Introduction

Dominique Valteau-Couanet, SIOOPEN President

The SIOOPEN AGM took place in Jerusalem 9-11th October 2018. Thanks to the great organization by Shifra Ash, Isaac Yaniv and their team, we had a very pleasant and fruitful meeting, in a wonderful place and in a town filled with history. This was the opportunity to thank Isaac Yaniv for his major input in the SIOOPEN during the warm and very pleasant dinner gala.

SIOOPEN is growing up after Germany and the Netherlands becoming participating countries last year, Croatia and Lithuania joined SIOOPEN this year. We are now 33 participating countries.

It is thus, more than ever, very important to circulate information from and to the different countries and between the speciality committees. The SIOOPEN executive committee had two strategic meetings in Annecy and in Jerusalem. We agreed that in order to facilitate organisation of the speciality committees, Angelika Eggert would act as a link with the speciality chairs and coordinate feedback to the executive committee twice a year. In addition it was agreed that a short summary will be requested from each speciality committee, after each meeting, that can be shared on the SIOOPEN website. Ongoing trials as well as new ones will be closely followed to help to have a standardized process and help to speed up the opening of the studies, Juliet Gray will be in charge of this task. She will be also in charge of the SIOOPEN publication policy. Gudrun Schleiermacher will coordinate the progress of publications, following up of projects to help achieve publication.

The “other countries representatives” of the Executive Committee will each take responsibility for linking 4 to five other countries to help the participation of these countries in the different SIOOPEN activities. The allocation of countries will be agreed during the next executive committee meeting.

During the AGM, we thanked Julia Balaguer, Tom Boterberg and Godfrey Chan for their input in the Executive Committee and welcomed Adela Canete, Lieve Tytgat and Shifra Ash as new members. In addition we had the pleasure to identify Maja Beck Popovic as president elect. Everyone is very much involved to ensure that SIOOPEN is active, friendly with a fruitful collaboration.

In this issue

Update from the Surgery, Radiotherapy, Radiology, Pathology, Immunotherapy, Molecular Monitoring Group, Biology and New Drug Development Committees!

A newborn in SIOOPEN: European Molecular Tumor Board (EMTB)

Don’t miss these dates
SIOP-E General Meeting, taking place on May 20-25, 2019, in Prague

The SIOOPEN AGM 2019 will take place in Krakow on October 2-4, 2019
### Information about the SIOPEN European Molecular Tumor Board (EMTB)

While clinical tumor conferences often lack experts in molecular biology and bioinformatics, molecular tumor conferences have a strong focus on the interpretation of molecular data, but lack a comprehensive clinical view of the patient and the specific tumor entity. With the SIOPEN European Molecular Tumor Board (“SIOPEN EMTB”) we aim to combine all expertise to provide a rational recommendation for the therapy of a given neuroblastoma patient, taking both, the specific clinical course as well as the molecular data, into account. This approach is likely to provide the best solution for the individual patient. The team includes experts in bioinformatics, biology, immunology, radiology, nuclear medicine, stem cell transplantation, surgery, radiotherapy and pediatric oncology, all with specific expertise in the field of neuroblastoma.

The SIOPEN EMTB is independent of any molecular data analysis platform, but can also assist in planning, initiating and performing appropriate molecular analyses for any patient. The format of the EMTB will be a web-based conference (dial-in see below), that will be conducted every first Thursday each month from 5.00 -6.00 p.m. starting November 8st 2018 (as Nov 1st is a holiday in Germany).

The typical patient to be presented at the SIOPEN EMTB is a patient with a relapsed or refractory neuroblastoma, for whom a salvage therapy is being planned. However, any patient at any point of therapy may be presented.

To register a patient to be discussed within the SIOPEN EMTB, please complete the registration form and send it via email to angelika.eggert@charite.de or via Fax to +49 30 450 566906 at least three days prior to the next SIOPEN EMTB. Please note that the national PI should be informed about a patient registered. Submission of original data of molecular analysis, relevant images and previous recommendations of molecular tumor boards is appreciated, but not mandatory. Please attach any accompanying data or send it in on CD or USB Stick to Angelika Eggert (Postal Address: Prof. Dr. Angelika Eggert, Klinik für Pädiatrie m.S. Onkologie und Hämatologie, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin). A protected server for uploading data as well as radiologic images will be set up in the next weeks.

Treating physicians of any patient to be discussed are invited to dial in and are requested to give a brief overview of the patient’s clinical course. For each discussed patient, a written recommendation from the SIOPEN EMTB will be provided within four workdays.

