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Combination of Adoptive Cell Therapy and Radiotherapy in Cancer Management

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Abstract

Cancer remains a major health burden in the world, with the increasing cases and deaths. Adoptive cell therapy (ACT) is one of the immunotherapies which modifies immune system to recognize cancer cells, which is then transfused to induce antitumoral responses in the human body. ACT works by using cancer-specific immune cells, especially Natural Killer and T cells in the form of tumor-infiltrating lymphocytes, T-cell receptor or chimeric antigen receptor. As the combination therapy with radiotherapy, radiation is able to induce tumor-associated antigen (TAA) and major histocompatibility complex (MHC) class I expression, which leads to increased immune cells around the tumor. As the result, transferred ACT to the body may be able to proliferate and perform its function well. Moreover, radiotherapy is able to downregulate regulatory T cells and myeloid-derived suppressor cells which can inhibit the role of the immune system in attacking cancer. Clinically, studies combining radiation and ACT in cancer care are limited to several types of cancer, such as metastatic melanoma, nasopharyngeal cancer, lymphoma and non-small cell lung cancer. Radiotherapy is able to increase therapeutic efficacy, especially as a bridging therapy before ACT. Nevertheless, further trials to know the potency of combining ACT and radiotherapy in other types of cancer, especially in earlier stages are needed.

Keywords: adoptive cell therapy, radiotherapy, cancer, management

Introduction

Until now, cancer remains a global health burden. According to the GLOBOCAN report in 2018, there were 18.1 million people worldwide suffering from cancer with 9.6 million of deaths and this number is predicted to continue increasing.[1] In Indonesia, the number of cancer cases in 2018 reached 348,809 cases with 207,210 deaths.[2] This number has increased in the 2020 report into 396,914 cases and 234,511 deaths.[3]

In general, chemotherapy, radiotherapy (RT), and surgery are the main pillars of standard therapy for cancer.[1] Surgery and RT are the main therapeutic foundations for solid tumors. Chemotherapy can be curative or given in combination with surgery and RT. The principle for initial management of cancer focuses on extensive and radical surgery to prevent recurrence in the peritumor area. However, with the development of surgical techniques and RT as well as their combination with chemotherapy, radical surgery has been replaced with various less invasive techniques.[4]

Chemotherapy has quite abundant and severe systemic side effects. Cytostatic drugs generally have low specificity towards tumor with high toxicity.[5] In the last few years, researchers try to develop systemic therapies for cancer that are more selective with minimal side effects, one of which is immunotherapy.

The principle of immunotherapy is to use the component of the patient's immune system, such as antibodies, cytokines, and dendritic cells to selectively target tumor cells.[6] There are several types of immunotherapy that have been developed to date,

namely monoclonal antibodies, checkpoint inhibitors, adoptive cell therapy.[5]

Adoptive cell therapy is one type of immunotherapy that uses immune cells to attack cancer, such as using T cells and natural killer (NK) cells. T cell have specific immune response so that they can distinguish normal cells and cancer cells, as well as carrying out cloncal expansion in large numbers following their activation.[7] NK cells can recognize and kill abnormal cells, including cancer cells, one of which is through the release of cytolytic granules, such as perforin and granzyme.[8,9] Adoptive cell therapy has been studied in several clinical trials with quite promising results, and its utilization has been approved in several hematologic malignancy, such as acute lymphoblastic leukemia and non-Hodgkin lymphoma.[10]

Radiotherapy is a modality that has long been used as a cancer therapy by inducing cancer cell death and inducing anti-tumor immunity through the release of signaling molecules, which subsequently activate dendritic cells and tumor-specific T cells. Moreover, the use of radiation can increase the release of tumor-associated antigen (TAA) and make the tumor more susceptible towards the immune system.[11–13]

Looking at the similarities of both modalities in inducing the immune system, RT and ACT have the potential to induce anti-tumor effects in a synergistic manner. Based on this background, the current review article aims to discuss the potential combination of RT and ACT in cancer management.

