THERAPEUTIC EFFECT OF LOCAL HYPERTHERMIA TREATMENT COMBINED WITH ANTI-CD200 IMMUNOTHERAPY IN EMT6 BREAST CANCER

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DEDICATION

This thesis is dedicated to my beloved parents who taught me to always reach for the stars and my supportive husband who always reminds me to never give up in everything I do.

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ABSTRACT

Breast cancer is the leading cancer-causing death in women worldwide. Conventional cancer treatments have different therapeutic effects and commonly associated with side effects. Combinatorial therapies are typically used to overcome such limitation and reduce the likelihood of cancer recurrence. Hyperthermia (HT) is a less invasive cancer treatment ideal to treat superficial tumour and has shown promising outcomes in combination with the established immunotherapy. In EMT6 breast tumour, an elevated expression of CD200 has been associated with cancer progression. It was reported that the blocking of CD200/CD200R signalling resulted in an enhanced anti-tumour response. In light of this, the present study aimed to investigate the therapeutic effects of local HT in combination with anti-CD200 blockade therapy. Local HT protocol was established prior to the application of combined treatment. Breast tumours were induced by inoculating EMT6 cells subcutaneously at the right flank of Balb/c mice. On day seven post-inoculation, tumours were subjected to local HT treatment by near infrared radiation for three days. Tumour progression and mice survival were monitored and the influence on the immune response was evaluated. Results demonstrated that HT treatment reduced tumour progression and increased the median survival of tumour-bearing mice. Immunohistochemical analysis revealed a large area of necrotized tumour and there was an increase of Hsp70 expression observed around the treated tumour. This observation was accompanied with a significant reduction of proliferating cells when compared to the untreated tumour. Flow cytometry analysis of the lymph node showed an increase of dendritic cells activation and infiltration in treated mice. A higher level of IFN-γ, a pro-inflammatory cytokine but lower IL-10, an anti-inflammatory cytokine, were detected in blood of treated mice, as compared to untreated mice. In another experiment, mice were intraperitoneally injected with anti-CD200 antibody for blockade therapy in addition to HT. Following combined treatment, it was demonstrated that tumour progression was further delayed and the mice survival were greatly improved. In addition, an increase in the number of activated CD8 T cells were observed in the draining lymph nodes of the mice, along with infiltration of T cells, NK cells and B cells into the tumour. In contrast, tumour-infiltrated regulatory T cells and myeloid-derived suppressor cells were largely diminished from the tumour. Taken together, the present findings reveal the potential of combining local HT and anti-CD200 blockade in improving immunological response against breast tumour.

