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Effective treatment of metastatic cancer by an innovative intratumoral alpha particle-mediated radiotherapy in combination with immunotherapy: A short review

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Abstract. Alpha radiation is a lethal form of radiation whose short range limits its use for cancer treatment. A unique intra-tumoral alpha radiation-based tumor ablation treatment termed *Diffusing Alpha emitters Radiation Therapy* (DaRT) was developed and tested for tumor ablation and stimulation of anti-tumor immunity. Radium-224 loaded wires (Alpha DaRT seeds) are inserted into the tumors and release by recoil short-lived alpha-emitting atoms. These atoms disperse in the tumor at least 5 mm from the source and spray it with highly destructive alpha radiation. DaRT was found to destroy solid malignant tumors experimental animals and in patients with cutaneous malignancies. Tumor destruction resulted in activation of specific anti-tumor immunity. DaRT provides, for the first time, an efficient method for treatment of the entire volume of solid tumors by alpha radiation, and could be used not only as a local treatment but also as a therapeutic strategy to induce strong systemic antitumor immune responses, which will eliminate residual disease and metastases in distant sites. This combined treatment modality holds significant potential for the treatment of non-resectable human cancers.

1. Introduction

The use of alpha radiation for treatment of solid tumors is limited due to the short range of alpha particles in tissue. *Diffusing Alpha emitters Radiation Therapy* (DaRT), which was developed in our laboratories, can overcome this limitation and enable treatment of solid tumors. DaRT is the only efficient method for treatment of the entire volume of solid tumors by alpha radiation. Radium-224 loaded sources (DaRT seeds) are inserted into the tumors and release by recoil short-lived alpha-emitting atoms. The decay chain results in the production of Rn-220, Po-216, Pb-212, Bi-212, Po-212, Tl-208, and finally non-radioactive lead Pb-208 (Figure 1). These atoms disperse in the tumor, mainly by diffusion, to a distance of at least 5 mm and kill tumor cells of various histotypes. Thus, a sizable fraction of the tumor is irradiated by alpha particles, and because of their short half-life, the isotopes marginally disperse in the body [1-6]. DaRT was used for the treatment of experimental tumors and of patients with cutaneous malignancies.



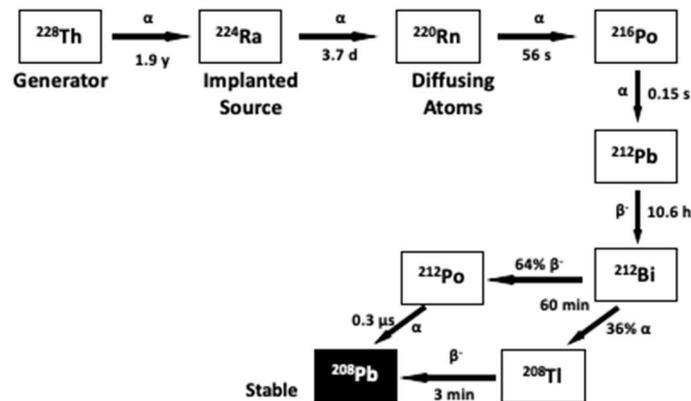


Figure 1. ^{224}Ra decay chain.

2. Results

2.1. Anti-tumor effects of DaRT

Treatment of experimental solid tumors in mice with Ra-224 loaded seeds yielded the following results:

- Significant retardation of tumor growth, tumor necrosis, extended survival, and reduced lung metastases in animals bearing murine squamous cell [1-3], lung [4], pancreatic [5], colon [6], prostate and breast [7] mouse derived tumors, and human derived tumors [8].
- Autoradiography measurements indicate that the alpha dose exceeds 10 Gy up to 2.5-3 mm from the seed, rapidly dropping to negligible levels at larger distances. The beta and gamma dose drop below 1 Gy ~3.5 mm away from the seed. The assumption that all beta and gamma emissions originate from the seed provides an excellent approximation to the case of ^{224}Ra daughter atom diffusion [1,2].
- An augmented level of local control was achieved when a combined treatment of Ra-224 wires and chemotherapy was applied [3-6].
- The radiosensitivity of tumor cells to alpha radiation was in correlation with their ability to avoid or repair double strand breaks.

Thus, DaRT is an effective alpha radiation-based treatment to for solid malignant tumors and can be further potentiated by chemotherapy. This combined treatment modality holds significant potential for the treatment of non-resectable human cancers.