**Dial-in info:**
The SIOPEN EMTB will be conducted using Skype Business. Physicians who present patients, as well as regular members of the SIOPEN EMTB will be invited via email (that contains all free dial-in information) the day before the SIOPEN EMTB. Free dial-in without invitation will be possible if you have installed Skype Business, or via a web app (cave: you need administrator rights to execute the skype business web app)

**Dates of EMTB:**
- Jan 10th, 2019
- Feb 7th, 2019
- Mar 7th, 2019
- Apr 4th, 2019
- May 2nd, 2019
- June 6th, 2019
- July 4th, 2019
- Aug 1st, 2019
- Sept 5th, 2019
- Oct 10th 2019
- Nov 7th, 2019
The Radiology subcommittee met for their first meeting on 10th October 2018 in Jerusalem.

Main aims of group:
• to provide criteria for structured reporting of imaging of neuroblastoma and creation of case report forms, aiming to warrant a uniform, systematic approach in reporting of neuroblastoma among centres and thus to improve the quality of data available
• to provide updated imaging guidelines especially focused on MRI for the study of primary tumour at diagnosis and for the evaluation of residual local disease after resection. The accurate evaluation of residual disease appears to be a critical issue especially with the forthcoming HR-NBL02 protocol, as randomization for a radiotherapy boost is provided in case of residual local disease
• To establish an e-platform for sharing the imaging of controversial cases with surgeons, radiotherapists and nuclear medicine colleagues. The recent availability of the QUARTET platform appears to be an excellent opportunity to this aim: therefore, the Radiology SC asks access to this platform

Pathology committee:
Chair: Michel Peuchmaur;
Members: Gabrielle Amann, Klaus Beiske, Catherine Cullinane, Emanuele D’Amore, Samuel Navarro, Angela Sementa

We plan to organise an additional SIOPEN Pathology meeting devoted to the organization of the European committee at the same time as the INPC (International Neuroblastoma Pathology Committee) meeting due to be held in Spring 2019 in Milwaukee, Wisconsin, US: The aims of this meeting will be::
• to appoint a new Chair (and/or secretary) for the SIOPEN pathology sub-committee.
• to introduce new candidates: Dr Creytens from Belgium, Dr Gengler from Switzerland, Dr Sartelet from France, Dr Stefanaki from Athens and Dr Tornóczi from Hungary.
• to organize during this meeting a session for reviewing cases of Peripheral Neuroblastoma Tumors both by SIOPEN Pathology sub-committee members and by new candidates.
• to organize after the Milwaukee meeting a joint training session on LINES cases with the new candidates to include application of INPC before they are directly responsible for reviewing such cases in their country.
• to discuss the opportunity of using potential immunomarkers for the further risk stratification within the International Neuroblastoma Pathology Classification, in order to validate them on an European cohort of HR-NBL1 cases, independent from the INPC cohort.
The Immunotherapy subcommittee convened in Jerusalem during SIOPEN AGM to discuss and better define immunotherapy perspectives for SIOPEN. The committee is growing in size, and now has 37 experts in the field of high risk neuroblastoma and immunotherapy. Sadly, Vito Pistoia, a highly recognized immunologist with seminal contributions in the field of translational immunotherapy of neuroblastoma, passed away in September 2018. He was a founder member of the Immunotherapy subcommittee and his expertise and contribution will be missed.

Following a detailed review of the current landscape of immunotherapeutic approaches in neuroblastoma the group worked towards immediate and long-term proposals to be addressed in the preclinical and clinical arena. Topics covered the current landscape of CAR-T cell approaches in neuroblastoma, perspectives with novel immunotherapy agents and combinations, current concepts in stem cell immunotherapy, as well as aspects in immune monitoring of clinical trials soon to open in SIOPEN. The main results and conclusions included that the major activities in the United States, China, Australia and Europe with CAR-T cells in neuroblastoma are encouraging.

However the lack the strong activity signal compared to pediatric leukemia emphasizes the need to further optimized the approach on several levels ranging from CAR design to evaluation of other antigens (ALK, B7H3, GCP2) as well as questions related to manufacturing. 

