The quality Targeting of Cancer Chemotherapy Using Non-Invasive Focused Resonance Nano-Permeabilization

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Abstract
Focused Resonance Nano-permeabilization (FORN) (US Patent 9,616, 245 B2-Apr 11th 2017) enables the 'targeted' delivery of chemo-therapeutic molecules using a safe, non-invasive, whole-body therapeutic device. The prototype device houses a gantry with specialized, near field, radio-frequency (RF) antennae and guns to deliver instantaneous, magnetic resonance. Drug focusing and delivery was enabled using FORN in a patient with advanced, loco-regionally recurrent, metastatic, nasopharyngeal carcinoma (NPC). Nonionizing, safe, extraneous-source radio-frequencies (RF) were delivered in the presence of an instantaneous magnetic field, to create temporary drug molecular weight-specific nanopores in the cell membrane of target lesions, concurrently with systemic chemotherapy. The high frequency RF is timed and delivered to regions of interest (ROIs) to span peak plasma concentrations of infused chemotherapeutic drugs over multiple treatment cycles. FORN-enabled chemotherapy-related adverse event evaluation and tumor response based on PERCIST 1.0 reflected improved clinical, anatomical and metabolic outcomes and significantly reduced myelosuppression in the patient who received 6+1 Cycles of combination chemotherapy, over an extended period of time. Functional Assessment of Cancer Treatment-Head & Neck (FACT-H&N) / Quality of Life (QoL) and Karnofsky Performance Status (KPS) reflected overall patient well-being. Recurrent, loco-regional disease, nodal, hepatic and skeletal metastases showed dramatic response on PET-CT follow up. Concurrent chemo-radiotherapy (CCRT) as a treatment paradigm is the standard of practice in locally advanced nasopharyngeal carcinoma (NPC).

Keywords
Focused resonance nano-permeabilization, Non-invasive targeted cancer drug delivery, Therapeutic device, Chemotherapy-related systemic toxicity, Effective palliation and clinical response.

Introduction
Targeting solid tumors - primary & metastatic - irrespective of their anatomical location in the body or pathological sub-type - and permeating drug molecules into the targeted tumor mass, will improve therapeutic outcomes and reduce life-threatening systemic toxicities induced by routinely administered chemotherapeutic regimens. Creating molecular dimension-specific temporary pores in the cell membrane using precisely computed, safe radiofrequencies (RF) from an external source, to noninvasively deliver the drug payload, is much less complicated and more cost-efficient than current or emerging invasive, drug delivery approaches. The short-comings of cancer chemotherapy plaguing the industry and patients that desperately need good drugs, can be circumvented with a patented technology called Focused Resonance Nano-permeabilization (FORN) [1].

Although on-going nanotechnology initiatives to deliver "targeted" nanoparticle-coupled drug pay-loads, or nano-variants of existing / new chemical entities are having transformational impact on drug-delivery, the field is fraught with technical and translational road-blocks. It is well documented that complex biological barriers are the major obstacles to treating diseases, and the challenges facing the development of nanoscale platforms to face the enormity of drug-induced toxicities are not simple to surmount [2].

FORN is a process by which the focused delivery of chemomolecules can be enabled by its concurrent use with planned, systemic (and/or oral) chemotherapy. Drug targeting of the chemotherapeutic molecules - carboplatin and paclitaxel during Cycle 2 through 6 and an additional Cycle 7, in a case of advanced, recurrent, metastatic, nasopharyngeal carcinoma (NPC) as part of a proof of concept pilot study, is reported. Systemic chemotherapy was enabled by the concurrent use of non-ionizing, safe radiofrequencies (RF) using specialized antennae in the presence of instantaneous magnetic resonance (MR). FORN is used to create temporary, drug molecular weight-specific nano-pores in the cell membrane of target lesions that are identified in the wholebody, based on pre-treatment MRI-derived proton density (PD) evaluations. High frequency RF is timed and delivered to target lesions, spanning peak plasma concentrations of Carboplatin and Paclitaxel drug until drug wash-out time. The whole body device that delivers the precisely pulsed RF and MR, houses a gantry of RF guns with specialized antennae. The prototype FORN device is modelled after the CE marked, stand-alone, patented legacy device [3] - the Cytotron used for Quantum Magnetic Resonance Treatment (QMRT) applied for tissue regeneration in musculoskeletal disorders like Osteoarthritis (OA), re-myelination in neuro-degenerative diseases like Multiple Sclerosis (MS) and the induction of apoptosis and degeneration of neoplastic tissues in cancer [4].

