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Tumor Necrosis in a Breast Cancer Case as a Result of a Novel Systemic Magnetic Nanoparticle Hyperthermia "First-in-Human" Safety and Feasibility Trial

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Abstract

Background: We report a case of a patient with metastatic breast cancer that was treated with a novel magnetic nanoparticle hyperthermia approach for the treatment of solid tumors comprising of systemic administration of iron oxide multicore encapsulated nanoparticles, named Sarah Nanoparticles (SaNPs), and Alternating Magnetic Field (AMF) irradiation.

Case description: The patient participated in an ongoing open label feasibility ascending dose study designed to evaluate patients with stage IV solid tumors. The primary objective of the trial was to assess the safety profile of the approach. Eligibility criteria included patients with a life expectancy of at least 30 days, histologically confirmed advanced metastatic solid tumors that have progressed on or after standard therapy. Toxicity was evaluated using standard criteria for the grading of adverse events and tumor response was assessed after a follow-up period of 30 days by evaluating changes in the treated metastatic sites. The case, a 39-year-old female, was diagnosed with invasive lobular breast cancer with multifocal leptomeningeal dissemination and was enrolled to the trial in accordance with the eligibility criteria.

The patient received a SaNP dose of 10% followed by an AMF irradiation dose corresponding to two irradiation intervals of 5 minutes each, and successfully completed the treatment procedures in accordance with the study protocol, demonstrating feasibility and good tolerability. Although tumor response was not expected at these first dose levels, MRI and CT results showed a significant effect in a breast tumor without any concomitant toxicities observed.

Conclusion: The treatment was proven safe and induced necrosis of a tumor mass in a case of advanced breast cancer.

Keywords: Solid tumors • Breast cancer • Magnetic hyperthermia • Iron oxide nanoparticles • Alternating magnetic field

Abbreviations: AEs: Adverse Events; AMF: Alternating Magnetic Field; CT: Computed Tomography; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; EPR: Enhanced Permeability and Retention; IO: Iron Oxide; MRI: Magnetic Resonance Imaging; NOAEL: No-Observed-Adverse-Effect-Level; SaNPs: Sarah Nanoparticles; SAEs: Serious Adverse Events

Introduction

Metastatic solid tumors are a major cause of cancer death and are associated with poor clinical outcome. Treatment of solid tumors involves the use of multiple modalities, such as surgery, systemic anti-cancer therapy and radiotherapy, alone or in combination or sequentially. Although progress has been made in the treatment of metastatic solid tumors, they remain mostly an uncurable condition, and the development of additional treatment options and disease management are needed.

The use of magnetic nanoparticle-based hyperthermia has been recognized as a potential strategy for the treatment of cancer [1]. The method, using colloidal dispersions of Iron Oxide (IO) nanoparticles was first developed for interstitial thermal therapy in locally recurrent prostate cancer and is minimally invasive [2]. Sarah Nanotechnology System, named after a patient who died of lung cancer, was developed by New Phase Ltd. as a non-invasive approach for the systemic treatment of metastatic solid tumors and comprises a ferrofluid of magnetic multicore IO nanoparticles, termed Sarah Nanoparticles (SaNPs) and an Electromagnetic Induction System (EIS). SaNPs are administered intravenously to the patients and accumulate in tumors through the Enhanced Permeability and Retention (EPR) effect. Following delivery and accumulation of SaNPs in the malignant tissue, the patients are exposed to regional non-ionizing Alternating Magnetic Field (AMF) irradiation with the EIS operating at a frequency of 290 ± 10% kHz and field strength between 9-10 mT (7.161-7.957 kA/m). Due to their superparamagnetic properties and unique design, SaNPs transform the electromagnetic energy into heat, reaching a pre-determined temperature of 50 ± 3 °C, allowing heating of the tumor cells where the nanoparticles are located and induction of sub-ablative hyperthermic cancer cell death as previously described [3].

Therapeutic efficacy studies in a murine metastatic cancer model, demonstrated the ability of the treatment to reduce cancer cell viability and the number and size of metastatic lesions [4]. Based on extensive pre-clinical testing, the approach was proven safe, non-toxic, and biocompatible in animal models without any harmful effects [5]. Therefore, a First-in-Human clinical trial was initiated (MOH_2021-20_987) to evaluate this novel therapy. To our knowledge, Sarah Nanotechnology System is the first hyperthermia treatment that uses systemic administration of IO multicore magnetic nanoparticles and regional AMF exposure that has entered a clinical trial.

