Re 188 Lipiodol Liver Cancer Project at KMCH, Coimbatore, India

This is a summary prepared by Dr Ajit Shinto.

Studies have proven the safety and efficacy of trans-arterial rhenium-188 HDD conjugated lipiodol (radio-conjugate) in the treatment of patients with inoperable hepatocellular carcinoma (HCC).
The radio-conjugate was prepared by using an HDD (4- hexadecyl 1-2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol) kit developed in Seoul National University Korea, and lipiodol. A WARMTH team headed by Dr Ajit Padhy was in Coimbatore, India to help us set up the protocol and radiochemistry in the month of August 2013.
Over a period of 12 months, 23 patients with inoperable HCC or metastatic liver lesions received at least one treatment of radio-conjugate. Only 1patient was re-treated for residual active lesion. The level of radio-conjugate administered was empiric with a range of doses between 60 to 200 mCi. Patients were followed for at least 12 weeks after therapy, until recovery from all toxicity. The clinical parameters evaluated included toxicity, response as determined by contrast-enhanced computed tomography, palliation of symptoms, overall survival, performance status (Karnofsky) and hepatic function (Child's classification). Liver function tests, serum alpha-fetoprotein (AFP) levels, and complete blood counts were done at each follow-up visit. Side-effects were minimal and usually presented as loss of appetite, right hypochondrial discomfort and low-grade fever, even at high levels of administered radioactivity. The symptoms resolved with simple supportive therapy within 3 days of onset. Liver function tests done at 48 and 96 hours showed normalization by 4 days post therapy in all cases and complete blood counts at 1 week, 4 weeks and 12 weeks showed no changes (no bone marrow suppression). Survival at 6 months was 100 %. We could achieve biochemical or imaging stability of disease in almost 50 % and partial or complete regression in another 35 % patients approximately.
Of the 23 patients treated so far, 22 are still alive and do come for regular follow up. All of them report good quality of life. The results of this study show that ^{188}Re-lipiodol is a safe and cost-effective method to treat primary HCC or metastatic liver lesions via the transarterial route. In terms of efficacy, it is potentially a new therapeutic approach for further evaluation by treatment of larger numbers of patients.
There are multiple centers in the country who have requested us to impart knowledge as well as training to set up a similar facility and we are enthusiastic in serving as the nodal training center in taking this modality forward. It would be the least that I can do to further Dr AKP's vision.

In addition, we have developed in house labeling procedures for Re-188 HEDP/Penta-DMSA and SN colloid for radiosynovectomy to make the Re generator more commercially viable. We have also implemented endovascular brachytherapy with Re 188 filled balloons to prevent in-stent restenosis in patients undergoing femoral/iliac artery stenting.

As we wanted to standardize the treatment protocol for these centers which were interested in taking up this therapy as well as to retain this niche modality under the pervasive umbrella of WARMTH, I thought it would be wonderful if we could get all the interested parties to sit down together and commit to a common vision. I attended the Gothenburg EANM meeting in Sweden this month precisely with this in mind and with generous as well as enthusiastic support from our president Prof. Dr. Richard Baum, met up with most of the concerned parties who were key to taking this proposal forward. This informal, round table meeting was extremely useful and all who participated aired their concerns, potential flaws or bottle necks in taking these forward as well as future solutions/suggestions.
The main agenda of the meeting could be summarized as follows:

1. Continuous, uninterrupted as well as cost effective Re-188 generator supply:
This was a prime concern as the generator used by us in India was from POLATOM and they have discontinued their production unit. So it was mandatory to find an alternate supplier who would be committed to this vision on a semi philanthropic basis also to see to the continuity of the project. In this regard we were successful to a large extent as 2-3 companies have stepped forward to see us through with long term commitments (ITG, IRE etc.).They have assured us that it would be called something like a 'WARMTH Re-188 Generator', which would be at 0.5 Ci and be supplied at competitive rates.

2. Standardization of the kits to be used for therapy:
This was of course, a major concern for all the parties as the kit which we have been using, given to us on a compassionate basis from Dr. Jeong's group at Seoul National University, is not a GMP certified product. However, we at Coimbatore have experienced good results and are confident of extrapolating our expertise as well as results to the other centers. But, the other source of concern was, how to standardize the supply as well as scale up the production capacity of the existing facility at SNU or to enable another unit to step into the production of similar kit with an aid/technology transfer enabled and guided by Prof. Dr. Jae Min Jeong. With regards to this concern, it has to be taken up judiciously as well as expeditiously, keeping in mind the initial objectives of the group which started this

therapeutic trial and who were the backbone of this project.
The other option would be to use Re-188 labeled with microspheres .A German group has already used this and standardized the dosimetry as well as labeling technique and Prof. Knut Liepe from this group was asked to present his data and provide suggestions too. We have spoken to a couple of vendors who will be sending us evaluation kits, so that we at Coimbatore will try and standardize the labeling and QC from our end also. This is just as a stand by, in case things are not moving forward.

3. Dosimetry

As it is known that the dosimetry used during the IAEA trial needs up-grading , it was our concern to establish a new dosimetry protocol, which is easy to use as well as can be extrapolated to most departments. Blood, urine sampling, SPECT, SPECT/CT and whole body image based dosimetry protocols were discussed and will be implemented at our department soon. The details of this will be reviewed in the next meeting.

4. Training and workshops:
It was suggested that there should be a Re-188 workshop to be held at Coimbatore, where in all interested hospital departments would be invited to participate in hands on radio-chemistry, dosimetric calculation as well as therapeutic techniques of Re-188 based Lipiodol, HEDP (bone pain palliation), colloid (radiosynovectomy) therapy, so that we at WARMTH may enable cost effective utilization of the generator for any of the centers who want to take it up. Industry partnership and potential sponsorship would have to be discussed further to enable this to happen.

It was also suggested to hold a similar workshop at the next WARMTH meeting at Innsbruck and that Prof. Dr. Irene V should be informed as well as permissions sought.

It was also suggested that KMCH, Coimbatore be a nodal training center under WARMTH for the Re-188 project and any centers interested may contact WARMTH , who could further direct them accordingly.

I have also discussed with IAEA for a technical co-operation project to develop this therapy in countries, who might be interested.

5. Phase II/III trial:

It was generally agreed that the co-ordination as well as funding of this would be difficult. However, if we satisfy certain conditions, it might be feasible for investors to take this product to the next level and even get an Asian approval for a standardized product; provided the above 4 points were met with.

Finally, it was appreciated that we are taking this effort to further the vision and enthusiasm which Dr Padhy displayed for Re-188 and many parties who have been touched by his presence have agreed to stand by hand hold us.