PMT3 study

Prospective Monoamine-producing Tumor study

Phase 3

An international multicenter prospective study of biomarkers for prediction of malignancy and hereditary pheochromocytomas and paragangliomas

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Project outline and justification for data/sample request

1. Investigators

1.1. Recipient Scientist, coordinator of the proposed project

Graeme Eisenhofer

1.2. Status of the Recipient Scientist

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1.3. Associated Investigators

Lead investigators at participating centres with approved PMT protocols: Felix Beuschlein (Munich), Martin Fassnacht (Würzburg), Jacques Lenders (Nijmegen), Andrzej Januszewicz (Warsaw) and Hendrik Lehnert (Lübeck).
ENS@T registry and eCRF support: Anthony Stell, Richard Sinnott (Melbourne)
Molecular genetics: Mercedes Robledo.

2. Project

2.1. Name of Project

Prospective evaluation of plasma and urinary monoamine-related biomarkers for prediction of malignancy and underlying germ-line mutations of tumour susceptibility genes in patients with phaeochromocytomas and paragangliomas (PPGLs)

2.2. Scientific context

At least 30% of all PPGLs have a hereditary basis due to germline mutations in now 11 identified tumour susceptibility genes. Cost-effective testing of these genes can benefit from consideration of specific gene-related clinical manifestations, with recent retrospective studies suggesting that this might include consideration of distinct profiles in monoamine metabolite profiles.

There are currently no firmly established reliable biomarkers to predict the presence or future development of metastatic disease in patients with PPGLs. Data from a recent retrospective study suggest that measurements of plasma methoxytyramine may be useful for this purpose.

2.3. Aim

Characterise the biochemical signatures of different types of catecholamine-producing PPGLs and prospectively determine whether this information can be used to predict tumour burden, the presence or subsequent occurrence of malignant disease and the relative likelihood of specific mutations as a cost-effective and efficient guide to genotyping.

This ENS@T project extends from several secondary objectives outlined in the ongoing multicentre Prospective Monoamine-Producing Tumour (PMT) study to which sic centers already contribute. Opening this part of the study to other members of ENS@T enables more extensive patient recruitment and also importantly aims to provide the infrastructure, resources and samples for related studies (headed by other investigators) for evaluation of other plasma and urine biomarkers for predicting underlying mutations or malignant behaviour (e.g., plasma microRNA profiles by Roland Därr and Jacques Rohayem, Dresden and urine proteomic profiles by Stephanie Fliedner, Lübeck). These related studies (in addition to other studies with other objectives) may thereby be piggybacked on the currently proposed study to allow efficient sharing of relevant data.

2.4. Methods

Patients are enrolled with informed signed consent either as currently achieved through the PMT clinical protocol or as also now proposed here via the ENS@T registry and biobanking protocol (Register und Biobank des European Network for the Study of Adrenal Tumours). Patients entering via the PMT tumour screening protocol only do so after entry into Phase 3 of the protocol, at which stage the presence of a PPGL is established. Patients entering through the ENS@T registry and biobanking clinical protocol are restricted only to those PROSPECTIVELY entered into the registry with newly established PPGLs.

Patient data, as detailed below, are entered into the PMT eCRFs (for patients entering via the PMT study) or the ENS@T PHEO registry. Blood and urine samples are collected according to available standard operating procedures (SOPs) before resection of tumours for biobanking and shipping to Dresden for analyses.

Data concerning all collected specimens, including their shipping to Dresden or other centres, are registered with the ENS@T biobank registry. Samples are shipped according to established SOPs and accompanied by electronic manifests.

Data from analyses at Dresden are entered into appropriate eCRFs or registries as well as provided back to the originating centres utilizing the same electronic manifests employed for sample shipping. Information provided back to originating centres includes predictions on size and locations of tumours, possible underlying mutations and presence or future development of malignancy. This information will be provided back to originating centres with Dresden investigators blind to the relevant information in the registry or eCRFs.

When possible, resected tumour tissue is also collected according to established SOPs, with banking at originating centres and records maintained at the ENS@T biobank registry. Small samples of tumour tissue are made available for analyses at Dresden for correlation of tumour tissue monoamine phenotypes with plasma and urine monoamine-related phenotypes. Such collected tumour tissue is also useful for related studies directed at establishing utility of specific tumour tissue biomarkers.

2.5. Requested clinical annotations (type, justification)

Inclusion criteria:

- informed written consent
- proven phaeochromocytoma or paraganglioma (based on histological examination of resected or biopsied tumour material)

- when tumour material is not available for histological examination (i.e., patients with metastatic disease) inclusion may be based on imaging evidence of metastatic disease (including functional imaging evidence) combined with either a past history of a pathologically proven PPGL or biochemical evidence of excess catecholamine production definitive for a PPGL).