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In this report, we present a case of advanced breast cancer showing the necrosis of a breast tumor mass following treatment with this new technology. The treatment was proven feasible, safe, and demonstrated encouraging results.

Case Presentation

Patient enrolment

The patient was enrolled in the trial conducted at the Galilee Medical Center in Nahariya, Israel. The medical center received approval from its Institutional Review Board (IRB) ethical committee and the local Ministry of Health (MOH). The patient received and signed an informed consent before initiating the treatment protocol.

The primary objective of the study was to assess the safety profile of the approach, including incidence and severity of Adverse Events (AEs) and Serious Adverse Events (SAEs) related to the treatment, characterized, and graded by the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, and to determine the Maximum Tolerated Dose (MTD) for the Sarah Nanotechnology System. The secondary objective was to evaluate initial signs of therapeutic efficacy based on clinical and imaging assessments.

Eligibility criteria included patients with histologically confirmed advanced metastatic solid tumors that have progressed on or after standard therapy, and patients who have refused to receive standard treatment. Additional inclusion criteria included resolution of all adverse events and at least 2 weeks of elapsed time since the last systemic treatment before enrolment to the study and documented progressive disease since the last therapy confirmed by Computed Tomography (CT) of the chest and abdomen, Magnetic Resonance Imaging (MRI) or PET/CT scans, including brain CT/MRI scans to exclude brain metastases. All imaging had to be performed up to 2 weeks before treatment. The patient had to be ≥ 18 years old with an Eastern Cooperative Oncology Group (ECOG) performance status scale of ≤ 2 and a life expectancy of at least 30 days. The patient was requested to fill in a metal questionnaire to confirm the absence of any electronic conductive implants or metals through the review of CT scans before treatment. An additional pain and discomfort questionnaire was filled in by the patient after treatment.

Study design

The study is an ongoing First-in-Human open label ascending dose trial designed to evaluate the feasibility and safety of treatment in patients (n=21) with advanced metastatic solid tumors.

The patient presented in this case report was part of a first cohort that received a single SaNP injection of 10% (first dose level) corresponding to 0.12 mg/kg followed by AMF irradiation comprising of two irradiation intervals of 5 minutes each with a total irradiation time of 10 minutes (first dose level).

The patient was screened based on the described protocol eligibility criteria and enrolled in the trial once written informed consent was obtained. During the screening visit, demographic information, and medical history were obtained and the metal questionnaire was filled. The ECOG performance status scale was also evaluated. The patient underwent toxicity analyses which included complete blood testing, urinalysis, CT, and MRI scans without contrast media before (baseline), after treatment, and at the end of the follow-up period of 30 days. Vital signs were monitored before, during, and after treatment. Measurements included ECG, monitoring of oral and body surface temperatures, blood pressure, Heart Rate (HR), and oxygen saturation.

Treatment method and dosing

SaNP dose volumes were determined according to the patients' weight on the day of treatment and the IO concentration of the nanoparticles batch. IO concentration was measured by Atomic Absorption Spectroscopy (AAS) and was 2.06-2.40 mg/mL. The dose was calculated based on the No-Observed-Adverse-Effect-Level (NOAEL) approach [6], in accordance with the FDA guideline for the estimation of the maximal safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers [7]. The NOAEL is the highest dose tested in an animal species that does not produce adverse effects and corresponds to a clinical SaNP dose, extrapolated from pigs to the Human Equivalent Dose (HED) [7]. The first clinical dose started at 10% of the 100% HED, after applying a safety factor of 10, according to the FDA guideline.