Loco-regional recurrence in the nasopharynx and metastases in the mediastinal lymph nodes, liver, dorsal vertebrae and iliac crest were simultaneously targeted with FORN in a carefully timed protocol.
Base-line chemotherapy induced adverse event evaluation, before applying FORN, and tumor response criteria based on PET-CT scans, were incorporated with chemotherapy cycles combined with the FORN protocol. Considering that most therapies offered in advanced stages of cancer offer little to no overall survival benefit, the use of a sophisticated yet safe, noninvasive RF and MR-mediated drug delivery technology like FORN, enhanced the therapeutic efficacy of cytotoxic chemotherapy; improved treatment outcomes; dramatically mitigated adverse systemic toxicities and improved Quality of Life (QoL) in this report of an NPC patient presenting with loco-regional recurrence and advanced, multiple metastases.

Case presentation and standard of care chemotherapy A forty-eight year old male patient of Anglo-Indian descent, under treatment for recurrent, metastatic, undifferentiated NPC at the Akika Center of the Japanese Cancer Research Foundation (JCRF), Japan, presented to the Manipal Hospital in Bangalore, India, in April 2013, with relapsed disease, following the 1st cycle of the 5th course of Carboplatin (CBDCA) + Paclitaxel (Total of 6 cycles were originally planned). Concurrent chemotherapy and FORN was initiated in consultation with the medical oncologists who afforded care for the patient in the study at the Akika Center of the JCRF, Japan and the Manipal Comprehensive Cancer Center (MCCC) and Hospital, in Bengaluru, India, together with the authors involved in the study. Detailed, anecdotal case history as well as Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N) questionnaires were initiated and maintained through the treatment period and follow up visits [5]. Karnofsky Performance Scale score (KPS/ K-score) [6] was used to assess QoL at specific time points in the study. Patient's clinical status was periodically recorded at baseline (before therapy) and at the completion of every chemo-cycle in the study.

**Disease and prior treatment history**

2005 (no details available from patient's medical record): A biopsy of a nasal polyp confirmed the diagnosis of locally confined, undifferentiated NPC. Patient was treated with CCRT in USA (6-Gy+weekly Cis-Diamminedichloride Platinum (CDDP) 33mg x 6 wks. (Cycle I) 2010 Nov: Palpable right neck node-confirmed as undifferentiated NPC. Treatment with Cisplatin (CCDP) x 6 wks . (Cycle II) given at JCRF.

2011 Feb: Swollen right lymph node (LN) diagnosed in JCRF as relapsed disease with recurrence in the LN. Cycle III with Cisplatin was discontinued due to severe vomiting and diarrhoea. Cisplatin was replaced with Docetaxel. Subsequently received 4 (Cisplatin) of 6 chemo-cycles in the US concurrently with 6 weeks of radiation.

2011 Feb 22nd III Cycle: DC regimen: Docetaxel 75mg/m2 and CDDP 75mg/m2

2011 Mar 15th: IV Cycle: Carboplatin (CBDCA) AUC 6 + Paclitaxel (PAX) #1-200ng/ m2

2011 Nov 10th: PET-CT confirmed metastatic axillary LN, gradually increasing in size.

2012 March 5th: Presented with cramps and numbness in fingers and pain in upper right hand.PET scan revealed enlarged right axillary LN. Biopsy confirmed relapse of undifferentiated NPC.

