TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2023;38(1):120–23
doi: 10.5505/tjo.2022.3865

REVIEW

Design Considerations for Clinical Trials of Radiotherapy Combined with Immunotherapy

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SUMMARY

The discovery of synergistic effects between radiation and immunotherapy in pre-clinical studies has encouraged researchers to conduct clinical trials testing the effects of combined therapy in patients. The first step in conducting any clinical trial is to define the hypothesis and core objectives. The challenge while developing trials analyzing combinations of immunotherapy and radiation therapy (RT) is to select an appropriate hypothesis that can be tested in the future research, as well as raising new questions for investigation. Here, we review some of the concerns and challenges for designing clinical trials of RT combined with immunotherapy.

Keywords: Clinical trial; immunotherapy; radiotherapy.

INTRODUCTION

Numerous clinical trials have been conducted concerning considerable numbers of patients and complicated treatment procedures. Nevertheless, translating potential treatments from preclinical studies to clinical practice includes many methodologic challenges. In this context, a valuable hypothesis is the most critical component in clinical trials. Only trials established on a clear, rational hypothesis can provide definite answers to specific questions that can be confirmed with the following experiments. Accordingly, the appropriate study design, arms, and the number of patients should be decided regarding the hypothesis. Eligibility and ineligibility criteria are essential to balance adequate patient recruitment and avoiding a heterogenous patient population. Another challenge is defining the primary and secondary objectives that may frequently include efficacy or toxicity, quality of life, and cost-effectiveness endpoints.

Trial Design

An important aspect of clinical trials is the choice of trial design, that is, whether the trial is meant to be observational or experimental. Observational studies, that is, cohort studies, case–control studies, and case series, often involve generating a hypothesis which leads to further questions to be asked. Experimental studies, on the other hand, aim to test established hypotheses and to evaluate the effects of planned interventions on a particular group of patients.

Experimental trials can be randomized or non-randomized, cross-over, or factorial.

Randomized clinical trials involve comparing two or more groups of patients with similar characteristics that are assigned randomly to different treatment groups or "arms;" the intervention is tested in one group, and the other group or groups are given standard treatment. The trial is evaluated in terms of its primary and secondary objectives, which usually

Received: November 24, 2022
Accepted: November 28, 2022
Online: December 16, 2022

Accessible online at:
www.onkder.org

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focus on the relative toxicity and effectiveness of the treatments being tested.[1]

One example of a randomized trial is PEMBRO-RT, in which immunotherapy and radiation were evaluated in 78 patients with metastatic non-small cell lung cancer who were treated with pembrolizumab with or without stereotactic ablative RT.[2] Subset analyses of the trial results showed that the combined treatment (pembrolizumab+RT) led to better overall response rates (ORR), but only for patients whose tumors did not express the ligand for the programmed cell death-1 receptor.

A different type of trial design, a cross-over study, involves comparing patients who receive the same treatment at different periods during the study. In other words, the study participants serve as their own controls. Cross-over studies therefore require fewer participants than a standard parallel, randomized, and controlled trial.

An example of a study with a cross-over design (NCT02710253) is an ongoing Phase II trial in which salvage RT is used in an attempt to induce systemic disease regression in patients with metastatic disease that has advanced during systemic immunotherapy. Patients in this trial can be "crossed over" to receive RT in addition to immunotherapy after progression.

Because most clinical trials of RT with immunotherapy being conducted at this time involve patients with metastatic disease, the characteristics of the patients in these trials are inevitably heterogeneous. Another type of trial designed to account for this heterogeneity is the basket trial, in which a specific investigational treatment is given to patients with different diseases or disease subtypes with the goal of identifying molecular or other characteristics that can affect response to treatment. Pembrolizumab was approved in one such basket trial of patients with metastases from different types of solid tumors with the shared characteristics of high microsatellite instability or deficiencies in mismatch repair.

Choice of Endpoints

The choice of endpoints is also crucial and endpoints are different in Phase I, Phase II, and Phase III trials. Phase I trials are designed to evaluate the safety of a proposed therapy intended to be an effective treatment without increased risk of unacceptable and potentially life-threatening toxic effects. Phase II trials mainly evaluate the effectiveness of an experimental treatment option compared with standard treatment. Phase II trials also assess toxicity to confirm that the incidence of dose-limiting toxicity is not higher than that associated with the standard treatment. Because Phase II trials often involve small numbers of patients, and the selection process may include some patient- or disease-related factors but not others, the conventional endpoint of overall survival (OS) cannot be assessed reliably and is thus inappropriate for Phase II trials. Therefore, OS is more often used as an endpoint in Phase III trials, which are typically more comprehensive and involve larger numbers of patients and longer-follow-up time. However, Phase II trials can be a less expensive and faster way to provide information on whether a proposed treatment is worth pursuing in a more comprehensive (and more expensive) Phase III trial.