Types of Adoptive Cell Therapy

There are several types of adoptive cell therapy based on how the cells are processed and transferred into an individual. In principle, based on the processing technique, adoptive cell therapy is divided into adoptive cell therapy isolated from tumor-specific T cells (from the tumor mass itself) and genetically modified T cells/NK cells in peripheral blood.[10,14,15]

Tumor-Infiltrating Lymphocytes (TIL)

TIL consists of a population of lymphocytes that attacks tumor tissue. TIL is an ACT based on isolation of tumor-specific T cells, which is derived directly from the tumor cells. The production of this adoptive cell therapy includes the isolation of T cells from tumor and ex vivo expansion. These cells are rapidly expanded with soluble anti-CD3 antibodies, IL-2, and irradiated allogenic or autologous feeder cells. Following the expansion process, TIL is re-injected into the same individual (autologous) after administration of non-myeloablative chemotherapy regimen. Immediately after infusion of TIL, a high-dose IL-2 bolus was administered to increase cell survival and clinical efficacy. TIL that is injected into a human's body will directly attack tumor cells.[10,14]

T-Cell Receptor (TCR)

TCR is the result of viral vector-based genetic modification which specifically expresses receptors that can recognize cancer antigens. T cells from autologous peripheral blood are obtained via leukapheresis process, which are then transduced with gamma-retrovirus or lentivirus vectors. The virus will incorporate the TCR gene into the host cell genome, especially through VDJ arrangement, so that there is a high TCR expression in the introduced cells. Every T cell expresses a unique TCR heterodimer that can react with specific peptide fragments (epitopes) bound to MHC molecules. The binding between the surface glycoproteins of $CD8^+$ and $CD4^+$ T cells with MHC class I or II on the surface of the antigen will initiate the immune response induction process. Similar to TIL, the majority of patients in clinical protocols with TCR gene therapy will be conditioned in a lymphodepletic state prior to T-cell infusion. IL-2 injection after T-cell infusion is also applied in this method.[10,14,16]

Chimeric Antigen Receptor T Cells (CAR-T)

CAR-T cells are genetically constructed hybrid receptors which possess effector function of T lymphocytes and the ability of antibodies to recognize surface antigen with high specificity without using MHC. CAR could specifically attack parts of antigen, such as glycolipid, glycated protein, and conformational epitope that could not be detected by TCR. The production process of CAR-T cells begins with isolation of peripheral blood T cells using apheresis which is followed by ex vivo transduction process. This genetic engineering process is conducted to obtain an extracellular part that consists of a single-chain variable fragment (scFV) from the monoclonal antibodies that can recognize tumor-associated antigen (TAA), as well as intracellular part that is capable of carrying activation signals (CD3ζ chain) and co-stimulation of T cells (CD28 and 4-1BB/CD137). After antigen attachment to scFV, induction of cytotoxic activity of T cells occurs which results in decreased signaling via CD3ζ phosphorylation and additional signaling cascades via co-stimulatory domains. The methods commonly used to obtain CAR are by using retrovirus and lentivirus infection. When CAR-T cells are injected autologously into the body, these cells

migrate to thymus to proliferate before attacking the tumor directly.[10,14,17]

NK Cell-based Adoptive Cell Therapy

Production of NK cells for immunotherapy towards cancer cells is obtained from peripheral blood infusion, hematopoietic progenitor cell transplantation, umbilical cord-derived NK cells, or modified NK95 cell line.[19] Peripheral blood is the dominant source of both autologous and allogenic NK cells which involve the use of granulocyte-macrophage colony stimulating factor (GM-CSF).[20]