2.2. Activation of anti-tumor immunity following tumor ablation by DaRT

Ablation of the tumor by alpha particles can result in the release of tumor antigens and local inflammation which subsequently trigger a specific anti-tumor immunity [7]. In subsequent studies we examined the induction of anti-tumor immunity and the elimination of metastatic tumors following treatment of experimental tumors by Ra-224 loaded DaRT seeds combined with immunomanipulation.

Subcutaneous tumors from colon and breast carcinoma origin were treated with Ra-224 loaded stainless-steel wire(s) (DaRT seeds) with or without immunomodulating agents. Mice bearing DA3 mammary adenocarcinomas with metastases were treated each by intratumoral insertion of DaRT seeds in combination with prolonged supply of the myeloid derived suppressor cell (MDSC) inhibitor, sildenafil, in the drinking water, T regulatory cells inhibitor, cyclophosphamide, and the immunostimulant, CpG. Local tumor growth and the development of lung metastases were monitored.

Treatment of animals by DaRT combined with CpG, sildenafil and cyclophosphamide (immunomodulators, IM) significantly retarded tumor development and several tumors completely regressed (Figure 2).

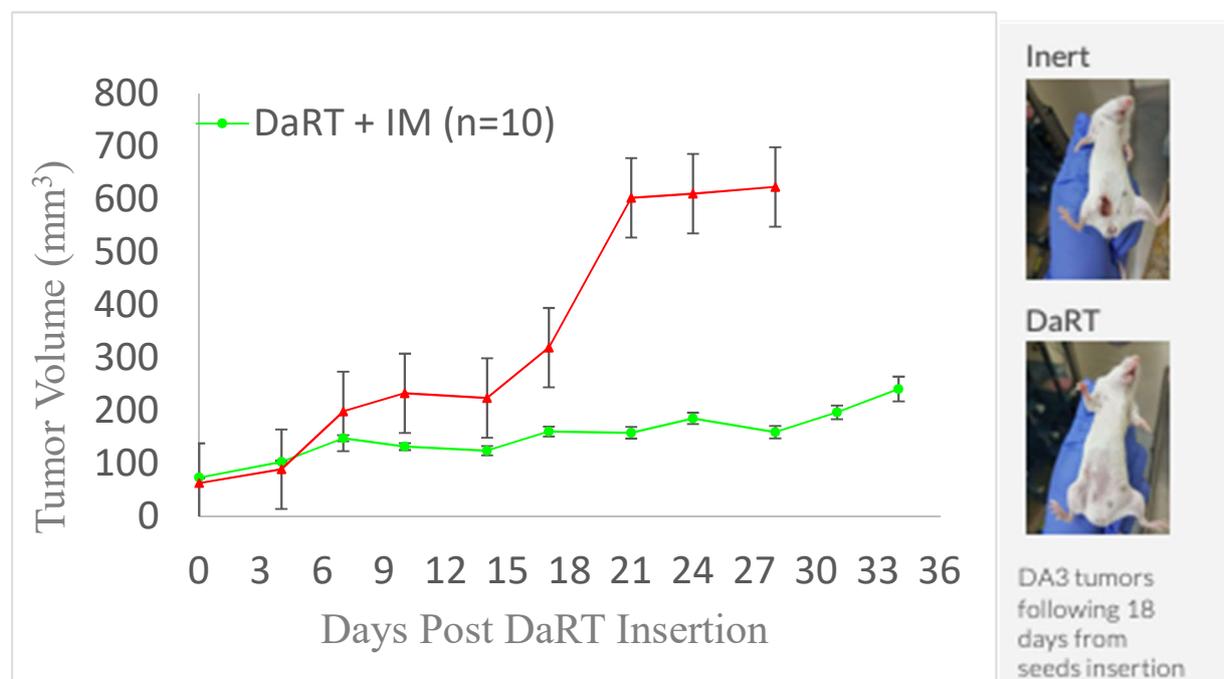


Figure 2. Tumor volume measurement of DA3 primary tumors treated with DaRT and immunomodulators. Mean tumor volume between groups was statistically significant on day 2 (\pm SEM. p (T-test) < 0.05).

