medicine in 2010 included patients with high risk neuroblastoma who had received many different induction regimens followed by high dose chemotherapy who had had at least a partial response. These patients were then randomised between 2 treatment arms and either received: 1) 13 cis retinoic acid & immunotherapy comprising chimeric (combined human and mouse) 14/18 anti-GD<sub>2</sub> antibody and interleukin 2 (IL-2) and granulocyte-macrophage colony stimulating factor (GM-CSF) or 2) 13 cis retinoic acid alone.

The encouraging results stated above prompted the UK/SIOPEN to modify the randomisation that had been proposed in the SIOPEN HR study between anti-GD<sub>2</sub> and 13 cis retinoic acid versus 13 cis retinoic acid alone, to ensure that all patients would receive immunotherapy (chimeric 14/18 anti-GD<sub>2</sub>). This is the same antibody as used in the US trial. There is an additional antibody available in New York called 3F8. This is a murine (mouse) antibody and has not been tested in a randomised trial.

By comparing anti-GD<sub>2</sub> immunotherapy and cytokines (IL-2 & GMCSF) versus no immunotherapy, it is not possible to determine whether it is the effect of the antibody or cytokines or both that has led to improved survival. Only by comparing each of these components individually will it be possible to determine whether all, or just one, are needed to give the results obtained in the US study. Chimeric 14/18 anti-GD<sub>2</sub> antibody has been used to treat patients after myeloablative therapy in a German study where it was not associated with improved survival, however this was a non-randomised study and it is not possible to conclude that antibody alone is not effective.

Based on the above the UK/SIOPEN devised a randomisation comparing antibody + IL-2 +13 cis retinoic acid versus antibody and 13 cis retinoic acid alone i.e. a 2 arm study. The study coordinators took the decision to use just one cytokine IL2 in combination with the anti-GD<sub>2</sub> antibody as there is both preclinical (animal) and clinical data which suggests that IL2 rather than GMCSF may be more effective. In addition it must be noted that there is no currently available supply of GMCSF for patients in the UK and Europe. The UK/SIOPEN randomisation will establish whether the antibody given with a cytokine IL2 is more or less

clinically effective than antibody given alone. Laboratory tests measuring markers of immunotherapy treatment will be included in the study.

Without testing the effect of antibody alone in a randomised study we will never know if these cytokines are necessary. The side effects of antibody given in combination with cytokines are more severe than with antibody alone and we really need to prove in a randomised trial whether they are necessary. In the UK where we have been giving immunotherapy for over a year now, we have noticed that in patients receiving both antibody and IL-2, the dose of antibody is sometimes having to be reduced due to the more severe side effects seen when they are given in combination.

13 cis retinoic acid is believed to work together with the antibody by making the neuroblastoma cells mature (differentiate) so that they express more GD<sub>2</sub> on their cell surface.

This randomisation has been approved by all UK/European regulatory authorities.

### **Current status of the antibody trial and Eligibility criteria**

In the UK immunotherapy has been available for over a year to all eligible patients on the current high risk neuroblastoma trial. To receive antibody patients must be eligible and consent to the randomisation between antibody & IL-2 and 13-cis retinoic acid v antibody and 13-cis retinoic acid alone.

Patients receive 6 courses of 13 cis retinoic acid and 5 course of immunotherapy. To be eligible patients must be registered on the High risk neuroblastoma trial, be within 9 months of diagnosis to the start of high dose chemotherapy and must begin 13 cis retinoic within 120 days of stem cell reinfusion following high dose chemotherapy.

For patients currently receiving treatment for high risk neuroblastoma who are currently ineligible for the antibody, we are pursuing a study giving this antibody as a continuous infusion with IL-2 and 13 cis retinoic acid and we hope to have this study open in the UK later this year.

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