In addition to the extraction of NK cells from peripheral blood, NK stem cells derived from bone marrow can be transplanted and induced to produce NK cells. The steps involve the recipient to be given immunosuppressant therapy initially with cyclophosphamide and fludarabine as nonmyeloablative lymphodepleting therapeutic regimen, and selection of NK cell donors will be conducted based on the compatibility of ligand-ligand, receptor-receptor, receptor-ligand genotypes, and B-haplotype scores. After genotypes criteria are matched, the induction of NK cell differentiation with cytokines, such as interferon-gamma and interleukin family can be initiated.[21]

The most recent application of NK cells is as Chimeric Antigen Receptor Natural Killer cells (CAR-NK), where NK cells are allogenically obtained to be modified on the extracellular, transmembrane, and intracellular regions. In general, the principle of producing CAR-NK does not differ from CAR-T. CAR-NK consists of CD3ζ in the intracellular, transmembrane, the CD8 region, and fragments of ErbB2-specific scFv antibody (FRP5) in the extracellular region. The antibody fragment of the extracellular region can be replaced to recognize different types of antigens.[22]

Combination of ACT and Radiotherapy in Cancer Signalling Pathways

In general, adoptive cell therapy has been commonly performed on patients with various types of tumor and has shown quite promising results. However, research shows that the effectiveness of adoptive cell therapy can be improved through addition of RT. The possible mechanism to explain the synergistic effects of both therapy was shown in the an experiment using mouse model to inhibit tumor progression. A pre-clinical study in C57BL/6 mice that were given donors from OT-I/CD45.2/Rag−/− mice which expressed transgenic TCR that recognized epitopes ($OVA_{257–264}$, SIINFEKL), has shown that mechanically, radiation was proven to increase the release of antigens that were associated with tumor and facilitate the process of cross-presentation by dendritic cells and maturation of the antigen-specific lymphocytes. Moreover, radiation can also enhance the homing process of the TAA-specific T cells through the release of CCL_5, $CXCL_9$, and $CXCL_{11}$ from tumor cells. Radiation also increases the proliferation and effector functions of adoptively transferred T cells and antigen-specific endogenous T cells.[12]

Radiation can also increase the expression of MHC class I molecule. This indicates that radiation can also increase the expression of TAA and MHC class I molecules on the surface of tumor cells which can play a role in antigen presentation. In addition, studies have also shown that the proportion of irradiated tumor cells demonstrated significant difference in phagocytic efficiency of dendritic cells compared with those that did not receive irradiation. Furthermore, the evaluation results of the correlation between phagocytosis and maturation of antigen-specific T lymphocytes can significantly promote cell proliferation. From all the obtained information, it can be inferred that radiation facilitates the cross-priming process in antigen-specific T lymphocytes. Not only increasing the expansion and migration of $CD8^+$ T cells that were adoptively transferred to the tumor sites, radiation also promotes endogenous maturation of antigen-specific T lymphocytes.[12]

In addition to increasing the ACT as an antitumor immune system of an individual, ionizing radiation was also shown to weaken tumor cells so that they are easily attacked by adoptive cell therapy. A study by Garnett et al. showed that radiation increased the expression of Fas (CD95) gene in murine tumor cells expressing CEA antigen. Thus, radiation weakens the tumor cells and eases the T cell therapy to work optimally.[23] This is in line with a study by Lai et al. in 2019 which showed that 5-10 Gy radiation increased the susceptibility of tumor cells towards cytotoxicity induced by cytotoxic T lymphocytes. Fas-Fas ligand pathway is a major molecular pathway that can induce apoptosis which contributes with cytotoxic activity from cytotoxic T lymphocytes.[12]