Note: Patient samples may be sent to Dresden ahead of surgical resection and establishment of the formal diagnosis outlined above for inclusion. However, the patient is only included in the study and data are only entered into the registry once the formal diagnosis is made.

Minimum clinical annotations:

- criteria for initial suspicion of tumour
- date of informed consent
- year of birth (month if permitted)
- gender
- if patient has had a previous PPGL
  - number of previous PPGLs
  - Date(s) diagnosed
  - Resected (yes/no)
  - Location(s)
  - Dimensions (x, y, z but at least 1 dimension)
  - Presence of residual disease (YES/NO) and if yes information as to whether metastatic and locations of known metastases
- evidence of a hereditary syndrome, either through family history (with details), presence of clinical stigmata (with details) or findings of a germline mutation (with details)
- imaging evidence for the present prospectively established PPGLs, including imaging modality(ies), tumour location(s), tumour dimension(s) (at least 1 dimension) and any evidence of metastases with details of numbers and locations of metastases.
- If tumours have been resected, date of surgical removal, numbers of tumours resected, location of tumour(s), dimensions of tumour(s) in at least two of the three x, y, z dimensions at pathological examination, and any evidence of metastases from resected lymph nodes etc.

Minimum expected patient cohort per centre: Fifteen patients or 5% of total cohort (aim at 300 including at least 50 with malignant disease).

Data acquisition via PMT eCRFs or ENS@T registry.

2.6. **Requested samples (type, justification of sample size)**

- Plasma (heparinised - 2 x 2 mL for shipping to Dresden)
- Urine (from 24 hr urine, no preservative 2 x 2 mL for shipping to Dresden)
- Germline DNA or EDTA blood for molecular genetics
- tumour tissue when resected (1 x 25 mg for catecholamine measurements at Dresden)

Note: The above samples reflect minimum requirements – additional samples should be collected for banking at originating centres and may also be required for related studies as called for.

2.7. Expected results

Based on already published retrospective studies there is a high likelihood that results from the proposed prospective series will support the underlying hypotheses that profiles of catecholamine metabolites can be used to both predict presence of metastatic disease and underlying germ-line mutations. Two main publications are expected with other secondary publications likely.

2.8. Projected time frame

As of August 2012 with 4 centres enrolling patients over a mean of 1.5 years there have been approximately 60 PPGL patients enrolled into the protocol, including 12 with metastatic disease. There are now 6 contributing centres with approved PMT study protocols. Through this proposal it is aimed to open up the study to at least 6 additional centres. Which should make it possible to enrol 300 patients with PPGLs within 3 years. Therefore the deadline to end data and specimen acquisition is set at October 1, 2015 or three years after protocol approval. Data analysis will be completed within 3 months after this deadline with expected submission of manuscripts in 2016.

3. Publication policy

1. Recipient scientist formally agrees with the provider(s) - at the time of the request or soon after the provider(s) have accepted the collaboration - the(ir) presence (if any) as co-authors in the publications originating from the collaboration.

2. Number of authors per centre and order of authorships are specified as follows:
   1-3 co-authors per centre depending on patient numbers provided as defined in the minimum clinical annotations and projected time frame. Depending on the contribution of each centre or if number of authors has to be limited on the basis of a specific journal style co-authors will be represented as “on behalf of ENS@T” and placed in an appropriate list depending on the Journal format (acknowledgment or collaborators list). In this case the recipient scientist will contact all provider(s) and obtain agreement.

3. Other investigators who have not contributed significant patient material or information may also be included as coauthors, this based on contributions to other parts of the study (e.g., contributions to eCRF and registry development; analyses of DNA).

4. The authors agree to acknowledge ENS@T contribution: “This project has been supported by the European Network for the Study of Adrenal Tumours (ENS@T).” (For ENS@T-CANCER related projects: “The research leading to these results has received funding from the Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 259735.”)

4. Conditions of data use

1. The Recipient scientist will use the data for research purposes only.

2. The data will be used by the Recipient scientist solely in connection with the Research Project as outlined above.

3. The Recipient scientist shall use the data in compliance with all applicable laws and government regulations of the Recipient's country.

4. The Recipient Scientist shall not release the data to any person other than the personnel under the Recipient Scientist’s direct supervision.

5. When the Research Project is completed, a detailed description of the use of the data will be made available to the appropriate ENS@T Working Group.

6. In the event that a journal publication or scientific article is published based on use of the data, the Recipient Scientist will send a copy of such publication, or the publication cite, promptly after it becomes available to the Recipient, to the appropriate ENS@T Working Group

21. August 2012

Date Signature

5. **Conditions of biomaterial usage**

Any use of biomaterial for purposes other than outlined in this study will only be with written approval of centres contributing such biomaterial.