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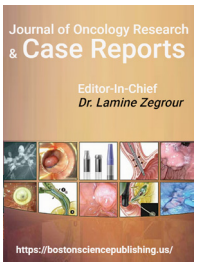

Combination Therapies in Merkel Cell Cancer – Synergy between Immunotherapy and Radiotherapy

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A B S T R A C T

Introduction: Merkel cell cancer (MCC) is a rare and aggressive skin cancer, often associated with Merkel cell polyomavirus (MCPyV) infection and prolonged exposure to ultraviolet radiation. Due to its high recurrence rate and metastatic potential, innovative therapeutic strategies have been explored to improve clinical outcomes. The combination of immunotherapy and radiotherapy (RT) has shown promise, taking advantage of the ability of immunotherapy to stimulate the immune system and the efficacy of RT in localised tumour destruction.

Methodology: This study is based on a review of the scientific literature, analysing articles published between 2005 and 2024 in databases such as PubMed, Scopus and Web of Science. Studies that investigated the EFFICACY of immunotherapy combined with RT in treating MCC, considering clinical, biological and therapeutic aspects, were included. The selection of articles followed strict criteria, prioritising research with significant samples and well-established methodologies.

Results: The data analysed indicate that immunotherapy, especially immune checkpoint inhibitors such as avelumab and pembrolizumab, effectively activates the immune system against tumour cells. When combined with RT, a synergistic effect is observed, where radiation-induced tumour destruction can increase the release of tumour antigens, enhancing the immune response. Clinical studies suggest that this combined approach improves overall survival and reduces the rate of disease recurrence. Discussion: The combination of immunotherapy and RT in MCC represents a significant advance in the treatment of this aggressive neoplasm. RT acts directly to reduce tumour burden, while immunotherapy stimulates the immune system to recognise and eliminate remaining malignant cells. However, challenges such as immune-mediated side effects, tumour resistance, and the need for personalised protocols still need to be overcome. Future studies should focus on optimising the dose and therapeutic sequence, in addition to identifying predictive biomarkers for better patient selection. Conclusion: The synergy between immunotherapy and RT in MCC has shown promising results, improving treatment response and increasing patient survival. The integration of these approaches may represent a new paradigm in oncology, allowing for more effective and personalised treatments. However, additional research is needed to refine protocols and minimise adverse effects, ensuring that this strategy is widely applicable in clinical practice.

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Introduction

Merkel cell carcinoma (MCC) is a rare but highly aggressive cutaneous neoplasm with an estimated annual incidence of 0.7 cases per 100,000 individuals (Afanasiev et al., 2013; Akaike et al., 2024). Despite its rarity, MCC is known for its aggressive clinical behaviour, with a high rate of recurrence and metastasis, resulting in a mortality rate that exceeds that of melanoma in advanced stages (Becker et al., 2017). The treatment of MCC has evolved significantly in recent decades, with the introduction of immunotherapy, particularly immune checkpoint inhibitors, such as anti-PD-1/PD-L1, which have demonstrated objective response rates (ORR) of up to 56% in clinical trials (Bichakjian et al., 2018). However, therapeutic resistance and disease progression remain significant challenges, especially in patients with metastatic disease (Topalian, Taube, & Pardoll, 2020).

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Radiotherapy (RT), widely used in the localised treatment of MCC, has well-documented immunomodulatory effects, including the release of tumour antigens and the activation of local and systemic immune responses, known as the abscopal effect (Deng et al., 2014). The combination of immunotherapy and RT has been explored in other cancer types, such as melanoma and lung cancer, with promising results, suggesting that this approach may also be beneficial in MCC (Rittmeyer et al., 2017).

The MCC is frequently associated with immunosuppression, either due to underlying clinical conditions, such as organ transplantation or human immunodeficiency virus (HIV) infection, or due to chronic use of immunosuppressants (Wong et al., 2015). This association reinforces the importance of therapeutic strategies that restore immune function, such as immunotherapy. However, immunosuppression can also limit the efficacy of these therapies, making it crucial to explore combination approaches that enhance the immune response (Kaufman et al., 2016). Furthermore, the presence of Merkel cell polyomavirus (MCPyV) in approximately 80% of MCC cases offers a unique opportunity for the development of targeted therapies, such as vaccines or antiviral therapies, that can be combined with immunotherapy and RT (Golden et al., 2014). RT, in turn, has traditionally been used in the localised treatment of MCC, with local control rates ranging from 70% to 90% (Cowey et al., 2017). However, its role in the treatment of metastatic disease is limited, especially in patients with multiple distant lesions. The discovery of the abscopal effect, in which RT to a primary lesion induces an antitumor response in distant metastatic lesions, has opened new perspectives for the use of RT in combination with immunotherapy (Cowey et al., 2017). This approach has the potential to transform the treatment of advanced MCC, offering a therapeutic alternative for patients who do not respond to immunotherapy alone.