ABSTRAK

Kanser payudara merupakan penyumbang utama kepada kematian akibat kanser bagi wanita di seluruh dunia. Rawatan kanser konvensional mempunyai kesan terapeutik yang berbeza dan sering dikaitkan dengan kesan sampingan. Kaedah rawatan gabungan sering digunakan bagi mengatasi kelemahan tersebut dan mengurangkan kebarangkalian daripada kanser berulang. Hipertermia merupakan rawatan kanser kurang invasif yang ideal untuk kanser superfisial dan telah menunjukkan hasil yang memberangsangkan apabila digabungkan bersama imunoterapi. Di dalam tumor EMT6, peningkatan pengekspresan CD200 telah dikaitkan dengan kemaraan kanser payudara. Kajian melaporkan bahawa penyekatan pengisyaratan antara CD200 dan CD200R menunjukkan peningkatan tindak balas anti-tumor. Justeru, kajian ini bertujuan untuk menyelidik kesan gabungan hipertermia lokal dan terapi sekatan CD200. Protokol hipertermia lokal telah ditetapkan sebelum rawatan gabungan. Sel kanser payudara EMT6 telah diinokulasi secara subkulitan pada sisi kanan badan mencit Balb/c. Pada hari ketujuh selepas inokulasi, tumor dirawat dengan hipertermia lokal melalui radiasi inframerah dekat selama tiga hari. Pertumbuhan tumor dan kemandirian mencit kemudiannya dipantau dan kesan terhadap tindak balas imun juga dinilai. Hasil kajian mendapati hipertermia mampu mengurangkan pertumbuhan tumor di samping meningkatkan median tahap mandiri mencit yang menanggung tumor. Analisis imunohistokimia menunjukkan sebahagian besar kawasan tumor yang dirawat adalah nekrotik dan terdapat peningkatan pengekspresan protin kejutan haba (Hsp70) di sekitar tumor. Pemerhatian ini disertai dengan pengurangan penggandaan sel yang ketara jika dibandingkan dengan tumor yang tidak dirawat. Analisis sitometri aliran pada nodus limfa nyahairan menunjukkan peningkatan pengaktifan dan infiltrasi sel dendritik pada mencit yang dirawat. Paras sitokin pro-keradangan, IFN-γ yang lebih tinggi dan sitokin anti-keradangan, IL-10, yang lebih rendah telah dikesan dalam darah mencit yang dirawat, berbanding dengan mencit yang tidak dirawat. Dalam eksperimen lain, mencit disuntik secara intraperitoneum dengan antibodi CD200 untuk gabungan terapi sekatan bersama rawatan hipertermia lokal. Susulan rawatan gabungan, perkembangan tumor semakin tertangguh dan kemandirian mencit bertambah baik. Selain itu, pemerhatian menunjukkan peningkatan bilangan sel T CD8 yang diaktifkan di dalam nodus limfa nyahairan, di samping peningkatan bilangan sel T, sel pembunuh semulajadi (NK) dan sel B di dalam tumor. Sebaliknya, kajian menunjukkan pengurangan sel T pengawalatur dan sel penindas yang berasal dari mieloid (MDSC) di dalam tumor. Secara keseluruhannya, kajian ini menunjukkan potensi menggabungkan hipertermia lokal dan sekatan CD200 dalam meningkatkan tindak balas imun terhadap kanser payudara.

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LIST OF ABBREVIATIONS

AF488	-	Alexa Fluor 488
AF568	-	Alexa Fluor 568
ATCC	-	American Type Cell Culture
BSA	-	Bovine Serum Albumin
BTAK	-	Breast tumour amplified kinase
CSCs	-	Cancer Stem Cells
CD	-	Cluster of differentiation
CLL	-	Chronic Lymphocytic Leukaemia
CNS	-	Central Nervous System
CTL	-	Cytotoxic T Lymphocytes
CD200R	-	CD200 Receptor
DAPI	-	4′,6-Diamidino-2-Phenylindole
DLN	-	Draining lymph node
DNA	-	Deoxyribonucleic Acid
Dok2	-	Docking Protein 2
EDTA	-	Ethylenediaminetetraacetic Acid
FACS	-	Fluorescence-activated cell sorting
FDA	-	Food and Drug Administration
FSC	-	Forward scatter
G-CSF	-	Granulocyte Colony Stimulating Factor
GM-CSF	-	Granulocyte-macrophage colony stimulating factor
HBSS	-	Hanks' Balanced Salt Solution
HRP	-	Horseradish Peroxidase
HT	-	Hyperthermia
H&E	-	Hematoxylin-Eosin
H_2SO_4	-	Sulphuric Acid
ICI	-	Immune Checkpoint Inhibitor
IgSF	-	Immunoglobulin Super Family
IFN	-	Interferon
IL	-	Interleukin