SaNP administration

Sterile SaNPs were manufactured in a clean room, supplied as a dispersion in water (B|BRAUN Melsungen AG, Germany) and administered to the patient diluted in 5% glucose (B|BRAUN Melsungen AG, Germany), used as a vehicle, *via* an intravenous infusion under control of a syringe infusion pump (Agilia® SP MC). SaNPs used for magnetically mediated hyperthermia included multicore encapsulated IO nanoparticles with a size ranging between 90-165 nm with narrow size distribution, negative zeta potential values within the range of (-5)-(-30) mV, and a Specific Adsorption Rate (SAR) of magnetic nanoparticles of 475 ± 17 [W/g]. SaNP preparation for infusion was done freshly at sterile conditions on the day of treatment. Before dilution, SaNPs were sonicated for 6 minutes in a water bath sonicator at room temperature to ensure a homogenous dispersion. An infusion of saline (0.9% sodium chloride) was administered for approximately 30 minutes prior to SaNP administration and immediately after its completion to maintain the patient hydrated. SaNP doses were administered as a single infusion at a constant rate of 3mL/kg/hr. and filtrated during the injection procedure through a 5-micron filter to prevent the infusion of aggregates and as required by USP <788> for particular matter in injections and parenteral infusions.

AMF irradiation

AMF irradiation was conducted using an Electromagnetic Induction System (EIS) comprising of 3 main adjunct devices: an electromagnetic induction coil with a width of 635.5 ± 0.50mm, high of 435.5 ± 0.50mm, and length of 230 ± 0.50mm, a Radio Frequency (RF) generator, and a chiller that utilizes a closed loop circulating-water system maintained at 20 °C in the coil. The EIS was manufactured by Ultra Flex Power Technologies Co. Ltd., (Sofia, Bulgaria) for New Phase Ltd. and is presented in Figure 1, together with the coil dimensions.

A major challenge in the field of magnetic hyperthermia for cancer treatment is the generation of eddy currents or loops of electrical current within the treated subject. Eddy currents are a direct consequence of the applied AMF, which is used to excite the nanoparticles in the tumor, they run through the resistive tissue resulting in undesired heating of normal tissues that must be minimized [8]. This was achieved by cooling the patient using a specially designed circulating-water Cooling Blanket System (CBS) and thermal monitoring of the irradiated area during AMF application. The AMF area of exposure included the thorax and abdomen (e.g., torso).

For thermal monitoring, the surface temperature of the irradiated area in the patient was continuously measured using Infrared (IR) fiber optic temperature probes (Optocon AG, Dresden, Germany). The probes were placed at different positions on the patient's skin, and they operate at 2 Hz with a ± 0.1 °C resolution. The position of the probes was chosen based on a thermal analytical model aimed to predict the generation of hot spots and placed so that the temperature distribution across the torso area covered by the CBS was constantly monitored [9]. The position of the probes is described in Figure 2A.

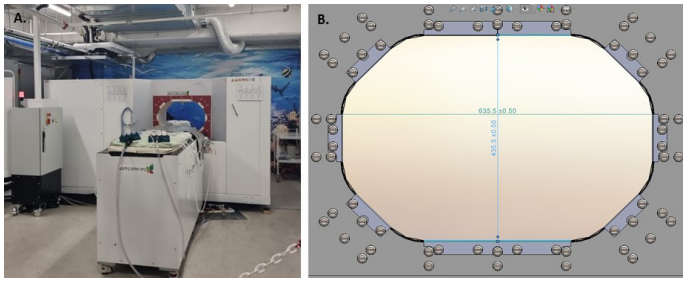

Figure 1. A) Clinical Electromagnetic Induction System (EIS) operating at a frequency of 290 ± 10% kHz and field strength between 9-10 mT (7.161-7.957 kA/m) and **B)** coil dimensions.