2012 March 28th to June 27th: 6 cycles of chemotherapy (carboplatin and paclitaxel) planned at the JCRF. Treatment discontinued after 4 cycles since CT scans after 2nd and 4th chemo-cycles showed no sign of tumor or lymphadenopathy. The CBDCA + PAX# 2-5 resulted in near complete response.

2013 Feb 18th: Pain in right hand combined with cramps and swelling in fingers. CT scan showed loco-regional recurrence of NPC (not ruled out), mediastinal lymph nodes, and multiple skeletal and liver metastases. (Report based on PET-CT of March 4th 2013 done at JCRF).

2013 Mar 27th: CBDCA + PAX # 6 started at JCRF. Significant adverse effects reported. Patient decided to travel to Bengaluru, India to receive un-interrupted chemotherapy +FORN 2013 April 23rd: Day 1: Suggested 6 cycles of Carboplatin (CBDCA+PAX #6) by the Consultant Medical Oncologist at the MCCC in Bengaluru, India.
Baseline / PET-CT scan was obtained prior to chemotherapy planning at the JCRF-Akika, Japan. Periodic post-chemotherapy and FORN assessments were done using ultrasound, CT/MRI or PET.

Chemotherapy infusion schedule and FORN

The first cycle of CBDCA + PAX course # 6 was given at JCRF, Japan. Significant adverse effects were reported by the patient. The patient travelled to Bengaluru, India to continue his chemotherapy schedule under the care of the oncologist at the MCCC and S-CARD for concurrent chemotherapy-enabled FORN. The route and time of administration of the Carboplatin and Paclitaxel was determined and fixed on Day 1 of chemotherapy cycle # 2 given at MCCC. After chemo was administered, patient was transferred to the FORN facility and treatment was administered as per protocol. The details of drugs administered in each of the chemo-cycles with respective pharmacokinetic details critical to the concurrent application of the FORN protocol, is summarized in and detailed in Supplemental Table 1.

![Image](image-url)

**Table 1.** Radiology reports of PET-CT findings are summarized over the time period of March 2013 to January 2014 showing remarkable disease-free survival for nodal, skeletal and liver metastases.

A PET scan was repeated after Cycle # 6 was completed. Evaluation of tumor response was done using PERCIST 1.0 criteria [8,9]. Based on the residual marginal SUV in one mediastinal lymph node, Cycle 7 was planned with the oncologist and enabled with FORN. The patient returned to Japan in September 2013 to resume work.

**Results**

Improvements in symptoms of nausea, fatigue, weight loss, and other related events, determined with the use of patient interviews and FACT-H&N, QoL and KPS-S questionnaires, reflected very good responses. Patient consistently reported that the intensity of side effects commonly experienced in Japan during the course of treatment, was minimal when chemotherapy cycles were administered concurrently with FORN. No episodes of vomiting, diarrhoea or other major gastrointestinal (GI) symptoms were experienced. Patient had Grade 2 increase of 4-6 stools/day over the baseline - after routine chemotherapy without FORN, when assessed based on criteria laid down by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) [10]. More significantly, the patient's overall recovery from any side-effects, were faster. The blood work and adverse events/toxicity profile after the 1st course of the CBDCA/PAX # 6 cycles done at the JCRF, Japan, after the chemotherapy infusion without FORN, is shown in Supplemental Table 2 as an XL spread sheet on pages 2 and 3.
All subsequent hematological work-ups and toxicity related parameters evaluated after each chemotherapy + FORN cycle (4, 5, 6, and 7) is also seen in Supplemental Table 2. Tumor response criteria were evaluated comparing previously refractory lesions using PERCIST 1.0 for metabolic and metastatic disease as seen in PET-CT scans.