ITIM	-	Immunoreceptor Tyrosine Based Inhibitory Motifs
KO	-	Knockout
KX	-	Ketamine/xylazine
MAPK	-	Mitogen-Activated Protein Kinase
MDSC	-	Myeloid Derived Suppressor Cell
MFI	-	Mean Fluorescence Intensity
MOM	-	Mouse on Mouse
NaCl	-	Sodium chloride
NIR	-	Near Infrared Radiation
NK	-	Natural Killer
NO	-	Nitric Oxide
NPXY	-	Asn-Pro-Xaa-Tyr
PBS	-	Phosphate-buffered saline
PCNA	-	Proliferating Cell Nuclear Antigen
PI	-	Propium Iodide
PTB	-	Phosphotyrosine-binding
RasGAP	-	Ras GTPase Activating Protein
RIPA	-	Radioimmunoprecipitation Assay
ROS	-	Reactive Oxygen Species
RPMI	-	Rosewell Park Memorial Institute
SSC	-	Side scatter
TAMC	-	Tumour Associated Myeloid Cell
TBS	-	Tris Buffered Saline
TGF-β	-	Transforming growth factor beta
Th	-	Helper T Cells
TIB	-	Tumour-Infiltrating B cells
TIL	-	Tumour-Infiltrating Lymphocytes
TNF	-	Tumour Necrosis Factor
Tregs	-	Regulatory T Cells
UKM	-	Universiti Kebangsaan Malaysia
UPM	-	Universiti Putra Malaysia
UTM	-	Universiti Teknologi Malaysia
wIRA	-	Water-filtered Infrared A

LIST OF SYMBOLS

hr	-	Hour
i.p.	-	Intraperitoneally
min	-	Minutes
s.c.	-	Subcutaneously
× g	-	Times gravity (centrifugal force)

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CHAPTER 1

INTRODUCTION

1.1 Background of Research

Cancer has become the major concern in public health worldwide since its discovery. To date, breast cancer is known as the number one cancer-causing death among female globally. The statistics was reported to increase every year with 1.17 and over 2.2 million cases estimated in 2012 (Torre *et al.*, 2015) and 2020 (Sung *et al.*, 2021), respectively. In Malaysia, breast cancer is ranked as the leading cancer incidence with 8418 cases reported in 2020 and this value is predicted to increase to almost double in 2040 (Globocan, 2020). Nevertheless, the global mortality rate has substantially declined over the last decades (Parkin *et al.*, 2005; Torre *et al.*, 2015; Bray *et al.*, 2018). Despite there was a slow declining of the ratio in recent years, but the highest mortality was reported in less developed or slowly developing countries (Goodarzi *et al.*, 2020). Besides early detection (Ginsburg *et al.*, 2020), the incremental of cancer treatment options and effective adjuvant modalities is the major factor for the overall declining of mortality rates. However, the outcome of the standard core treatments including surgery, chemotherapy, radiation therapy is relatively poor. This may be due to the risks and side effects that are associated with the treatments, such as pain, toxicity and high rate of cancer recurrence. Nevertheless, the latest developments in breast cancer treatment are promising (Kolberg and Hoffmann, 2020). In fact, there is a growing interest in therapies that enhance the performance of immune response as they can promote anti-tumour immunity which is the most important aspect in tumour eradication (Li *et al.*, 2020c)

Hyperthermia (HT) has been widely demonstrated in many preclinical and clinical trials as an immunotherapeutic agent (Lee *et al.*, 2018). HT can be divided into three main categories; local, regional, and whole-body HT, where their application is often dependent on the type and the severity of the cancer (Jha *et al.*, 2016). For

instance, local HT is used to treat localized, solid tumour and is thus suitable to treat early stage of breast tumour (Gao *et al.*, 2016; Oldenborg *et al.*, 2019). The fundamental of HT is the induction of heat by increasing the core body or specific tumour region to a certain temperature, as heating the tumour could weaken or kill the tumour cells (Hu *et al.*, 2020). Fever-range or mild temperature; 39°C – 41°C and moderate HT, 41°C – 45°C have different effects in killing the tumour cells in which both of these temperature range were chosen for current clinical practice since they are readily attainable and well tolerated (Mallory *et al.*, 2016). Nonetheless, the consistency of preferred temperature range and temperature doses remain controversial. In the context of adjuvant therapies, the direct damage of the tumour cells due to the elevated temperature results in an increased of tumour cells sensitivity to other treatment modalities such as chemotherapy and radiotherapy (Jha *et al.*, 2016; Kolberg and Hoffmann, 2020). This explains why HT is often combined with either chemotherapy or radiotherapy in clinical setting.