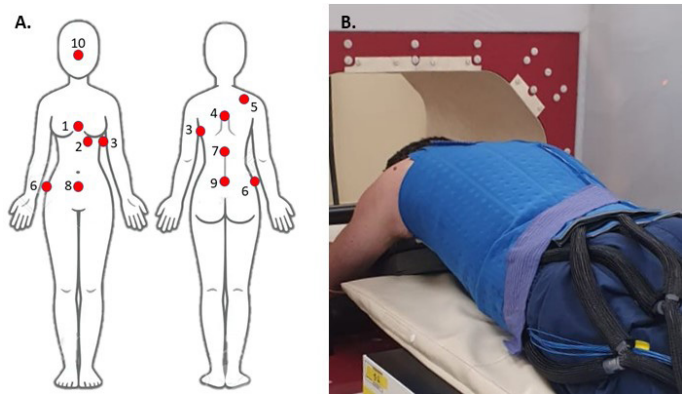

Figure 2. A) Temperature probe positions: Probes 1, 2, 3, and 4 were located on the upper body area and included the sternum (probe 1), inframammary fold (probe 2), right lung (probe 3), and upper back (probe 4). Probes 6, 7, 8, and 9 were located on the lower body area and included the waist (probe 6), mid back (probe 7), abdomen (probe 8), and lower back/lumbar area (probe 9). Probe 5 was located on the shoulder, outside CBS, and used as a reference. Probe 10 was used for the measurement of oral temperature and **B)** For cooling purposes, a circulating-water CBS connected to a chiller was placed around the patient's torso. Temperatures were continuously monitored.

The CBS comprises a warp around blanket and a chiller unit designed to fit a human torso, cool the patient's skin during AMF irradiation and regulate body temperature (Figure 2B). Prior to AMF irradiation, the patient was administered an antacid solution to neutralize gastric acid, minimize electric conductivity and unwanted heating of the stomach, and was then covered with the CBS so that the area of exposure was completely covered to allow a continuous flow of cold water around it. The patient, lying on the bed in a prone position, was then positioned in the center of the coil and AMF application commenced 4 hours post SaNP infusion. AMF irradiation of the patient was conducted intermittently at 10 mT (7.957 kA/m) for 10 minutes, divided into two intervals of 5 minutes each with a break of 7 minutes in between (Figure 2).

Follow-up

Study follow-up examinations included blood testing and urinalysis at baseline, 4 hours, 72 hours, two weeks after treatment, and after the follow-up period of 30 days. Blood samples for hematology, clinical chemistry, and urinalysis were collected and handled at these time points for the patient (Table 1). Hematology parameters included: White Blood Cell (WBC) and Red Blood Cell (RBC) counts, hemoglobin, hematocrit, Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC), Red Blood Cell Distribution Width (RBCDW), platelet, neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts. The following clinical chemistry parameters were evaluated: Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST), alkaline phosphatase, Gamma-Glutamyl Transferase (GGT), Creatine Kinase (CK), total bilirubin, Blood Urea Nitrogen (BUN), creatinine, calcium, phosphorus, total protein, albumin, globulin, glucose, cholesterol, triglycerides, sodium, potassium, chloride, and ferritin. Coagulation was examined by measuring activated Partial Thromboplastin Time (aPTT), fibrinogen, and Prothrombin Time (PT). Urinalysis included color and appearance, specific gravity, pH, protein, glucose, bilirubin, ketones, and blood presence.

Adverse events were assessed after treatment and at each study visit and recorded on a Case Report Form (CRF). SaNP accumulation and clearance in and from target organs was evaluated by MRI. Changes in tumor size and tumor response were evaluated by CT scans which included both target (tumor/s) and non-target lesions. Response criteria were as follows: Complete Response (CR) defined as disappearance of the treated target tumor/s; Partial Response (PR) defined as at least a 30% decrease in the longest dimension of the treated target tumor/s; Progressive Disease (PD) defined as at least 20% increase in the longest dimension of the treated target tumor/s; and Stable Disease (SD) defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD in the treated site/s.

Results

Feasibility and toxicity

The patient, a 39-year-old female, was diagnosed with Invasive Lobular Carcinoma (ILC) ER/PR positive, HER2 negative, with multifocal leptomeningeal (spinal) dissemination. The patient's weight on the day of treatment was 65 kg.

The patient received a 10% SaNP dose followed by AMF irradiation of the torso, conducted for two intervals of 5 minutes each and succeeded to complete the treatment in accordance with the study protocol, demonstrating feasibility of the approach and good tolerability. Although tumor response was not expected at these first dose levels, MRI, and CT results showed a reduction and significant morphological changes and necrosis in a breast tumor mass.

SaNP administration procedure was successful, and no systemic toxicity was observed. There were no significant differences in any of the vital sign parameters measured for oral temperature, blood pressure, HR, and saturation between pre- SaNP, during, and post- SaNP administration. No irregular changes were observed in the ECG readings of the patient before and after SaNP injection.

