**Initial Findings of Immunostimulating Interstitial Laser Thermotherapy of Solid Tumours**

Immunostimulating interstitial laser thermotherapy (imILT) is a treatment protocol for solid tumours developed to destroy the tumour at the treatment site while simultaneously inducing an immunologically mediated systemic response against the treated tumour type. Previously clinical treatment data of the method has been presented and in this progress report, a broader array of indications are described. It details the initial findings of the clinical study programme designed to evaluate the safety and usability of the equipment. Thus far, twelve patients exhibiting a wide variety of solid tumours are included in the programme and are described. These early indications point to a satisfactory safety profile and important user feedback from the treatment sessions.

**Introduction**
Local control of cancer is very important, especially in early stages of the disease, and is standard practice in treatment of many tumour types. Local destruction of tumour tissue is available using a wide range of different modalities such as radiotherapy and thermotherapies. Many, if not all, of these local techniques have been shown to induce immunologically mediated systemic anti-cancer effects, abscopal effects. This provides a potential treatment option for metastases at distant sites, even for the micro-tumours that are not yet visible to the radiologist. Interstitial laser thermotherapy, heat generated by laser light, has proven to be both a safe and a very controllable modality to achieve tissue destruction. Aiming to maximise the chances of abscopal effects, a low-temperature laser thermotherapy protocol was developed. This protocol, called Immunostimulating Interstitial Laser Thermotherapy (imILT), has been and is being thoroughly studied pre-clinically in vivo and is currently under investigation in a multi-centre clinical study programme.

A laser unit capable of keeping the exterior of the targeted tumour at constant temperature was developed. The construction of the system consists of a laser generator providing laser light to a silica optical fibre, which is inserted into the tumour, causing heat as the light is absorbed by the tumour tissue. A temperature probe connected to the laser unit is placed in the periphery of the tumour and regulates the laser output, keeping the temperature at the rim of the tumour constant (Figure 1).

Pre-clinical experiments showed that temperatures of 46°C in the periphery of the tumour induced more powerful abscopal effects than higher temperatures and lower temperatures were unable to cause complete tumour destruction at reasonable treatment times. Ensuring total tissue destruction at the chosen temperature requires a prolonged exposure time, 30 minutes, compared to other ablative techniques.

**Technical Specifications**
The TRANBERG Thermal Therapy System is a medical device developed specifically for imILT. The novelty with this system is the automatic tissue temperature control achieved with a feedback system that adjusts the light dose according to the temperature measured in the tissue. The energy source is a built-in laser diode that emits light at a wavelength of 1064 nm up to 25 W continuous wave. The wavelength used by this system is in the near infrared region and is commonly used for laser ablation procedures because of its deeper penetration capabilities. The light is delivered to deeply situated tissues in a minimally invasive way by means of a laser applicator, specifically a non-cooled radial-emitting or diffuser-tipped optical fibre with a construction tailored to enhance its thermal and mechanical stability. The radial emitting fibre creates spherical ablation volumes and the diffuser tipped fibre results in ellipsoid ablation volumes. (Note: please note that the lengths and widths in the tables of original reference are reversed.) This type of laser applicator was used to supply between 1 W and 18 W optical power to the treatment site for the cases presented in this publication. The insertion of the applicator in the target is performed using an introducer by computed tomography (CT) or ultrasound image guidance.

Throughout the imILT treatment, the temperature is measured using an external temperature probe positioned at the edge of the targeted tumour volume. The probe communicates the temperature directly to the laser unit to control the treatment and the resulting outcome in terms of ablation size. The temperature reached in the tissue varies depending on the position of the temperature measurement, the distance from the laser applicator, the treatment stage and the tissue type and condition. While the tumour border is kept at a temperature around 46°C, the tissue closer to the applicator reaches temperatures higher than 100°C during warm-up, when the laser is continuously running.

**Immunological Response**
Local ablation has been shown to induce immunologically driven anti-cancer using a wide range of modalities. This has been experimentally shown to be partly dependent due to the release of cancer antigens. imILT was developed to optimise the immunological events evoked by thermal therapy by operating at a low temperature believed to coagulate less antigens and disturbance to surrounding tissue. imILT treatment results in immediate local tissue destruction and cell activation. Subsequent immunological
Previous Clinical Experience and Current Clinical Study Programme

Prior to the initiation of the currently ongoing clinical programme, 72 patients were treated using the imILT protocol but using a prototype of the currently developed equipment. The malignancies included breast, liver, lymph nodes and pancreas. To retrieve data for safety and feasibility of the imILT treatment, a clinical programme is currently being implemented at six university clinics in Europe. The individual studies cover a variety of solid malignancies of the breast, pancreas, liver, lymph nodes and melanoma. The current data comprises data from the first twelve patients that have been treated within the clinical programme. The clinical programme was initiated in 2015 and is expected to be concluded in December 2017. All studies are performed according to GCP-ICH and have been approved by local ethics committees at the respective study site. On-site monitoring is performed on a regular basis by external, qualified monitors. Study protocols all have an open, non-randomised design with descriptive statistics. Study specifics are summarised in Table 2. For a full list of participating investigators and clinics, please see acknowledgements.

Clinical Findings

Study Population

Patient demographic data and tumour types treated have been summarised in Table 2. Data cutoff was June 6, 2017. Total number of patients in the study programme was 12, of which eight were male and four were female. The patients were between the age of 41 and 83 years at the time of imILT treatment. The performance status (ECOG) of the patients were either 0 (n=5, 63%) or 1 (n=3, 38%).