In addition to providing statistically meaningful information to distinguish the effects of one treatment over another, the primary endpoint in randomized, Phase II, and Phase III trials should also be clinically meaningful for patients and society. The traditional "gold standard" endpoint has been OS, but progression-free survival (PFS) is also being evaluated as a clinically meaningful and specific parameter. Other endpoints used in trials of immunotherapy versus chemotherapy, or in early trials evaluating the addition of RT to immunotherapy, are the ORR or the abscopal response rate (that is, the response rate of disease at unirradiated sites). The classic system for assessing response has been the Response Evaluation Criteria in Solid Tumors, but trials involving immunotherapy increasingly use a slightly different version, the immune-related response criteria.[3]

Other aspects to be considered in the choice of trial endpoints are toxicity and cost-effectiveness. First, differences in toxicity can be clinically meaningful, but the greater concern may be differences in efficacy. For example, studies in which one treatment modality is added to another to treat metastatic disease cannot be expected to be less toxic than either modality used alone, but could be more effective in controlling disease than either modality used alone. The relatively new endpoint of cost-effectiveness represents an attempt to incorporate efficacy, safety, and quality of life into a single quantitative metric.

Another important consideration in designing trials of RT and immunotherapy for patients with metastatic disease is the choice of inclusion and exclusion criteria, that is, characteristics that would include or exclude patients from a given trial. Reviewing the past and current literature is crucial for defining appropriate criteria and endpoints for all clinical trials. Precise identification of inclusion and exclusion criteria helps

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to balance the number of patients needed within a predefined accrual time with maintaining the homogeneity of the results to the greatest extent possible. Although accrual rate and study criteria can be amended over the course of a trial, that necessarily increases the time and cost of the trial. Indeed, the previous studies that included patients with a broad spectrum of metastatic diseases are giving way to more modern trials in which the inclusion criteria are stricter as reliable data on whether and how a particular treatment works are obtained.

Another factor to consider in the choice of trial endpoints is that patients with metastatic disease often receive more than one form of immunotherapy over time, with RT usually used if the disease progresses. Therefore, endpoints that focus solely on survival may be inadequate for such trials. More meaningful endpoints may be the development of resistance to immunotherapy or the immune-boosting effects of RT on the development of resistance. Indeed, the slope and tail of the survival curve for long-term survivors may be useful for distinguishing the effects of combination immunotherapy and RT over the longer term (e.g., up to 3 years after the treatment).

Yet another factor in the choice of trial endpoints is the complexity of the effects of high-dose RT on the immune system at both the systemic and tumor-microenvironment levels.[4] On the one hand, RT triggers cell death pathways and promotes the secretion of cytokines and chemokines and the release of tumor neoantigens. On the other hand, high-dose RT also leads to suppression of T cells and the production of tumor growth factor-β by different mechanisms. Thus reaching reliable and reproducible results will require evaluating both the antitumor effects and immune-suppressive effects of RT.

This complexity underscores the importance of choosing translational-science endpoints that consider the choice of sample type, the time at which to collect them, and the methods to evaluate them. For example, flow cytometry phenotyping of blood and biopsy samples can reveal a wealth of detail regarding the status of both the innate and adaptive immune systems. Flow cytometry findings can be complemented with those of multiplex immunofluorescence staining of tissue samples to reveal spatial aspects of how specific immune-cell populations are distributed within the tumor microenvironment. Translational endpoints from clinical trials can also provide information on the T-cell immune repertoire, which could be useful for future research on the design of prophylactic or curative vaccines.

Tumor-specific epitopes are known to differ among patients due to gene mutations, variations in antigen processing, and the diversity of the human leukocyte antigen (HLA) haplotypes. Detailed analyses of tumor biopsy specimens, obtained repeatedly over time, can help to determine the immunogenicity of these peptides, and tracking changes in epitopes may help to overcome acquired resistance to therapy. An alternative approach would be to evaluate circulating tumor cells obtained from whole-blood samples to identify tumor mRNA or epitopes. However, longitudinal analyses such as these pose significant challenges with regard to patient participation, cost, and resource availability.