During AMF exposure, no significant changes nor differences were observed for vital sign parameters measured for oral temperature, blood pressure, HR, and saturation between pre- AMF and post- AMF application, except of a rise in HR which was observed between the start of AMF irradiation at 91 bpm reaching 146 bpm at the end of the AMF cycle (5-7-5 minutes), however, after 10 minutes the HR was reduced to 102 bpm, returning to baseline. According to the clinician, this rise could have been a reaction to the heating or from the patient being stressed.

During AMF irradiation the patient was covered with the CBS and temperatures were monitored using IR optic probes as described above. The use of temperature probes, placed on the skin of the patient's torso, and one monitoring the patient's oral temperature during AMF exposure allowed tracking of changes on the body's surface and oral temperature in real time and provided a good indication of the patient's clinical and thermal condition during irradiation. After the patient was centered in the coil area, in a prone position, the CBS chiller was activated until the water reached 20 °C and CBS reached 24 °C. During the 7 minutes break CBS remained operating.

There were no significant deviations in the monitored temperatures, and CBS was able to control the body temperature throughout the irradiation. The average surface temperature measured at the start of the first irradiation cycle was 26.25 °C and at the end was 26.97 °C. The average surface temperature during the second irradiation cycle remained stable and was at start 26.25 °C and 27.57 °C at the end. Oral temperatures recorded were 37.36 °C and 38.46 °C at the start and end of the first irradiation cycle, respectively, and 38.16 °C and 38.57 °C at the start and end of the second irradiation cycle.

Blood testing included complete clinical pathology of hematology, clinical chemistry, coagulation, and urinalysis. No treatment-related abnormal clinical pathology or urinalysis results were identified. Some fluctuations were observed, attributed to the disease stage. The hematology results were mostly normal with low values in the hemoglobin, hematocrit levels and some of the cell blood counts (WBC and lymphocytes) at baseline and throughout the follow-up period, regardless of treatment. Blood cells count results were not measured after the irradiation, but no deviations from the baseline were observed compared to the other time points and by the end of the follow-up period of 30 days.

In the liver functions, a 1.5- fold increase was observed in the ALT levels after 72 hours (61 U/L) compared to baseline (39.1 U/L) and in the AST levels 4 hours after SaNP administration (40.4 U/L), and after the irradiation (43.5 U/L) compared to the baseline (32.4 U/L). GGT levels were high and above the normal range at baseline which decreased from 55.4 to 30 and 22.5 U/L at two- and four-weeks post treatment, respectively, and within the normal range (9-36

Table 1. The patient's laboratory test results.