Not only in T cell-based adoptive cell therapy, adoptive NK cells also showed synergistic results when given together with radiation therapy. Yang et al.'s study showed that in vitro x-ray-based irradiation with low dose was proven to have various effects to NK cells, including expansion, cytotoxic activity, and molecular mechanism of cells.[24] The molecular mechanisms of the

synergistic therapy of adoptive NK cells and radiation can be represented through 3 main mechanisms, namely NK cytotoxicity, tumor infiltration, and cytokines. Administration of low-dose radiation was proven in studies to increase the NK cytotoxicity.[25] A possible mechanism that may explain this finding is that induction of NK cell cytotoxicity occurs without changing the phenotype of the NK cells itself, for instance expression of NK1.1, NKG2D, CD69, and 2B4, or changes in the level of apoptosis.[26] A study using mice model explained that mice that were given low-dose radiation experienced stimulation of innate immunity as well as suppression of of pro-inflammatory response.[26,27] A preclinical murine study also showed that murine NK cells can be reactivated with IL-12, IL-15, and IL-18 in vitro and exert potent anti-tumor activity against tumors.[28] The IL-12/IL-15/IL-18-preactivated NK cells showed higher numbers and persistent effector function that is more potent with combination of radiotherapy. All the evidence support the synergistic effects of adoptive NK cell therapy and radiation therapy (especially in a low dose) to activate the anti-tumor cytotoxicity and production of cytokines in adoptively transferred NK cells.

Combination of Adoptive Cell Therapy with Radiotherapy – Clinical Aspect

To answer the question regarding the role of combination of ACT and RT in cancer patients, a literature search was conducted systematically as presented in the supplementary data. Based on the literature search, the articles were selected based on the study eligibility criteria. From 3 databases, there were 843 records identified. After further selection, there were 91 articles excluded due to irretrievable full-text articles and 747 articles were excluded since they did not meet the study inclusion and exclusion criteria (did not discuss or only discussed either RT or adoptive cell therapy only, case reports, preclinical studies, studies using Mandarin and Spanish). There were no duplicates found between the databases.

Moreover, there was a meta-analysis and a literature review that were excluded since there were studies in the meta-analysis that compared the combination of modalities other than RT and TSA with TSA only, which did not fulfill the study eligbility criteria. However, citation alert was set on those two articles, and one article from each was successfully obtained (a total of 2 articles from citation alert). Finally, there were 7 articles that were systematically reviewed.

Based on the systematic search, there were 7 articles that discuss the combination of ACT and RT. All the 7 articles were published between 1997-2020, with the majority are clinical trials, especially phase I and II clinical trials. Moreover, there was one case series with 12 patients and one retrospective cohort. In total, there were 444 patients involved in all the 7 studies. The studies involved patients with lymphoma, metastatic melanoma, nasopharyngeal carcinoma (NPC), and post-surgical lung cancer. More specifically, most studies involved patients with lymphoma and melanoma.[29–35]

Based on the case series by Sim et al., patients with stage I-IV DLBCL/transformed follicular lymphoma had refractory disease following administration of last line chemotherapy/recurrent patients, radiation with 6-30 Gy (2-4 Gy per fraction) was given before CD19-specific CAR-T therapy. Radiation was given as bridging therapy prior to infusion of CAR-T. At the end of the study, there were 45% of patients achieving CR after 3.3 months follow-up.[31]

A retrospective cohort study conducted by Wright et al. showed that among 31 patients with refractory/relapsed B cell lymphoma, CAR-T therapy could increase patients' survival. In the study, patients who were given CAR-T with bridging RT had 1-year survival of 80%, while those without briding RT had 1-year survival of 66.8%.[35]

In addition to case series and retrospective cohort study, various clinical trials also demonstrated quite promising results from the combination of ACT and RT. From the studies we obtained, there was one study for each phase 1, 2, and 3, as well as 2 clinical studies that did not mention about the phase of their trials. The effectiveness of each clinical trial is displayed in **Table 1.**[29,30,32–34]

Overall, the clinical studies on several types of cancer showed superior efficacy in the group receiving combination radiotherapy before or concomitantly combined with ACT compared with the group receiving adoptive cell therapy only. Studies in various types of cancer, such as metastatic melanoma, NPC, B cell lymphoma, and NSCLC type of primary lung carcinoma showed that combination of both therapeutic modalities can increase the therapeutic efficacy in managing cancer significantly. This is attributed to the preparatory regimen process which can condition the cancer patients into the lymphodepletic state and ease ACT to enter and recognize cancer cells and their antigens so that the tumor cells can be attacked more effectively. There was no assessment on the best timing

Table 1. Studies included from the systematic search results.