The approach with hu3F8 and GD2/GD3 bivalent vaccines were also discussed in the group, based on published data and information available from recent meetings. However it was difficult to clearly define the position of these agents in view of the SIOPEN development strategy, which needs further exploration. Signals from clinical using haploidentical stem cell transplantation suggest an allogeneic anti-tumor effect augmented by anti-GD2 antibody, however there is no randomized trial to clearly identify this effect. A trial proposal was presented, which was considered highly interesting, and further refinement related to the control arm are next steps. Finally, the implementation of the analysis of tumor microenvironment in planned immunotherapy trials by analysis of immune signatures of tumor-cells and stroma cells was identified as an immediate topic to further elaborate in a joint meeting with the Biology Group at the spring meeting 2019.

Recent publications

Ladenstein R et al “Randomised use of Interleukin-2 with anti-GD2 antibody ch14.18/CHO in High Risk Neuroblastoma patients. Results of HR-NBL-1 /SIOPEN study” Lancet Oncology. Accepted for publication

Siebert N et al. “Impact of HACA on immunomodulation and treatment toxicity following ch14.18/CHO long-term infusion with interleukin-2: results from a SIOPEN phase 2 trial” Cancers Accepted for publication October 2018

The presence of guests from COG (Paul Sondel; Julie Park) during the immunotherapy subcommittee meeting was enriching the discussion within SOIPEN by sharing transatlantic perspectives related to immunotherapy of neuroblastoma.
The surgical committee’s major achievement this year was a SIOPEN, COG and GPOH initiative leading to the implementation of an international standard for systematic surgery report for neuroblastoma as a (e-CRF). This report consists of three sections (general information, intraoperative details including IDRFs and complications). Our aim is for it to included in the new high-risk protocol and completed on line prospectively, by the surgeon him/herself, or the referent surgeon of the country. The current plan is to disseminate this form and to evaluate its feasibility and usefulness in the future protocols. This initiative will be presented at SIOP 2018 to raise awareness of this international collaboration.

After a short survey on the practice of minimally invasive surgery in neuroblastoma treatment, a larger study was performed collecting 279 patients over 7 countries and 19 centers. 30% presented at least one IDRF. Complete or near complete resection was achieved in 83% of cases, conversion occurred in 9% and surgical-related morbidity in 11%. The paper will be presented in the next SIOP meeting. Finally a work still ongoing aimed at evaluate the influence of residues on the outcome of HR patients in 13 centers from 8 countries. All the post-operative imaging (66% CT scan) were reviewed. Residue was present in 47% of cases but was of very low volume, under 5 ml in 80% of cases and did not seem to influence OS and EFS.

Aims of group
1- to disseminate the surgical e-CRF as widely as possible in order to ensure the quality of the surgical data entered in the new HRNBL2;
2- to be able to study the outcome according to quality of resection and surgical related morbidity;
3- to access to the QUARTET platform in order to share imaging in difficult cases raised by the new HR protocol
4- to analyze the data of the LINES protocol in order to be able to re-stratify IDRFs after chemotherapy and to identify which patients may benefit from surgery after chemotherapy in the groups where the indication of surgery was left pending if IDRFs remain positive.

Recent publications


Presentations and abstracts
CP Van de Ven, et al.
SIOP, Kyoto October 16th - 19th 2018

Minimally invasive surgery for Neuroblastic tumours, a SIOPEN international study.
Hany Gabra, et al
SIOP, Kyoto October 16th - 19th 2018

Radiological description and impact on outcome of postoperative residue after high-risk neuroblastoma surgery
S. Irtan, et al
SIOP, Kyoto October 16th - 19th 2018

The influence of surgical excision on survival in high-risk neuroblastoma revisited after introduction of ch14.18/cho immunotherapy in the HR-NBL1/SIOPEN trial
R. Ladenstein, et al.
ANR, San Francisco, May 9th - 12th, 2018

The influence of surgical excision on survival in high-risk neuroblastoma revisited after introduction of ch14.18/cho immunotherapy in the HR-NBL1/SIOPEN trial
R. Ladenstein, et al.
SIOP, Kyoto October 16th - 19th 2018
The SIOPEN Biology Group, now consisting of members from 17 neuroblastoma biology reference laboratories, has continued its activities in the field of molecular diagnosis of neuroblastoma as well as important contributions to both translational and fundamental research projects. Following Peter Ambros’ announcement of retirement from the position of chair of the SIOPEN biology group, Gudrun Schleiermacher was elected chair, and Sabine Taschner-Mandl secretary of the SIOPEN biology group for the next 4 years.