Hematology							
Test	**Normal Values**	**Baseline**	**4 hrs after SaNP**	**After AMF**	**72 hrs**	**2 wks**	**4 wks**
RBC (x10e6/ul)	4.00-5.50	3.61	3.78	NA	4	4.1	3.74
Hemoglobin (g/dl)	12.00-16.00	10.4	11.1	NA	11.4	11.6	10.9
Hematocrit (%)	35.00-47.00	31.7	32	NA	35.8	35.7	31.8
MCV (fl)	80.00-100.00	87.8	84.7	NA	89.5	86.8	85
RBCDW (%)	11.0-14.0	13.8	13.7	NA	13.9	13.8	134
MCHC (g/dl)	32.00-36.00	32.8	34.7	NA	31.8	32.3	34.3
MCH (pg)	27.00-32.00	28.8	29.4	NA	28.4	28	29.1
Platelet count	150.00-450.00	183	191	NA	169	187	178
WBC (x10e3/ul)	4.50-11.00	3.3	3.27	NA	2.93	3.28	2.44
Neutrophils (absolute) (x10e3/ul)	1.80-8.00	2.17	2.21	NA	1.98	2.25	1.43
Lymphocytes (absolute) (x10e3/ul)	1.00-4.80	0.71	0.71	NA	0.54	0.6	0.67
Monocytes (absolute) (x10e3/ul)	0.00-0.80	0.23	0.24	NA	0.13	0.19	0.21
Eosinophils (absolute) ((x10e3/ul)	0.00-0.45	0.17	0.09	NA	0.22	0.1	0.12
Basophils (absolute) (x10e3/ul)	0.00-0.25	0.02	0.02	NA	0.02	0.01	0.01
Clinical Chemistry							
Test	**Normal Values**	**Baseline**	**4 hrs after SaNP**	**After AMF**	**72 hrs**	**2 wks**	**4 wks**
ALT (U/L)	0.00-55.00	39.1	55.1	54.1	61	37	13.2
AST (U/L)	5.00-34.00	32.4	40.4	43.5	33	23	19.9
Alkaline Phosphatase (U/L)	40.00-150.00	128	134	127	143	136	107
GGT (U/L)	9.00-36.00	55.4	57.1	59.2	42	30	22.5
Creatine Kinase (U/L)	29.00-168.00	80	90.8	88	89	114	102
Total Bilirubin (mg/dl)	0.20-1.20	0.64	0.73	0.79	0.79	1.36	1.54
Urea Nitrogen (mg/dl)	9.80-20.10	9.39	8.77	11.58	-	-	-
Creatinine (mg/dl)	0.57-1.11	0.6	0.58	0.55	0.62	0.65	0.67
Calcium (mg/dl)	8.40-10.20	9.42	9.45	9.28	9.7	9.85	9.64
Phosphorus (mg/dl)	2.30-4.70	4.01	-	4.01	4.2	4.6	4.49
Total Protein (g/dl)	6.40-8.30	6.46	6.73	6.29	6.88	7.43	6.81
Albumin (g/dl)	3.40-4.80	3.96	4.28	3.93	4.3	4.6	4.29
Globulin (Calculated)	2.30-3.50	2.5	2.45	2.36	2.58	2.83	2.52
Glucose (mg/dl)	70.00-100.00	106.63	89.84	85.4	99	99	86.2
Cholesterol (mg/dl)	-200	133.8	147.8	142.2	163	154	142
Triglycerides (mg/dl)	-150	128.2	115.9	88.8	158	120	107.5
Sodium (mmol/l)	136.00-145.00	138.2	136.8	137	137	139	137
Potassium (mmol/l)	3.50-5.10	3.68	3.69	3.76	3.8	4.3	4.01
Chloride (mmol/l)	98.00-107.00	105.4	107.1	107.2	101	102	104
Ferritin (ng/ml)	13-150	56.39	60.19	55.8	43	40	75.57

U/L). It should be noted that all liver function parameters returned to a normal level by the end of the follow-up period, including GGT, which may suggest some degree of improvement in these parameters. The increases in AST and ALT liver enzymes observed in this patient close to the treatment could be indicative of SaNPs' uptake by the liver and their subsequent clearance. In this patient, the glucose level at baseline was relatively high (106.6 mg/dL), it decreased 4 hours after the injection and after the irradiation to lower and normal levels of 89.8 and 85.4 mg/dL, respectively, and remained within normal levels (86.2 mg/dL) at the end of the follow-up period. No changes were observed in the coagulation parameters and in the urinalysis results after the treatment and during and after the follow-up period (data not shown). The patient's laboratory test results are shown in Table 1.

MRI and CT assessments

CT imaging of the patient with contrast agent before treatment revealed multiple tumor masses in the right breast with a large tumor of a size of 2.6 × 3.2 × 3.7 cm and metastases in the lymph nodes (right axilla), liver, stomach wall, left ovary, and bones. CT imaging after treatment showed a reduction in the same lesion with a size of 2.3 × 3.0 cm, and significant morphological changes involving tumor necrosis. In addition, the patient reported a palpable reduction in the size of the tumor and a softer texture. Although a complete necrosis of the tumor mass was radiologically seen due to a small decrease in tumor diameter the patient was categorized as having SD. Imaging results are shown in Figure 3.

Potential accumulation of macromolecular compounds and nanoparticles in tumors results from the EPR effect, a pathophysiological phenomenon that enables progressive accumulation of anticancer materials in the tumor vascularized area and thus achieve passive targeted delivery and retention into solid tumor tissue [10].

SaNPs can be detected by MRI due to the superparamagnetic properties of the IO-containing nanoparticles. MRI assessments were intended to examine whether SaNPs accumulate in the target tumors and metastases. The method measures the response (relaxation) time of the perpendicular proton spins to the magnetic field of the MRI. The brightness of the image is determined by an inverse relationship to the relaxation time, so that a fast response time produces a darker image. The results of the MRI scanning for this patient demonstrated that there was a significant difference between the response time post SaNP injection which was significantly faster due to the presence of SaNPs in the tumor as well as in the target organ (e.g., breast), compared to the baseline scan. Signal intensities after the follow-up period increased due to time-dependent clearance of the SaNPs from both the tumor and the breast. Results are shown in Figure 4.