Author, Year	Objectives	Study Design	Study Location	Sample Size	Patient Characteristics	Intervention and Control	Results
Qu et al., 2020[30]	To examine the efficacy and toxicity of CAR-T cell therapy following chemotherapy /radiotherapy in R/R DLBCL patients.	Phase II clinical trial	Suzhou, China	10 R/R DLBCL patients (4 patients receiving chemotherapy + CAR-T; 6 patients receiving RT + CAR-T)	Median age: 48 years and 63 years for chemotherapy group and RT CAR-T group respectively) Stage I-IV DLBCL patients with the majority on stage III-IV (9 patients)	Chemotherapy combination (GemOx or ESHAP); RT before CAR-T therapy with a total dose of 40 Gy/20 fractions within 4 weeks. CAR-T cells which target CD19/CD20/CD22 were modified from patients' or donor's blood collected by apheresis.	Within 2 months following CAR-T infusions, 25% of patients of chemotherapy group achieved CR; in the RT group, 33% of patients achieved CR while the remaining reached PR (p=0.033). There was one patient with recurrence that achieved CR following RT. CRS and neurological toxicity incidences were higher in the chemotherapy group (100 and 75% vs 0% in the RT group). Hematological toxicity (neutropenia, anemia, and thrombocytopenia) occurred in both groups. Other toxicities included hypoxia, hypotension, heart failure, and acute kidney injury (higher in the RT group).
Sim et al., 2019[31]	Presented a case series of patients receiving radiation as a bridging therapy prior to CAR-T cell infusions.	Case series	Florida, USA	12 pasien	12 patients with stage I-IV DLBCL/transformed follicular lymphoma with 8 refractory patients following last line of chemotherapy and 4 patients newly diagnosed with recurrence.	Radiation of 2-4 Gy per fraction with a total dose of 6-30 Gy. Radiation was given prior to giving CD19-directed CAR-T cell therapy (axicabtagene ciloleucel/axi-cel).	CR at the end of evaluation (patients were followed for a median of 3.3 months) was found in 45% of patients (only 11 patients can be evaluated). There was no significant toxicity found during radiation. 3 out of 11 patients experienced CRA or neurotoxicity following axi-cel infusion.
Dudley et al., 2008[29]	To evaluate the safety and regimen efficacy using TBI and ACT.	Sequential clinical trial	Bethesda, USA	93 patients with metastatic melanoma	Age range: 11-70 years; Male: 26 patients; Female: 17 patients. 43 non-TBI, 25 TBI 2 Gy, and 25 TBI 12 Gy)	Lymphodepletion with cyclophosphamide and fludarabine with or without 2 or 12-Gy TBI. Autologous transfer of TIL and IL-2 were then performed on patients.	Showed an objective response of 52% and 72% (2 and 12-Gy TBI). PR: 44% and 56% (2 and 12-Gy TBI). CR: 8% and 16% (2 and 12-Gy TBI). PR and CR on patients without TBI intervention are 39.5% and 9.3% respectively.

Table 1. Studies included from the systematic search results (continue).