In the field of molecular diagnosis, in addition to the determination of MYCN, a genomic copy number profile is decisional in particular for patients enrolled in the low/intermediate risk sections of the LINES study, with an online review implemented throughout participating SIOPEN biology reference laboratories. Many laboratories are also participating in precision medicine initiatives (such as INFORM2, MAPPYACTS, IThER) with an aim of characterization of molecular targetable alterations which could then orient towards targeted treatment approaches within biomarker stratified early clinical trials. A neuroblastoma molecular tumor board will aim at exchange of experience in this context.

Several important SIOPEN analyses of retrospective sample collections focusing on an in-depth characterization of specific patient cohorts have been published recently or are currently ongoing: for instance an in-depth molecular analyses of tumors from patients enrolled in LINES study group 8 (NB stage INRG L2, no MNA, > 18 months), HR-NBL01 patients aged 12 – 18 months; study of the ALK genomic status; study of genomic alterations in targetable or other genes based on an NGS panel; clinical relevance of heterogeneous MYCN amplification; and definition of an ultra-high risk, medium risk and low risk group based on a combined genomic and MRD analysis in a SIOPEN HR-NBL01 cohort.

Further projects will also aim at a validation of neuroblastoma patient subgroups defined by associations of genomic alterations such as activation of different telomere maintenance mechanisms (e.g. ATRXdel / Alternative Lengthening of Telomere (ALT) and TERT overexpression/rearrangements) and RAS/MAPK/p53 alterations.

Collaborative research programs will focus on further elucidation of telomere maintenance mechanisms in neuroblastoma, and seek to define the best strategies to analyze telomere maintenance mechanisms in a clinical setting.

Liquid biopsies are a strong tool for studying different aspects of neuroblastoma biology. Circulating tumor DNA found in blood and bone marrow can be used for determination of spatial and temporal heterogeneity, as well as detailed study of clonal evolution, and also present a formidable tool for determination of minimal residual disease when using sensitive techniques such as ddPCR. Furthermore the study of circulating free mRNAs or exosomes can provide additional important biological information. Thus, in addition to a SIOPEN biology group meeting held in Vienna in February 2018, important joint meetings between members of the SIOPEN biology group and MMR group now bring together expertise of different activities in the field of liquid biopsies, with groundbreaking meetings already held in Amsterdam in June 2018 and during the SIOPEN AGM in Jerusalem. Further collaborations are also planned with the New Drugs / NDDS as well as the Immunology group.

The SIOPEN biology group members participated actively at the ANR 2018 meeting in San Francisco, and are already looking forward to the ANR2020 meeting in Amsterdam!

The SIOPEN biology group faces an ambitious program of molecular analyses of both the primary tumor and liquid biopsies within the future HR2 protocol, and financial support for laboratory activities, sample and data management as well as well-organized database structures are of crucial importance for the success of these initiatives.
New Drug Development committee
Chairs: Lucas Moreno and Angelika Eggert

We live in exciting times in the SIOPEN Drug Development Group. Our two cooperative randomised clinical trials for relapsed and refractory patients, RIST and BEACON, are recruiting well and it is expected that they will complete recruitment for the current randomisations soon. We continue to encourage recruitment to ongoing trials in order to speed up the development of new drugs. We are working to incorporate the evaluation of a chemoimmunotherapy strategy with anti-GD2 targeted therapy added to conventional chemotherapy in a future amendment of the BEACON trial.

During this year, we also have started to plan future trials for relapsed & refractory neuroblastoma, once BEACON and RIST close. A number of early clinical trials are coming to reality thanks to our collaboration with ITCC, including the ESMART and INFORM2 personalised therapy trials opening in an increasing number of European countries. An algorithm for the treatment of patients with relapsed neuroblastoma is under development and will soon be disseminated to all SIOPEN members. As mentioned in a specific session above, a molecular tumour board with specific neuroblastoma expertise to discuss options for targeted therapies matched to the patient’s genomic profile has been developed and will start on November 8th 2018. This virtual meeting will be open to all SIOPEN members which will be able to present their complex cases and have obtained molecular data of the respective patients. After discussion in the board, a treatment recommendation including potential targeted therapy clinical trials available across ITCC/Europe will be given. A recent call for people wishing to join the group has been sent by SIOPEN, but is still time to join, if people is interested in joining our group. There is plenty of work to do and we welcome new members.

Recent publications
Risk stratification of high-risk metastatic neuroblastoma: A report from the HR-NBL-1/SIOEN study.

Phase I results of a phase I/II study of weekly nab-paclitaxel in paediatric patients with recurrent/refractory solid tumours: A collaboration with innovative therapies for children with cancer.