In another study where DA3 tumor bearing mice were treated by DaRT combined with the 3 immunomodulators, out of 20 mice in the DaRT plus immunomodulators group, in three the tumors completely regressed, 16 regressed but recurred, and one outgrow. In the control group, one tumor regressed, eight showed a partial response and 11 grew progressively. DaRT with the 3 reagents reduced the lung metastatic burden. Only 30% of treated animals carried lung metastases compared with 55% of the mice treated with an inert wire and the three reagents, and 100% in DaRT treated animals. Tumor bearing mice treated with DaRT and the immunomodulators displayed a significant resistance to the growth of a tumor re-challenge, as compared to the control [9].

In a subsequent study [10] the antitumor immune response induced by destruction of colon cancer CT26 derived tumors by DaRT was investigated and attempts were made to amplified it by various TLR agonists. Treatment of solid tumors in the skin by DaRT concomitantly with the TLR3 agonist, poly I:C, inhibited tumor growth relative to poly I:C or DaRT alone. DaRT used in combination with the TLR9 agonist, CpG, resulted in tumor rejection in 41% of the animals while DaRT with the TLR1/2 agonist XS15 resulted in 20% tumor-rejection. DaRT in combination with CpG, the Treg inhibitor and the MDSC inhibitor caused tumor rejection in 51% of the animals, compared to only 6% when immunomodulation or DaRT was used alone, and 0% in DaRT alone treated animals. Challenge and Winn assays revealed that these high cure rates involve a specific immunological memory against CT26 antigens but not breast carcinoma (DA3) derived cells [10].

Treatment with DaRT in combination with immunostimulators such as polyIC^{PEI}, significantly attenuated the growth of highly metastatic triple negative breast tumors in mice and eliminated lung metastases. DaRT combined with such immunoadjuvants, and inhibitors of regulatory T lymphocyte or myeloid derived suppressor cells, cured colon and breast carcinoma tumor bearing mice.

We suggest that DaRT acts in synergy with immunomodulation to induce a specific and systemic antitumor immune response. This strategy may serve as a safe and efficient method not only for tumor ablation, but also for *in situ* vaccination of cancer patients.

2.3. Clinical trials in which DaRT seeds were used to treat SCC cancer patients.

- Twenty-four cancer patients (ages 61-102), with histopathological confirmed skin or oral cavity SCC, and tumor size ≤ 5 centimeters in the longest diameter, were treated by DaRT seeds (1 cm long and 0.7 mm in diameter) each carrying a dose of 2 μCi , placed up to 5 millimeters from each other. Two to four weeks after implantation the seeds were removed, and six weeks after treatment CT was performed to assess the effect of treatment. The age of the patients ranged between 61 to 94 (median 81). Twelve tumors were treated within radiation failure fields (Radiation dosage >60 Gy). All tumors responded to treatment; Complete response was achieved in 78% of the patients and 22% showed a partial response. With a median follow up of 7 months (ranged from 1 month to 21 months), there were 5 local recurrences. Median overall survival was 18.53 months and disease-free survival rate of 91.7% and 55.6% at 3- and 21-months, respectively [11].
- Blood and urine samples were taken at days 5, 11 and 30 post treatment, and measured to determine the specific activity of ^{212}Pb . The measured ^{212}Pb activities in blood and urine samples were consistent to leading order with the predictions of the biokinetic model (12). The average alpha particle dose to the kidneys and bone marrow was 2 ± 1 cGy and 0.9 ± 0.6 cGy respectively.
- In this feasibility and safety human study it was demonstrated that alpha particles-based treatment (DaRT) exhibit enhanced radiobiological potential. After a long term follow up. The treatment was effective against radio-resistant SCC tumors. No major toxicity was noted during a median follow up of 12 months [11].
- In a clinical study, DaRT treatment of an SCC patient, resulted in the manifestation of anti-tumor immunity (abscopal effect). A woman affected by lower limbs metachronous cSCC had 3 lesions on her legs. DaRT was delivered by Ra-224 loaded wires (DaRT seeds) inserted into one lesion. Follow up examinations revealed a progressive reduction in volume of the treated lesion as well as in the distant two untreated ones. Complete remission of both treated and non-treated lesions was assessed by dermoscopy and confocal laser microscopy and confirmed by biopsies. It is evident that alpha particle treatment of cSCC can cause an abscopal effect [13].

3. Conclusions

DaRT is an effective treatment to destroy solid malignant tumors. Ablation by alpha particle (DaRT) turns the tumor into its own cancer vaccine and could be used not only as a local treatment but also as a therapeutic strategy to induce strong systemic antitumor immune responses, which will eliminate residual disease and metastases in distant sites. This combined treatment modality holds significant potential for the treatment of non-resectable human cancers.

4. References

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