Author, Year	Objectives	Study Design	Study Location	Sample Size	Patient Characteristics	Intervention and Control	Results
Li et al., 2015[32]	To evaluate the safety and antitumor activity of TILs post-CCRT in patients with advanced nasopharyngeal carcinoma.	Phase I clinical trial	China	23 patients with newly diagnosed nasopharyngeal carcinoma (3 patients did not receive intervention due to failure to produce sufficient TILs prior to infusion).	Age: 28-62 years; Patients with stage III-IV (AJCC 2010) without distant metastasis, undifferentiated carcinomas (WHO type III)	Single-dose $2.6x10^9$ TIL dan pemberian CCRT (chemotherapy with cisplatin 100 mg/m^2 was administered on days 1, 22, and 43); radiation with a dose of 70/60-66/54-Gy in 30-32 fractions.	3 patients that did not receive TILs had CR. Among the patients with TIL infusion, 18 patients achieved CR, 1 patient had PR followed by progressive disease, and 1 patient had PR followed by recurrence in 6 months. Response was evaluated until 12 months post-radiation. One week following administration of TILs, plasma EBV DNA was not detected in all patients (including the 6 EBV DNA-positive patients). 1 and 6 months post-therapy, 1 and 3 patients displayed a detectable EBV DNA titer. EBV antigen-specific T cells in peripheral blood were found in 13 patients post-therapy. When given the ACT, there were no infections, fever, or allergies in the patients. 15% of patients had grade 1 or 2 mucositis, 5% of patients exhibited vomiting, and 1 patient had grade 3 leukopenia and neutropenia.
Kimura et al., 1997[33]	To determine the benefits of ACT with LAK cells and IL-2 as an adjuvant therapy to surgery.	Randomized controlled phase III clinical trial	Chiba, Japan	174 patients with post-surgical primary lung carcinoma	Stage I-IV NSCLC. Median age: 59.5 and 60.3 (standard therapy group and combination therapy group). The ratio between female and male: 2:12.	Group A: combination of surgery/chemotherapy/RT with immunotherapy. Group B: standard therapy (surgery/chemotherapy/RT) ACT with IL-2 ($3,5x10^5$ U/day) and LAK ($1-5x10^9$ cells/shot) every 2-3 months after surgery for 2 years.	The 5- and 9-year survival rates for group A vs group B (54.4% vs 33.4%; 52% vs 24.2%). The median survival time for group B was 2.01 years, whereas for Group A could not be determined (since it has not been reached until the end of observation (6 years)). In cases with no curative intention, the median survival time for group A and B were 2.4 and 1.5 years. The side effects of ACT were fever and shaking chills on the day when LAK cells were administered, which resolved following the infusion. There were no side effects related to viral and bacterial infection. There was a patient which had hypotension due to vasodilatation 3 hours post-injection, which then recovered, there was no known association between the symptoms with the given therapy.

Table 1. Studies included from the systematic search results (continue).

Author, Year	Objectives	Study Design	Study Location	Sample Size	Patient Characteristics	Intervention and Control	Results
Goff et al., 2016[34]	To evaluate the addition of TBI to ACT (with TILs).	Randomized controlled trial	USA	101 patients with metastatic melanoma (51 patients received NMA only and 50 patients received NMA+TBI).	Median age: 45 years (NMA only group), 47 years (NMA+TBI).	NMA chemotherapy (cyclophosphamide 60 mg/kg/day for 2 days and fludarabine 25 mg/m^2/day for 5 days), with or without TBI of 1200 cGy (2Gy, 2x daily for 3 days), with subsequent TIL and IL-2 therapy.	24% CR in both groups. CR in NMA+TBI vs NMA only: 24% vs 24%. 30% PR in both groups. PR in NMA+TBI vs NMA only: 38% vs 22%. Toxicity was more related to chemotherapy and IL-2 administration. The observed toxicity included infection (febrile, neutropenia, bacteremia, urinary tract infection), thrombotic microangiopathy, and atrial fibrillation. Toxicities were found more often in the group receiving TBI.
Wright et al., 2020[35]	To report the use of bridging RT in 30 days prior to tisa-cel or axi-cel CAR-T cell therapy, including factors that influence CRS and neurotoxicity.	Retrospective cohort	USA	31 patients suffering from relapsed/refractory B cell lymphoma (13 patients were given tisa-cel and 18 patients were given axi-cel).	Patients with stage II-IV relapsed/refractory aggressive B cell lymphoma (the majority: DLBCL)	Tisa-cel or Axi-cel after or without bridging RT 37.5 Gy (2.2-4 Gy per fraction) <30 days before infusion with CAR-T. 5 patients received bridging RT, 26 patients did not. Bridging RT was performed on patients with chemorefractory disease, bulky lesions, and symptoms related to cancer.	The 6-month and 1-year OS of all patients: 83.6% and 69.1%. The 6-month and 1-year OS of patients with bridging RT: 100% and 80%. The 6-month and 1-year OS of patients without bridging RT: 80.4% and 66.8%. CR was found in 1 out of 5 patients receiving bridging RT and 8 out of 21 of patients without briding RT. Grade 1 and 2 toxicities were found in all patients receiving bridging RT with complaints of fatigue, nausea, dysgeusia, dysphagia, radiation dermatitis, and limb edema. Following administration of CAR-T, patients with bridging RT did not experience CRS or grade 3-5 neurotoxicity, however 2 patients had grade 1-2 neurotoxicity. In the group without bridging RT, 11 patients had grade 1-2 CRS and 6 patients with grade 3 CRS. Grade 1-2 and grade 3-4 neurotoxocity occurred in 5 and 4 patients respectively.