Because interactions between HLA-peptide complexes and T cell receptors also affect the immunogenicity of tumor epitopes, other evaluations should include the diversity and clonality of the T-cell receptor repertoire and the transformation of T cells after RT and immunotherapy. The presence of highly diverse receptor repertoires among tumor-infiltrating T cells has been linked with better responses to primary and metastatic disease.[5]

The persistent exposure of T cells to antigens and inflammatory signals leads to a slow loss of effector function known as "T cell exhaustion",[6] which is known to be associated with poor outcomes in cancer. Immune exhaustion can be determined by evaluating the expression of protein or RNA for PD1, lymphocyte-activation gene 3, T cell immunoglobulin mucin 3 (TIM3), and T cell immunoglobulin and ITIM domain (TIGIT) using flow cytometry or RNA sequencing. Beyond T-cell exhaustion, the cytotoxic capacity of T cells can be determined by measuring the expression of proteins like granzyme B or cytokines like TNFα and IFNγ by T cells on *ex vivo* stimulation with tumor epitopes. Detailed analyses of these phenotypes could eventually help to determine the probability of response in clinical trials.

Other issues to be considered in designing clinical trials that combine RT with immunotherapy are the timing and sequence of the two modalities for multisite oligometastatic tumors and the length of the interval between them. Another consideration is whether the combined therapy contributes to health-care value. Although adding RT to immunotherapy has been found to improve response rates in some situations, the ultimate aim is to maintain improved results and cost-effectiveness in the long-term relative to standard-of-care treatments. The financial cost of adding RT to immunotherapy presumably would be lower than the cost of switching to a different type of immunotherapy to address acquired resistance.

CONCLUSION

Combining RT with immunotherapy is a new focus in current clinical trials and endpoints are evolving from the traditional OS, PFS, and toxicity to a more molecular-translational basis with an emphasis on disease control and quality of life. In this context, comprehensive preparation is needed to balance patient accrual with cost-effectiveness and the value of the results. The heterogeneity of metastatic cancer emphasizes the importance of designing trials with sufficient statistical power for subset analyses to obtain reliable data and to distinguish patient subpopulations for subsequent trials.

Peer-review: Externally peer-reviewed.

Conflict of Interest: JWW reports research support from GlaxoSmithKline, Bristol Meyers Squibb, Merck, Nanobiotix, RefleXion, Alkermes, Artidis, Mavu Pharma, Takeda, Varian, Checkmate Pharmaceuticals, HotSpot Therapeutics, Inc., Gilead and Kiromic. JWW serves/served on the scientific advisory board for Legion Healthcare Partners, RefleXion Medical, MolecularMatch, Merck, AstraZeneca, Aileron Therapeutics, OncoResponse, Checkmate Pharmaceuticals, Mavu Pharma, Alpine Immune Sciences, Ventana Medical Systems, Nanobiotix, China Medical Tribune, GI Innovation, Genentech and Nanorobotix. JWW serves as consultant for Lifescience Dynamics Limited. JWW has/had Speaking Engagements for Ventana Medical Systems, US Oncology, Alkermes, Boehringer Ingelheim, Accuray and RSS. JWW holds/held stock or ownership in Alpine Immune Sciences, Checkmate Pharmaceuticals, Healios, Mavu Pharma, Legion Healthcare Partners, MolecularMatch, Nanorobotix, OncoResponse, and RefleXion. JWW has accepted honoraria in the form of travel costs from Nanobiotix, RefleXion, Varian, Shandong University, The Korea Society of Radiology, Aileron Therapeutics and Ventana. JWW has the following patents; MP470 (amuvatinib), MRX34 regulation of PDL1, XRT technique to overcome immune resistance. MD Anderson Cancer Center has a trademark for RadScopalTM. The rest of the authors disclosed no competing interests.

Financial Support: None declared.

REFERENCES

1. Sezen D, Verma V, He K, Abana CO, Barsoumian H, Ning MS, et al. Considerations for clinical trials testing radiotherapy combined with immunotherapy for metastatic disease. Semin Radiat Oncol 2021;31(3):217–26.
2. Theelen WSME, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts JGJV, et al. Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: Results of the PEMBRO-RT phase 2 randomized clinical trial. JAMA Oncol 2019;5(9):1276–82.
3. Hodi FS, Hwu WJ, Kefford R, Weber JS, Daud A, Hamid O, et al. Evaluation of Immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol 2016;34(13):1510–7.
4. Deng L, Liang H, Fu S, Weichselbaum RR, Fu YX. From dna damage to nucleic acid sensing: A strategy to enhance radiation therapy. Clin Cancer Res 2016;22(1):20–5.
5. Rudqvist NP, Pilones KA, Lhuillier C, Wennerberg E, Sidhom JW, Emerson RO, et al. Radiotherapy and CTLA-4 blockade shape the TCR repertoire of tumor-infiltrating T cells. Cancer Immunol Res 2018;6(2):139–50.
6. Jiang Y, Li Y, Zhu B. T-cell exhaustion in the tumor microenvironment. Cell Death Dis 2015;6(6):e1792.