

Modulated electro-hyperthermia as an immune-modulator with checkpoint inhibitors and radiotherapy

Carrie Anne Minnaar¹, Jeffrey Allan Kotzen²

¹ University of the Witwatersrand, Radiobiology, Johannesburg, South Africa.

² Wits University Donald Gordon Medical Centre, Radiation Oncology, Johannesburg, South Africa

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Modulated electro-hyperthermia as an immune-modulator with checkpoint inhibitors and radiotherapy

C.A. Minnaar¹; J.A. Kotzen²;

¹ University of the Witwatersrand, Radiobiology, Johannesburg, South Africa.

² Wits University Donald Gordon Medical Centre, Radiation Oncology, Johannesburg, South Africa

INTRODUCTION:

Abscopal Effect: Ionizing radiation (IR) is known to occasionally induce a systemic response to local disease, which appears to be mediated by immune responses triggered by IR.

Modulated Electro-Hyperthermia Modulated electro-hyperthermia (mEHT) is a targeted and specialized HT technique which selectively affects the cell membrane of malignant cells, inducing several immunological processes which can be harnessed for the management of malignancies.

Relevant Research There is an ongoing Phase III randomized controlled trial in South Africa investigating the effects of the addition of mEHT to standard chemoradiotherapy protocols for locally advanced cervical cancer (including HIV-positive patients). 54 participants in each treatment group had disease outside of the radiation field before treatment. At six months post-treatment a complete metabolic response of all disease inside and outside of the radiation field was seen in the 13 mEHT group participants (24.1%), compared to 3 control group participants (5.6%), Chi2, Fisher's exact: p=0.013). The effect was seen equally in the HIV-positive and -negative participants.

The authors propose that this is due to the immune modulating effects of mEHT potentiating the abscopal effect of IR. These significant results prompted a literature search for ongoing or completed studies on HT or mEHT, immune checkpoint inhibitors (ICI), and IR.



OBJECTIVE:

To review available literature and studies, including ongoing studies on HT or mEHT, immune checkpoint inhibitors (ICI), and IR, in order to ascertain whether there is a gap in the knowledge which warrants further development of trials/studies on the combination of mEHT and ICI with IR.

METHOD:

We reviewed trials in clinicaltrials.gov and PubMed using the search words "Hyperthermia", "immune checkpoint inhibitors", and "cancer". Ongoing and completed studies were included on ICI-naïve patients from ClinicalTrials.gov. Studies using whole body irradiation or proton therapy were excluded.

RESULTS:

ClinicalTrials.gov: 17 trials met all the criteria except for the inclusion of HT. ICIs used included durvalumab + tremelimumab, nivolumab, ipilimumab, pembrolizumab and atezolizumab. Two studies included HT but not IR. No results included mEHT. No results were returned on HT or mEHT combined with ICI and IR in PubMed, although several reviews detailed the immunological effects of HT and mEHT and the suggested a benefit to its combination with IR and ICIs.

Phase II Studies involving Capacitive RF Hyperthermia

2017	recruiting/ ongoing	pembrolizumab	Mesothelioma	NCT03393858
2017	recruiting/ ongoing	pembrolizumab	Abdominal metastases	NCT03757858

RESULTS Continued:

Observational Studies on ICI and IR

2017	recruiting/ ongoing	Any tumours	metastatic tumours	NCT03042156
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Phase I Studies on ICI and IR

2018	not yet recruiting	Ipilimumab Nivolumab	NSLC metastatic	NCT03509584
2018	recruiting/ ongoing	Durvalumab Tremelimumab	Metastatic gyn cancers	NCT03277482

Phase II Studies on ICI and IR

2016	recruiting/ ongoing	Nivolumab	Metastatic renal cell carcinoma	NCT03469713
2016	recruiting/ ongoing	Durvalumab	Metastatic colon and lung	NCT02888743
2016	completed	Ipilimumab	Metastatic melanoma	NCT02406183
2016	recruiting/ ongoing	Pembrolizumab	Metastatic melanoma	NCT02562625
2016	recruiting/ ongoing	Pembrolizumab	Upper GIT metastatic	NCT02830594
2017	recruiting/ ongoing	Tremelimumab Durvalumab	Metastatic	NCT03212469
2018	recruiting/ ongoing	Pembrolizumab	Metastatic unknown primary	NCT03396471
2018	recruiting/ ongoing	Durvalumab Tremelimumab	Metastatic SCC, Head and neck	NCT03283605
2018	not yet recruiting	Tremelimumab Durvalumab	Metastatic bladder	NCT03601455
2018	recruiting/ ongoing	Nivolumab Ipilimumab	Metastatic melanoma	NCT03354962

Phase III/Randomised Studies on ICI and IR

2018	not yet recruiting	Nivolumab\atezolizumab pembrolizumab	NSLC metastatic	NCT03774732
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CONCLUSION:

mEHT has a clear and strong immune modulating effect, however it has not yet been investigated combined with ICI and IR.

The results of the South African trial on LACC, the literature on the immune modulating effects of mEHT, and the renewed interest in the abscopal effect induced by ICIs plus IR, strongly motivates the design of a trial on the combination therapy of mEHT, ICI and IR.

The authors declare that they have no conflict of interest.