ACT: adoptive cell therapy; CAR-T: chimeric antigen receptor T cells; CCRT: concurrent chemoradiotherapy; CR: complete responses; CRS: cytokine release syndrome; DLBCL: Diffuse Large B-Cell Lymphoma; EBV DNA: Epstein Barr Virus Deoxyribonucleic Acid; GEMOX: Gemcitabine and Oxaliplatin; ESHAP: Etoposide, Cisplatin, Metilprednisolon and Cytarabine; IMRT: Intensity-modulated radiation therapy; LAK: lymphokine-activated killer; NMA: Non-myeloablating; NSCLC: non-small cell lung cancer; OS: overall survival; PR: partial response; R/R: recurrent/refractory; RT: radiotherapy; TBI: total body irradiation; TIL: Tumor-infiltrating lymphocytes; WHO: World Health Organization

* no explanation was provided in the studies regarding the patients' tumor stage

of ACT administration before or after radiotherapy /chemotherapy in all study.

Toxicity comparison from combination of the two therapeutic modalities

This systematic review has proven that combination of adoptive cell therapy and RT in various types of cancer is a safe therapy to be implemented. Nevertheless, several particular side effects which occur during CAR -T cell infusion therapy, such as CRS and neurotoxicity, and side effects during radiation require further attention. The summary of toxicity profile from various modalities of combination therapy is presented in Table 1.[31–33,35–37]

Conclusion

There are several types of ACT, namely TIL, TCR, CAR-T cell, and NK cell-based adoptive cell therapy (especially CAR-NK). The distinct types of ACT were different in terms of how they were processed and transferred into the individuals. When combining ACT with RT, radiation can result in the release of tumor associated antigen (TAA) and expression of Major Histocompatibility Complex (MHC) class I from tumor cells, as well as increasing the number of immune cells located around the tumor. This would then cause the ACT that has been transferred into the body to proliferate and exert its function more optimally. Furthermore, radiation can also reduce the number of regulatory T cells and myeloid derived suppressor cells that inhibit the immune cells from working properly.

Clinically, until now, research on the combination of radiation with ACT is still limited to only several types of tumor cells, such as metastatic melanoma, NPC, lymphoma, and NSCLC. Radiotherapy may increase the therapeutic efficacy, especially as a preparatory regimen prior to ACT. In terms of toxicity, patients receiving combination therapy did not show significant toxicity, which confirms the therapeutic safety. Nevertheless, further clinical triails are required to validate the findings, especially in other types of cancer in earlier stage and the best timing on the administration of ACT when combined with chemo/ radiotherapy to develop the utilization of the combination therapy in daily clinical practice.

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