Our current primary aim is to evaluate the independent prognostic and predictive power of neuroblastoma mRNAs detected by quantitative reverse transcriptase polymerase chain reaction (RTqPCR) in bone marrow aspirates, blood and peripheral blood stem cell harvests (PBSCs) from children with neuroblastoma. We are also investigating the predictive and prognostic value of circulating small RNAs including microRNAs.

Fifteen countries are collaborating in the study of neuroblastoma mRNAs in children enrolled in HR-NBL-1/SIOPEN. To date over ten thousand samples have been analysed in seven reference laboratories for tyrosine hydroxylase and paired-like homeobox 2B mRNAs using standard operating procedures (Viprey et al, EJC, 43, 341-50, 2007).

In an independent cohort we have validated that high levels of neuroblastoma mRNAs in blood at diagnosis identifies 1 in 5 children who have a particularly poor outcome (Viprey et al, JCO, 32, 1074-83, 2014). We have also confirmed the predictive power of neuroblastoma mRNAs in bone marrow aspirates at the end of induction treatment. For the first time we have demonstrated that high levels of mRNAs in bone marrow taken pre- and post-treatment for minimal disease predicts poor outcome (Burchill, in preparation).

In additional studies we have shown that high levels of neuroblastoma mRNAs in blood and bone marrow taken from infants and toddlers (Corrias et al, PBC, 65, e27052, 2018) and in PBSCs from children with stage M disease (Burchill, in preparation) portends poor outcome. The potential value of neuroblastoma mRNAs in the drug refractory and relapse setting is being evaluated in the BEACON phase II trial.

Four countries are investigating the predictive and prognostic value of circulating microRNAs. In a proof of concept study microRNAs in exosomes isolated from plasma samples have been shown to predict response to induction-chemotherapy and may be markers of sensitivity or resistance to specific drugs (Morini, in preparation).

Thank you to all the people who are contributing to the success of these studies and to the funding bodies across Europe that continue to make our collaborative efforts possible.

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**SIOPEN MOLECULAR MONITORING GROUP**

Chair Sue Burchill

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**SIOPEN MMG Reference Laboratories**

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**Countries participating in the study of neuroblastoma mRNAs and the number of samples by country**
**Nuclear Medicine Committee**  
Chair: Hélène Gauthier

2018 Nuclear Medicine Meetings

i) **SIOPEN Spring meeting in Annecy (4-6th April 2018):**
Topics discussed included:
* the best platform for centralization of the NM images. The group concluded the urgency of reviewing the Quartet –EORTC platform, in order to verify its suitability for NM imaging.
* A specific NM - eCRF to include in the central database of the new HR-2 protocol.

ii) **EANM’18 Congress in Dusseldorf (13-17th October 2018):**
This included a joint Symposium 3- Interactive: Paediatrics /SIOPEN Session on neuroblastoma, Chairpersons Rita Castellani, on behalf of SIOPEN and Zvi Bar-Sever on behalf of EANM–pediatric interest Group. Three invited speakers, L.Biassoni, A.Picardo, and M. Hofman, summarized the most important results of the NM imaging in neuroblastoma, talking about mIBG scans (planar and tomographic) FDG-PET, F-DOPA-PET, 68Ga.DOTATOC.

iii) Jerusalem AGM-SIOPEN meeting (9-12 October 2018): 14 colleagues attended the NM subcommittee, including 12 NM and 2 paediatric oncologists. Discussions included:
* The necessity to systematically perform SPECT imaging in each mIBG exam, including if possible the Upper Hemi-Body.
* The platform for the imaging centralization: agreed that that an urgent decision needed as to which platform to use.
* The e-CRF proposal for NM imaging
* Helen Gauthier, from Lille, was elected as new chairperson of the NM Subcommittee.

Other activities:

i) New scoring work

In October 2017 Keosys and Eusa pharma requested that the NM Subcommittee score additional mIBG scans for those patients treated with immunotherapy. Between January and the first week of February 9 NM SIOPEN specialists performed the first step of this work, by reading about 133 new scans. The second step of this work, officially started on June 2018, is still ongoing.


For the HR 2 neuroblastoma protocol, on the last January 2018 the whole text concerning NM procedures, in particular the NM Appendix and the related bibliography was concluded and sent in France. The last version of this text, after a further revision, has been sent in France on April 17 2018. The first version of the specific eCRF proposal for NM procedures was completed in June and sent in France on the end of July. It will be further discussed just before the effective starting of the new protocol.

Publications of NM SIOPEN Subcommittee 2017-2018