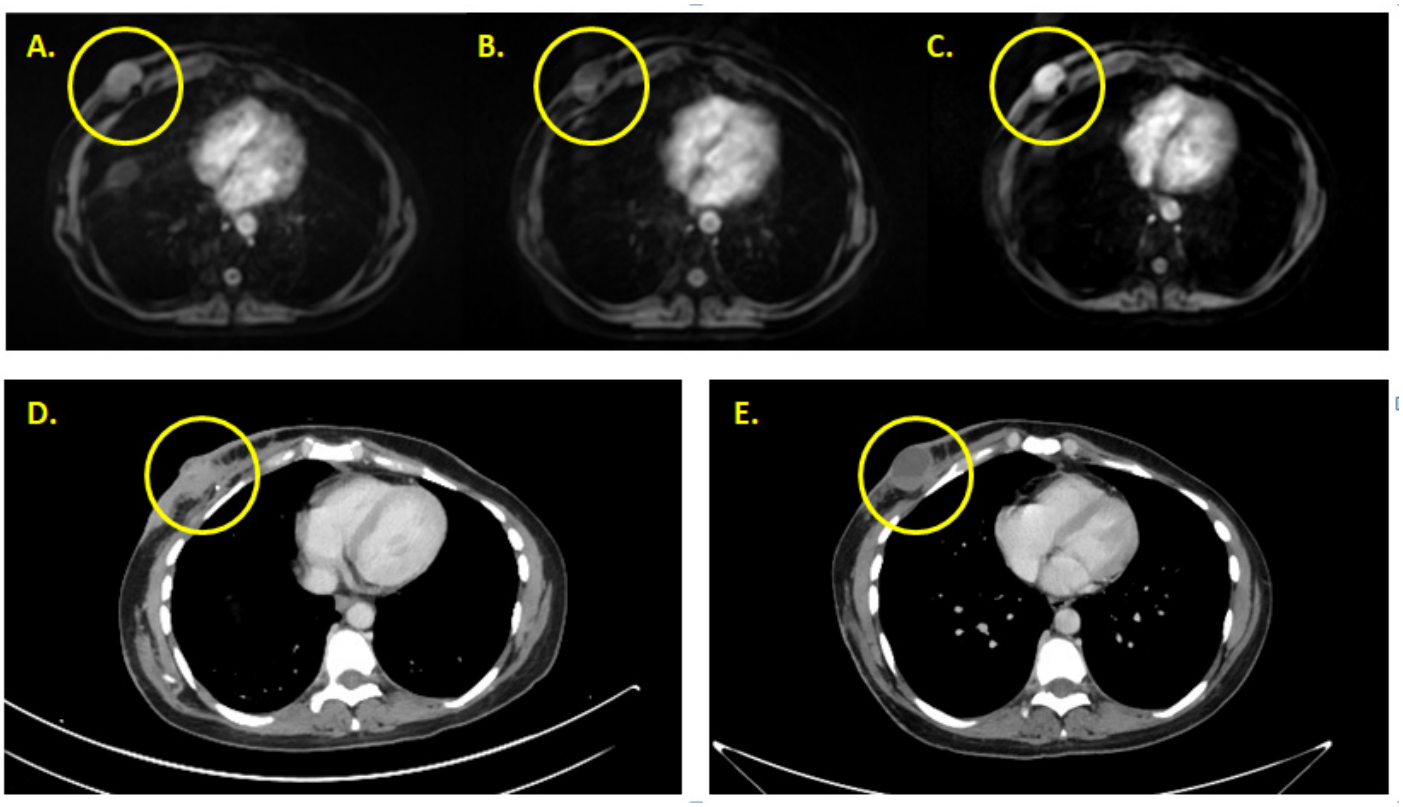

Figure 3. MRI and CT scanning of patient with stage IV breast cancer injected with a 10% SaNP dose+AMF (10 mT). Yellow circles denote Regions Of Interest (ROIs) of a metastatic solid tumor. MRI scans were obtained using a T2* mapping mode: **A)** Baseline, **B)** 4 hours after SaNP injection, **C)** 30 days after SaNP injection and **D & E)** CT results at baseline and after the follow-up period of 30 days.

