Standard of Care investigations for patients with neuroblastoma

Patients with newly diagnosed disease

Full assessment should include:

- Cross-sectional imaging of primary tumour site.
- Cross-sectional CNS imaging should be performed in patients with high risk disease and in all infants. There should be a low threshold for performing in other patients.
- 123-I mIBG imaging, ideally with SPECT as well as planar imaging, with assignment of a semi-quantitative SIOPEN score (1). If the primary tumour is MIBG negative, then whole body FDG PET imaging is recommended.
- Biopsy of primary tumour. Immunohistochemistry should be performed locally and INPC subgroup assigned (2). Tissue should also be frozen and sent to the Northern Genetics Service Cytogenetics laboratory (Newcastle) for cytogenetic analysis.
- Collection of bilateral bone marrow aspirates* and trephines
    - Trephines should be assessed locally by immunohistochemistry (IHC) using at least 2 specific markers, and the percentage of neuroblastoma involvement quantified (3)

    * Bone marrow aspirates – see research samples below

- Urine catecholamines (spot urine sample)

Patients with evidence of relapse or disease progression:

Full reassessment should be performed, as detailed above, including CNS imaging. This should include a further biopsy if possible. Biopsy tissue should be sent for full cytogenetics and recruitment to SMPaeds considered.

Reassessment:

Assessment of response to treatment should be in line with the International Neuroblastoma Response Criteria (4).

- In patients receiving front line treatment for high risk disease, a full reassessment should be performed at:
    - End of induction chemotherapy
    - Prior to myeloablative chemotherapy
    - Post myeloablative chemotherapy
    - Post differentiation therapy and immunotherapy

    Assessments at other time points including post-operative imaging of site of primary tumour and repeat bone marrow assessment prior to differentiation and immunotherapy can be considered according to local practice.

- In patients with localised, non-high risk disease, imaging of involved sites should be performed after every 2-3 cycles of chemotherapy.

- Prior to surgery, CT angiogram is recommended as part of surgical planning. In addition, renal isotope scan (DMSA) should be performed if tumour encasing renal vessel and potential renal damage is thought as IDRF.

- In patients with relapsed / refractory disease, reassessment of primary and metastatic disease should be performed after 2 cycles of second/subsequent line chemotherapy. The frequency and nature of further disease evaluations thereafter will depend on the extent of disease and the clinical stability of the patient, but in general patients having active treatment (whether standard or experimental) will require re-assessment of disease every 6-12 weeks.

Off-treatment surveillance

There is no international consensus as to the frequency and nature of surveillance investigations following completion of treatment. However in the UK, current practice and standard of care is usually:

- Imaging of primary tumour site (ultrasound or cross-sectional imaging) every 3 months in first year, and then potentially less frequently.
- MIBG / (PET) imaging only in patients with residual MIBG (PET) positive disease at the end of treatment; 3 monthly in first instance
- Bone marrow aspirates / trephines, only in patients with residual bone marrow disease at the end of treatment; 3 monthly in first instance
- Urinary catecholamines; 3 monthly in first year

Research samples in children with neuroblastoma

Although not a standard of care, it is encouraged that patients/families/carers are approached where possible to seek consent for tissue to be stored in the CCLG tissue bank and also that bone marrow aspirates/trephines and blood samples are sent to Leeds for assessment of minimal residual disease (MRD). However, parents should be aware that both tissue banking and MRD are research activities, and no patient specific feedback from these will be provided to clinicians or families

Ideally consent for the CCLG Tissue Bank should be sought at the earliest appropriate opportunity, although it is recognised that this is not always possible. In view of this, the tissue bank ethics allows samples to be collected for research prior to consent, although consent must be secured within 2-3 months of taking the sample. This covers initial two bone marrow aspirates (one right, one left, not pooled) and blood samples, potentially taken prior to a confirmed diagnosis.

The CCLG Tissue Bank consent covers sending bone marrow and blood samples to the Leeds Children's Cancer Research Group for MRD analysis Samples should be sent in PAXgene™ blood RNA tubes and LAM tubes. Bone marrow aspirates in LAM tubes should be sent to Leeds on the day of sampling; please contact Leeds to set up an MTA prior to sending samples directly to Leeds. During the interim period between any open SIOPEN clinical trials for patients with high-risk neuroblastoma we request that CCLG centres complete an enhanced (but limited) form providing patient clinical detail and outcomes for any patients consented to the tissue bank. These recommendations are made to assist in the collection of valuable tissue for biological studies in a

defined patient group with associated clinical data during this interim period. The samples to be sent to the CCLG tissue bank include:

i) Frozen tumour at diagnosis (primary tumour or biopsied metastatic site).
ii) Paraffin tissue at diagnosis (primary tumour or biopsied metastatic site including bone marrow trephine if infiltrated).
iii) 5ml Blood sample collected in an EDTA bottle for germline DNA extraction- can be done whenever the patient has a reasonable white blood cell count.
iv) 2-5ml plasma collected in an EDTA tube at diagnosis.

All the above except blood for germline DNA should be repeated if the patient relapses

Please see guidelines for sample collection and storage prior to transfer to the CCLG tumour bank on the CCLG website

References

1. Lewington V, Lambert B, Poetschger U, Sever ZB, Giammarile F, McEwan AJB, et al. (123)I-mIBG scintigraphy in neuroblastoma: development of a SIOPEN semi-quantitative reporting ,method by an international panel. Eur J Nucl Med Mol Imaging. 2017;44(2):234-41.
2. Shimada H, Umehara S, Monobe Y, Hachitanda Y, Nakagawa A, Goto S, et al. International neuroblastoma pathology classification for prognostic evaluation of patients with peripheral neuroblastic tumors: a report from the Children's Cancer Group. Cancer. 2001;92(9):2451-61.
3. Burchill SA, Beiske K, Shimada H, Ambros PF, Seeger R, Tytgat GA, et al. Recommendations for the standardization of bone marrow disease assessment and reporting in children with neuroblastoma on behalf of the International Neuroblastoma Response Criteria Bone Marrow Working Group. Cancer. 2017;123(7):1095-105.
4. Park JR, Bagatell R, Cohn SL, Pearson AD, Villablanca JG, Berthold F, et al. Revisions to the International Neuroblastoma Response Criteria: A Consensus Statement From the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol. 2017;35(22):2580-7.