All patients included in this report were treated using the TRANBERG Thermal Therapy System and radial emitting fibres. The tumour types subjected to imILT treatment include primary breast cancer (n=1), breast cancer metastasis (n=1), colon cancer metastasis (n=2), malignant melanoma metastasis (n=2), pancreatic carcinoma (n=3) and primary pancreatic carcinoma (n=5). All tumour types except pancreatic cancer were treated percutaneously, while the primary pancreatic carcinoma were imILT treated in open surgery. The treatment sites included pancreas, liver, subcutaneous soft tissue, breast and abdominal lymph nodes.

Due to comorbidity, the patients included in this study programme have had numerous prior treatments. Two of the malignant melanoma patients had undergone immunotherapy before receiving imILT treatment but not during the study period (Table 2).

Table 2. Patients included in the study programme.

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>1</td>
<td>8.3%</td>
</tr>
<tr>
<td>Breast cancer metastasis</td>
<td>1</td>
<td>8.3%</td>
</tr>
<tr>
<td>Colon cancer metastasis</td>
<td>2</td>
<td>16.7%</td>
</tr>
<tr>
<td>Malignant melanoma metastasis</td>
<td>2</td>
<td>16.7%</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>3</td>
<td>25%</td>
</tr>
<tr>
<td>Primary pancreatic carcinoma</td>
<td>5</td>
<td>41.7%</td>
</tr>
</tbody>
</table>

Inclusion criteria common for all studies within the study programme include patients: ≥ 18 years of age, have histologically confirmed solid tumour, ECOG performance status ≤ 2, stable hematologic, renal and hepatic functions and informed verbal and written consent to participation in the trial. Common exclusion criteria include: known HIV positive patients, active autoimmune disease, systemic corticosteroid medication, bleeding disorders or anticoagulant medication and pregnancy.
Average age (range) 62 (41-83)

Gender (n=9)
- Male 8 (67 %)
- Female 4 (33 %)

ECOG performance status 06 (67 %)

Most common tumor types
- Pancreatic 6 (67 %)
- Malignant melanoma 2 (22 %)
- Breast 2 (22 %)
- Colorectal 2 (22 %)

Most common treatment sites
- Pancreas 5 (56 %)
- Liver 3 (33 %)
- Subcutaneous 2 (22 %)
- Breast 1 (11 %)
- Abdominal lymph nodes 1 (11 %)
- Total 9 (100 %)

Prior immunotherapy 2 (22 %)

SAE 1 (11 %)

Table 2: Study population. Baseline characteristics of patients of all sponsor-initiated studies (n=9). 1. The gender, total number of patients included in the study, tumour types and treatment sites are given for the total study population (n=12). All other data refer to data derived from the sponsor-initiated studies (n=9). 2. At the time of inclusion in the study.

Safety and Usability of Equipment

One serious adverse event (SAE) has been reported to CLS (Table 2) within sponsor initiated studies, which is 11% of the total number of patients (n=9).

The usability data of the TRANBERG Mobile Laser unit during imILT treatment has been summarized in Figure 3. A score of 1 = easy and a score of 4 = difficult. No statistical analysis is possible yet due to the low number of subjects, but a tendency toward different scores between the study sites can be seen. The initial interpretation is that removal, handling of disposables and sterile access are seen as less complicated while placement of fibres and probes is perceived as more difficult. The feedback of the handling of the laser unit is more variable and needs further analysis to evaluate.

Radiology

Radiological evaluation using CT and/or MR was performed before imILT, in close proximity after treatment and at follow-up visits in all studies. A typical example of the result of ablation can be seen in Figure 4, of imILT treatment of primary pancreatic cancer. Tumours less than 30 mm in diameter, which have been possible to treat radically, were treated successfully. Larger tumours, which were not possible to ablate radically, were initially treated as well but showed continued growth after treatment.

Figure 3: Assessment of imILT equipment usability. Score of 1 = easy and a score of 4 = difficult.

Figure 4: A. Preprocedural axial CT image. Metal stent is visible in the common hepatic duct adjacent to the tumour in the head of pancreas (white arrow). B. Post-procedural axial CT image demonstrates low attenuation, indicating tumour destruction, within the tumour area (white arrow) nine days after treatment.

Summary and Conclusions

In summary, it can be concluded that the imILT can be performed safely and reasonably accurately. The frequency of SAEs and other complications is not higher than what can be expected based on previous knowledge of laser ablation and other local ablative techniques.

A major drawback in evaluating the current data set is the limited number of study subjects. Therefore, no statistical analysis of the data was performed but merely compiled and reported. Taking this into account, preliminary safety data and user feedback is very relevant and a requirement for larger, data-driven conclusive proof-of-concept studies.

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University Hospital, Stockholm, Sweden), Dr Salvatore Paiella (General and Pancreatic Surgery Unit, Pancreas Institute, University of Verona, Verona, Italy), Dr Olivier Turrini (Institut J. Paoli et L. Calmettes, Marseille, France), Prof. Thomas J. Vogl (University Hospital Frankfurt, Frankfurt, Germany). Radiology evaluations were performed locally at each study site as well as centrally by Dr Inger Keussen (Lund University and Skåne University Hospital, Lund, Sweden).

REFERENCES


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