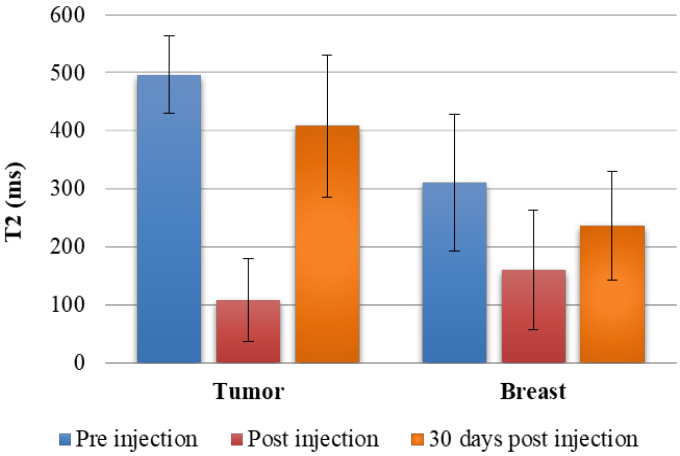

Figure 4. T2* mapping of signal intensities in the target tumor and breast measured in MRI scans at pre-injection (baseline), 4 hours post-injection and 30 days post-injection.

Adverse events

ECOG performance status of the patient was not affected by the treatment. In the pain and discomfort questionnaire filled after treatment, the patient reported feeling of heat in the lower back (lumbar) area, throughout AMF exposure which ceased after the treatment ended, defined as a grade 1 adverse event (e.g., mild, and asymptomatic). This was attributed to the generation of a hot spot in this area as predicted by a thermal simulation model [9]. Local pain was reported, which was transient and gradually faded. No additional AEs nor SAEs were identified during the treatment or follow up. The patient felt cold before irradiation and during the break while the CBS remained operating. Medium discomfort was described by the patient regarding the CBS wearing process and during its operation.

Discussion

We report herein initial clinical results of an advanced breast cancer case that participated in a First-in-Human trial evaluating the safety and feasibility of Sarah Nanotechnology System. The results demonstrate that SaNP administration followed by AMF application was not associated with any SAEs, except of a grade 1 AE involving transient local heat and pain in the lower back of the patient which ceased after the irradiation ended, and no clinical or humoral toxicity was observed at starting doses of 10% SaNP and 10 minutes of AMF irradiation, supporting a favourable safety profile compared to other standard therapeutic modalities.

The procedure of SaNP infusion was successful and an AMF strength of 10 mT (7.957 kA/m) was well tolerated by the patient although it requires optimization related to the patient's comfort during CBS use and irradiation.

To date, there are no other comparable systemic magnetic hyperthermia treatments but previous clinical trials using superparamagnetic IO nanoparticles for localized treatment of various cancer types including Glio Blastoma Multiforme (GBM), cervical cancer, soft tissue sarcoma, and prostate carcinoma have demonstrated that the treatments were well tolerated at magnetic field strengths of 3.8-13.5 kA/m in GBM patients, 3-5 kA/m and up to 8.5 kA/m in the upper thorax and pelvic areas, respectively, of patients with recurrent and residual tumors, and 4-5 kA/m in prostate cancer patients [11]. All the reported treatments had only minor to moderate AEs which included feelings of heat, increased HR or blood pressure, and superficial skin burns in some cases. Of note, these studies were thermo-ablative, utilized intratumoral administration of the nanoparticles and a local AMF applicator with a variable field strength as in the case of MagForce Nanotechnologies AG (Berlin, Germany) [12].

Conclusion

Based on the initial results in this patient, we cannot make a decisive conclusion regarding the clinical outcome, however, the results were promising and demonstrated a reduction in the size of a breast tumor mass which became necrotic after treatment suggesting that the approach is feasible, can be safely applied in humans, induce thermal tumor damage, and potentially leads to initial signs of therapeutic efficacy.

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Declaration of Interest

The authors declare the following competing interests: Sarah Kraus, Boaz Shalev, Shir Arbib, Pazit Rukenstein, Moshe Eltanani, Udi Ron and Ofer Shalev are employees at New Phase Ltd. Shaul Atar declares no conflict of interest.

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