| Sl. No | Drug | Molecular Mass | Dose | Mode of Administration | Peak Plasma Concentration Time | Half-Life | Drug Wash Out Time | Infusion Time at Manipulated Hospital | FORN Therapy Time at ONC/MD | Date |
|-------|------|----------------|------|------------------------|-------------------------------|----------|-------------------|-------------------------------------|-------------------------------|------|
| 1.    | Pentoxifylline & dl-hydroxy-pentoxifylline | 385.9g/mol | 260 mg | Infusion Over Three Hours | About 3 hrs | 246 mins (5.6 hrs) | 3 hrs (9:45 am to 12:45 pm) | 2hrs (2:30 pm to 3:40 pm) | 2hrs (2:30 pm to 3:40 pm) | 23/04/2018 |
| 2.    | Carboplatin (cis-Diammine[11-cyclobutenedicarboxyalato]platinum(II)) | 317.246g/mol | 600 mg | Infusion Over One Hour | 66-120 mins | 120 mins | 1 hr (12:45 pm to 1:45 pm) | 2hrs (2:30 pm to 3:40 pm) | 2hrs (2:30 pm to 3:40 pm) | 23/04/2013 |

### Chemo Cycle With Forn Discussion

The majority of patients with squamous cell carcinomas of the head and neck present with locally advanced tumors. The first-line treatment for NPC consists of combined modality management [11,12]. Despite these aggressive protocols, many patients develop loco-regional recurrences with or without metastasis. New technology, more effective and less toxic chemotherapy regimens, and targeted therapy offer new opportunities for treating NPC patients who require multiple chemo-cycles during the course of the disease. Considering that most therapies offered in advanced stages of the disease offer little to no overall survival benefit in NPC [13], the use of an effective drug delivery method to enhance therapeutic efficacy and circumvent systemic side effects was considered. Using FORN concurrently with systemic chemotherapy, in an advanced case of NPC with metastatic lymph nodes, skeletal and liver metastases; dramatically improved survival, tumor response and very good QoL [14,15]. This case is being presented with the intent to disseminate the potential application of a concurrent, non-invasive drug delivery technology to trans-permeate drugs intra-tumorally, in routine clinical practice, along with planned cancer chemotherapy. Electric field pulses reported as inducing transient permeabilization of drugs, have long been known, and extensively reported [16]. Probably the most important feature of a biomembrane is that it is a selectively permeable structure. This means that the size, charge, and other chemical properties of the atoms and molecules attempting to cross it will determine whether they succeed in doing so. Selective permeability is essential for effective separation of a cell or organelle from its surroundings [17]. While electro-permeabilization is a technique using short pulses of electrical fields to cause temporary holes in the cell membrane in vitro, nano-permeabilization is a technique by which temporary pathways are precisely created for a specific molecule based on its molecular weight and size, in vivo. In nanoperm permeabilization, as described in the FORN protocol used in this patient study, specific cells in the ROI were resonated in a high, instantaneous magnetic field, followed by the delivery of nanosecond radio-pulses that penetrate only such resonating cells. This process is achieved non-invasively, within the cells natural environment. Like electro-permeabilization, nanoperm permeabilization can be widely used for the introduction of molecules such as DNA, antibodies, enzymes, and drugs into cells [1]. Research and development for use of the FORN protocol with concurrent chemotherapy, has facilitated the delivery of a variety of small and very large molecule drugs into target tissue, noninvasively, despite all normally restrictive size and permeability constraints.