In administering HT, heat may come from various external sources where in recent decades, studies focused on four common heat delivery techniques; infrared radiation, radiofrequency, microwave and ultrasound. HT is found to be more attractive both by patients and physicians as it is non-invasive cancer treatment, with no incision, thus cause less scaring, less pain, short recovery time and most importantly longer relapse-free or disease free period in patients (Zhao and Wu, 2010; Oei *et al.*, 2017; Hurwitz, 2019). These promising therapy also results in the reduction in mortality, morbidity, hospital stay, cost and improved quality of life for cancer patients, initiating a change from open surgery towards less invasive techniques in the treatment of tumours (Timmerman *et al.*, 2009; Wu, 2013). In fact, HT can now be considered as the fourth pillars of cancer therapies, besides surgery, chemotherapy and radiotherapy (Jha *et al.*, 2016).

On the other hand, immunotherapy has shown a great promise in cancer treatment due to the basis of the therapy itself that trained the patient's own immune system to work harder or smarter in destroying tumour cells. In normal physiological condition, immune checkpoint signalling pathways that involved immune checkpoint molecules such as CTLA-4, PD-1/PDL-1 and CD200/CD200R are important to

prevent autoimmunity (Toor *et al.*, 2020). However, these inhibitory pathways could be exploited by the tumour cells for their own survival. Following the manipulation of immune system through several ways for example blocking a specific inhibitory action through antibody-blockade, the anti-tumour immune response is greatly improved (Pant *et al.*, 2020). Currently, the most notable and established immune-checkpoint blockade therapy is anti-CTLA-4 (Ipilimumab) and anti-PD-1 (Nivolumab), where their ability in treating cancer patients has been proved in clinical trials of multiple cancer types (Bowyer *et al.*, 2016; Radosa *et al.*, 2020). However, anti-CTLA-4 therapy is associated with risk of autoimmune diseases (Klocke *et al.*, 2016), while there were many reports on the cancer resistance to PD-1 blockade (Sun *et al.*, 2020).

In recent years, the ligand-receptor interaction between CD200 and CD200R has gained attention in immune-checkpoint blockade therapy due to its ability to modulate immune response in various cancer types (Curry *et al.*, 2017; Bisgin *et al.*, 2019; Rastogi *et al.*, 2020). CD200 has been proved as an immunosuppressive protein since its expression on tumour cells has been associated with disease progression, making it as a prognostic marker for cancer (Sun *et al.*, 2016; Chen, 2019). Recently, anti-CD200 antibody blockade has been the major focus of immunotherapy for several haematological malignancies (Rastogi *et al.*, 2020). In fact, this therapy has entered clinical trial phase to treat patient with chronic lymphocytic leukaemia and multiple myeloma (Mahadevan *et al.*, 2019).

Due to the discovery of CD200 overexpression on solid tumour including breast cancer (Gorczynski *et al.*, 2010, 2011; Curry *et al.*, 2017), anti-CD200 blockade in breast cancer is currently attractive to researchers as well. Notably, CD200 blocking antibodies not only restricted to CD200-expressing tumours but also to non-tumour expressed CD200 as both of them involved in the regulation of immune response. As reviewed in multiple literatures (Rygiel *et al.*, 2012; Podnos, 2015; Ngwa and Liu, 2019; Choueiry *et al.*, 2020), CD200/CD200R interaction was shown to suppress anti-tumour response and promote tumour tolerance. Meanwhile, blockade of the signalling by CD200 antibody resulted in tumour growth inhibition and enhanced anti-tumour response (Curry *et al.*, 2017; Gorczynski and Zhu, 2017; Rastogi *et al.*, 2020). Moreover, CD200 was found to be expressed on cancer stem cells (CSCs) with

approximately three-fold more of the CSCs compared to non-CSCs, suggesting CD200 possible role in immunoevasion of CSCs (Kawasaki and Farrar, 2008; Jung *et al.*, 2015).