Controlled drug delivery technology has advanced significantly in the last few decades, leading to the development of various clinical formulations improving patient compliance and convenience [18,19]. The critical intracellular target for cytotoxic drugs is dependent on intracellular concentrations of the drug moiety, and/or its metabolites, which in turn is dependent on membrane permeability [20]. Anti-tumoral drugs therefore need direct access to the cytosol to fully exert their cytotoxic potential. Lower doses than the ones required in classical protocols of chemotherapy regimens could also technically be used to achieve better therapeutic indices even with highly cytotoxic drugs [21]. Potentiating cytotoxicity of various chemotherapy agents and other targeted molecules can also be increased several fold by this focused internalization process enabled by the FORN protocol, just as how the cytotoxicity of Cisplatin is potentiated up to 70 times more in suspended cell cultures using electric pulses in vitro [16]. Such potentiation can be highly controlled using FORN, by in-putting delivery parameters like molecular mass of the drug / active metabolite, peak plasma concentration, total tissue volume and cell membrane characteristics. FORN used concurrently with conventional chemotherapy in this patient with recurrent, metastatic NPC, very clearly potentiated the anti-tumor effectiveness of Carboplatin and Paclitaxel, based on reviewing the disease response and clinical outcome. Drug delivery could be timed and precisely localized in vivo, to achieve the desired therapeutic impact without the somnolent cytotoxic adverse effects. The Institute for Safe Medication Practices (ISMP) using FDA data estimates the 2011 licensed drug death figure at 128,000. This excludes chemo drug deaths, which are classified as cancer deaths. Licensed drugs are the number 4 killer of human beings, according to the FDA's own figures. It is an epidemic. They refer to 2 million "Adverse Drug Reactions" which they call ADRs, and 100,000 deaths a year, with approved drugs.

A startling study by Public Health England and Cancer Research UK has found that cancer treatment itself may be killing up to 50 percent of patients [22]. In a first of its kind study, the researchers on this study dug deeper into cancer patients who died within 30 days of beginning their treatment, indicating that the treatment caused the death, not the cancer. Across the nation, they found that 8.4 percent of those undergoing treatment for lung cancer, and 2.4 percent of those being treated for breast cancer, died within a month of beginning treatment. Results varied greatly based on the hospital however, as an alarming 50.9 percent of those in Milton Keynes Hospital - UK, beginning chemotherapy treatment for lung cancer died within 30 days. Researchers noted that the total number of patients treated at the hospital was much smaller than the norm, but the numbers remain eye-opening, and the list is endless. Efficient and effective drug delivery processes are being increasingly reported in the literature to circumvent issues related to traversing the blood brain barrier (BBB) and improving bioavailability to enhance therapeutic effect. Ideal delivery systems should allow targeting of the drug to tumors. Improving therapeutic efficacy while simultaneously mitigating toxic side effects of commonly used cancer drugs; as well as reducing the iteration of new drugs in the pipeline, due to failed drug trials, is the hope. Although many advances in treatment have been made, they have yielded only modest survival benefits for cancer patients [2].
A major factor contributing to limitations in systemic delivery is dose-limiting drug toxicity. Safe chemotherapy need not be an oxymoron. For the longest time, chemotherapy has been a double-edged sword, with the balance tipping heavily against it, due to the dangers of systemic toxicities accompanying even the best of molecularly targeted agents in this day and age of personalized, precision medicine. Reports and studies have flooded the 'playing' field with every possible combination of drug molecules being used to achieve even minimal survival advantage in very aggressive brain tumors [23-25] as well as in the more long-drawn out but equally aggressive, treatment refractory NPC being discussed here [26-28]. The problem remains that very little consideration is applied to the QoL in these patients being subjected to random drug combinations, with no real understanding of synergies or complicated drug-drug interactions that could induce even more severe systemic toxicities! The challenge has been that the treatment does not specifically target cancerous cells, and randomly destroys normal, healthy, fast-dividing cells in its wake.

"Most cancer patients die of chemotherapy. Chemotherapy does not truly eliminate breast, colon, or lung cancers despite all the years of research and trial designs applied to date. The immune system is hit particularly hard by chemotherapy and the body often does not recuperate enough to adequately protect from common illnesses, leading to death [22]." The fact that chemo only contributes on average about 2% to overall survival rate, is very alarming, and not often discussed. It is important to remember that the "2.1% average" can be deceptive. Some cancers do respond better to chemo than others. According to a 2004 report by Morgan et al. "The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies was estimated to be 2.3% in Australia and 2.1% in the USA."

Technically speaking, an ideal delivery method would be one that achieves adequate coverage of tumor volume while minimizing unwanted toxicities. Optimal delivery requires three important components: 1) the ability to target the tumor while minimizing local and systemic effects; 2) applicability over a wide range of therapies, and 3) a safe, efficacious method of continuous delivery with non-invasive methods while monitoring volumes of distribution (Vd) of agents. Although promising results are now being reported with the use of NAB-paclitaxel combined with cisplatin (NAB-TP) for advanced NPC [31]; a drug used on our patient too, the anti-tumor efficacy in patients with locally advanced NPC needs to be viewed in the light of post-treatment quality of life in patients with multiple, severe metastatic disease as reported here, and managed with concurrent FORN. The toxicities induced by NAB-TP treatment were well tolerated and manageable in this patient, when it was administered concurrently with FORN. Given the protracted course of the disease, and the many cycles of CCRT and multiple chemo-drugs over the survival span of the patient, it was not surprising that he was finally diagnosed with liver failure and encephalopathy. Ironically, although the death certificate assigned the cause of death as metastatic liver disease, a very thorough radiological review of the final PET scan did not show any residual 'metabolically active' disease in the liver (and Table 1). Minimizing systemic exposure, thereby reducing the comorbidities in patients with advanced disease, will allow for significant improvements in quality of life and supportive care for the terminally ill. This outcome should also include improvement in symptoms and patient satisfaction, with reduced caregiver burden. The American Society of Clinical Oncology (ASCO) provided a provisional clinical opinion (PCO) that recommended that end of life counselling should be an integral component of treatment planning even at the earliest presentation of a patient diagnosed with cancer. More often than not, systemic chemotherapies that are given to advanced cancer patients, although essentially hoping to achieve palliation of some kind, are excessively toxic in these patients who are already severely immune-compromised and weakened both by the disease and multiple cytotoxic chemotherapy regimens. A very significant advantage of this process of concurrent chemotherapy with FORN is that it is not restricted to any specific type of drug molecule or solid tumor type.

Drug "focusing" is achieved by MRI derived tissue proton density determinations of ROIs, and creating drug molecule and size-specific temporary nano-pores to accentuate cellular permeability. The NPC case study reported here for the first time, details the procedure in one patient in a pilot study series, who received FORN for 6 consecutive chemotherapy cycles and survived with very good QoL despite the very advanced status of the disease. The pilot study being conducted to clinically validate the technology, included several other patients with a variety of advanced solid tumors like Stage I V Ovarian cancer on 1 cycle of systemic Carboplatin and Gemzar; advanced breast cancer with liver, lung and skeletal metastases on Ixempra + Capecitabine; Ca. Breast with liver, pelvic bone, left adrenal & brain metastasis on oral Lapatinib and Temozolamide; Hereceptin-failed breast cancer, with multiple brain metastases on palliative chemotherapy; Anaplastic Astrocytoma on oral Temozolamide + natural, large molecule Physalis minima; pediatric, recurrent, medulloblastoma on systemic Cyclophosphamide & Etoposide; adult glioblastoma on Temozolamide and natural Curcinomoids; and advanced, radiation-induced secondary, relapsed metastatic osteosarcoma on oral Sorefinib. In all these cases of advanced solid tumor patients, receiving either 'curative'chemotherapy as part of 'standard of care' treatment regimens or palliative chemotherapy, showed significant reduction in drug-induced adverse effects, tolerating previously intolerable, chemotherapy and having very active, good quality of life for the duration of FORN treatment. More studies that combine the power of pharmaco-kinetic and pharmaco-dynamic toxicity criteria, alongside quantitative evaluation of blood, tissue and excretion of infused drug and its active metabolites, over the period of a chemo-cycle, needs to be done. Parallel evaluation of criteria of myelosuppression and other adverse effects in a specific group of cancer patients with advanced solid tumors on different 'trial and error' chemotherapeutic regimens, would throw more light on the projected reduction of drug in systemic circulation during FORN. More importantly, improving and salvaging "failed" drug pipelines with novel drug moietyes, vaccines, genetic materials or any other molecules of interest in vivo, can facilitate novel drug discovery and improve patient compliance using FORN-enabled concurrent chemotherapy, in routine clinical practice.

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