Relevant to this review, in this study, HT treatment will be combined with anti-CD200 blockade therapy due to the large evidences that each of them influenced how immune system reacted to the tumour. Owing to the fact that CD200 is overexpressed on breast tumours and its presence has been proved to disrupt the killing of tumour, combining these modalities might attribute to powerful synergistic effect in enhancing the anti-tumour immune response.

1.2 Problem Statement

Local HT treatment has been proved as less invasive technique in treating breast cancer. Local HT is also known to be an immunotherapeutic agent as it activate the anti-tumour immune response by inducing Hsp70 expression (Unga and Hashida, 2014; Multhoff *et al.*, 2015). However, the existence of several HT techniques that employed different external heat source may results in different outcome. In fact, different thermal dose applied during the treatment has resulted in distinct effect in various tumour types (Toraya-brown and Fiering, 2014), which suggests the anti-tumour efficacy is greatly affected by a small temperature difference as well as types and severity of cancer. Perhaps, the greater challenge has been the development of efficient protocols to detect the temperatures induced and maintained during local HT, thus limiting a more widespread clinical adoption of local HT in cancer therapy. Hence, it is necessary to establish local HT by NIR approach in treating immunogenic EMT6 breast tumour and this has been one of the aims in the present study.

Over the years, HT has been widely used in preclinical and clinical trials as adjuvant to chemotherapy and radiotherapy to enhance the effects of those traditional therapies. Recent development in cancer research has also reported the combination of immunotherapy with HT where the heat acts as an enhancer for any intracellular and extracellular signalling to switch on or off. Although not yet assessed in clinical study, but preclinical works strongly suggest the combination of HT with immunotherapy

(Chen *et al.*, 2019; Liu *et al.*, 2019; Pan *et al.*, 2020). Given HT can stimulate the immune system including tumour-specific T cells responses, the addition of HT to immunotherapy specifically immune checkpoint inhibitor is likely to augment clinical benefits obtained with immune checkpoint inhibitor alone.

However, in the context of breast cancer, the combination of HT with immune checkpoint inhibitor always focused on the FDA-approved drugs (targeting CTLA4 and PD-1) (Li *et al.*, 2020c). While this is understandable, efforts should also be put to CD200/CD200R inhibitory signalling as the overexpression of CD200 has widely been reported in breast tumour (Gorczynski *et al.*, 2011; Curry *et al.*, 2017). Besides, manipulation of this pathways would result in lesser autoimmune problem as CD200-deficient mice do not developed any autoimmune conditions, unlike in CTLA-4-deficient mice (Klocke *et al.*, 2016). As local HT can be very selective and could induce subsequent systemic anti-tumour response, the addition of CD200 mAb would certainly enhance its therapeutic efficacy, suggesting it as an interesting modality in creating synergistic effect with HT. Moreover, since immunoevasion capabilities of cancer stem cells (CSCs) have been reported due to tolerogenic response facilitated by CD200 (Kawasaki *et al.*, 2007; Zhang *et al.*, 2016), it is thus likely the combination of local HT and anti-CD200 blockade not only could kill the tumour but also might offer clinically valuable therapeutic advantage in terms of preventing the cancer relapse.

1.3 Objective of Research

The main objective of this study is to investigate the synergistic effect of local hyperthermia by near infrared radiation (750 watt) combined with anti-CD200 blockade therapy. In order to achieve this main objective, the specific objectives were determined and are as listed below:

(a) To establish the thermal dosage (temperature and frequency) of local HT treatment by near infrared radiation on EMT6 mouse breast cancer.

(b) To determine the effect of local HT treatment on tumour inhibition through the evaluation of tumour growth profile, histopathological and immunohistochemical analysis.

(c) To evaluate the immunomodulatory effect of local HT treatment by measuring the activation and infiltration of immune cells and immune-related molecules through flow cytometry analysis, immunohistochemical analysis and ELISA.

(d) To investigate the effect of local HT in combination with anti-CD200 blockade therapy in reducing tumour growth.

(e) To elucidate the involvement of immune cells and immune-related molecules in local HT combined with anti-CD200 blockade therapy in enhancing the anti-tumour response.

1.4 Scope of Research

This research consists of two stages that involve the use of EMT6 murine breast tumour model. The therapeutic effect in breast tumour following the combination of local HT treatment and anti-CD200 immunotherapy were determined. The first stage focused on the monotherapy of local HT treatment that was applied by using Hydrosun 750 water-filtered infrared A lamp. In order to ensure the efficacy of local HT by near infrared radiation at power output 750 Watt, the optimum temperature and frequency of the treatment was firstly established. Tumour growth profile was recorded, and histopathological examination was conducted to evaluate the tumour inhibition following treatment. The second stage involved the application of combined local HT and anti-CD200 blockade therapy on tumour-bearing mice, which was followed by the analysis of immune cells and immune-related proteins in tumour tissue post treatment. The analysis involved in the study includes immunohistochemical analysis, flow cytometry analysis and ELISA.

Various markers related to tumour cell formation and proliferation such as proliferating cell nuclear antigen (PCNA) as well as heat shock protein 70 (Hsp70);

which is an important marker for HT treatment was examined. Beside this, the level of tumour-infiltrated immune cells such as CD8 T cells, CD4 T cells, regulatory T cells (Tregs), dendritic cells (DC), natural killer (NK) cells, B cells and myeloid derived suppressor cells (MDSC) were evaluated. In addition, immune-related proteins such as Th1 cytokines (IL-2, TNFα, and IFN-γ) and Tregs-releasing cytokines (IL-10 and TGFβ), and chemokine in the breast tumour tissues post-treatment were measured. Any positive changes in the expression of these markers due to HT alone or combined treatment may provide useful insight on their involvement in tumour milieu following treatments. Apart from that, possible underlying events involved in the combined treatment modalities were elucidated at the end of the study.

1.5 Significance of Research

The goal of this study is to explore the treatment that could manage tumour efficiently and avoid the possibility of cancer relapse in the future. The combination of these two modalities may be advantageous in terms of triggering the immune response towards cancer cells which lead to the inhibition of tumour growth, enhanced anti-tumour response and subsequently reduce the mortality rate due to breast cancer. Fundamental knowledge from this study may have a direct implication in breast cancer treatment in clinical setting. Besides, this research would highlight the benefit of using non-invasive treatment combined with immunotherapy in treating breast cancer, which will subsequently reduce the economic burden in the management of breast cancer.

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LIST OF PUBLICATIONS

ISI/WoS indexed Journal

1. **Wan Mohd Zawawi, W. F. A.,** Hibma M.H., Salim M. I., Jemon K., (2021). Hyperthermia by Near Infrared Radiation Induced Immune Cells Activation and Infiltration in Breast Tumor. *Scientific Reports,* 11 (1), 1-13.

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1. Radzi, M. R. M., **Wan Mohd Zawawi, W. F. A.**, Zawawi, N., Jemon, K. (2020). Preliminary Evaluation on the EMT6 Breast Tumor Inhibitory Activity of Carbon Nanotubes with Hyperthermia. *AIP Conference Proceedings.* - Accepted

Indexed Journal

1. **Wan Mohd Zawawi, W. F. A.** and Jemon, K. (2016). Synthetic Biology for Breast Cancer Therapy. *Int. J. Innov. Comput.* 6(1), 16–21.

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1. **Wan Mohd Zawawi, W. F. A.**, Azahari, F. A. S., Azhari, H., Jemon, K. (2017). *In Vivo* Wound Healing Activity of Melaleuca Essential Oil-Based Cream. In *International Postgraduate Symposium in Biotechnology 2017.* Johor Bahru, Malaysia, pp. 77-80.

2. **Wan Mohd Zawawi, W. F. A.**, Salim, M. I., Jemon, K. (2018). Local Hyperthermia at 43°C Reduced Tumor Progression in EMT6 Murine Breast

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