Methodology

To prepare this review, the PubMed, Scopus and Web of Science databases were consulted, using the following search terms: "Merkel cell carcinoma", "immunotherapy", "radiotherapy", "combination therapy", "PD-1", "PD-L1", "abscopal effect". Studies published between 2005 and 2024, in English, that addressed the combination of immunotherapy and RT in MCC or cancers with similar characteristics were included. Narrative review articles, studies without relevant data or with deficient methodology were excluded.

Results

Immunotherapy with immune checkpoint inhibitors, such as anti-PD-1/PD-L1, restores T cell activity against the tumour by blocking the interaction between PD-1 (present on T cells) and PD-L1 (expressed by tumour cells) (Paulson et al., 2018). In MCC, PD-L1 expression is associated with a greater response to immunotherapy (Paulson et al., 2018). Studies have shown that the presence of the MCPyV virus, found in approximately 80% of MCC cases, can modulate PD-L1 expression and influence the response to treatment (Paulson et al., 2018). Activation of cytotoxic T cells (CD8+) is an essential component of the antitumor response mediated by immunotherapy, and the presence of T cell infiltrates in the tumour microenvironment has been correlated with better clinical outcomes (Nghiem et al., 2016). On the other hand, RT induces immunogenic cell death, releasing tumour antigens and activating dendritic cells, which promote the antitumor immune response (Nghiem et al., 2016). Furthermore, RT can increase the expression of PD-L1 in tumour cells, enhancing the response to anti-PD-1 (Nghiem et al., 2016). These mechanisms suggest that the combination of immunotherapy and RT can enhance the immune response, both locally and systemically. RT also promotes the release of pro-inflammatory molecules, such as cytokines and chemokines, which recruit immune cells to the tumour microenvironment, creating a more favourable environment for the action of immunotherapy (Nghiem et al., 2016). A crucial aspect of the synergy between RT and immunotherapy is the abscopal effect, in which radiation applied to a primary lesion induces an antitumor response in distant metastatic lesions (Nghiem et al., 2016). This phenomenon is mediated by systemic activation of the immune system, which recognises and attacks tumour cells in non-irradiated sites (Coggshall, Tello, North, & Yu, 2018). In MCC, where metastasis is common, the abscopal effect may represent an effective strategy to control disseminated disease.

In addition, RT can modulate the tumour microenvironment by reducing the presence of immunosuppressive cells, such as regulatory T cells (Tregs) and tumour-associated macrophages (TAMs), which inhibit the antitumor immune response (Coggshall, Tello, North, & Yu, 2018). The reduction of these cell populations creates a more conducive environment for the action of cytotoxic T cells, enhancing the efficacy of immunotherapy. Studies also suggest that RT can induce the expression of neoantigens, which are recognised by the immune system as foreign, increasing the specific immune response against the tumour (Dowlatshahi et al., 2013). This combination of immunomodulatory mechanisms makes RT a powerful ally of immunotherapy in the treatment of MCC.

Another important mechanism is the ability of RT to induce the formation of normal vascular pathways in the tumour, a process known as vascular normalisation (Veness et al., 2005). Vascular normalisation improves the delivery of oxygen and nutrients to the tumour, in addition to facilitating the infiltration of immune cells. This effect can increase the efficacy of immunotherapy, since the presence of T cells in the tumour microenvironment is essential for the response to treatment (Feng, Shuda, Chang, & Moore, 2008). Furthermore, vascular normalisation can reduce tumour hypoxia, which is associated with resistance to RT and immunotherapy (Ferris et al., 2016). Therefore, the combination of RT and immunotherapy may overcome multiple barriers to antitumor response, offering a more effective approach for the treatment of MCC.

Preclinical studies in MCC models have shown that the combination of RT and immunotherapy increases T cell infiltration into the tumour microenvironment and reduces tumour burden (Lebbe et al., 2015). In murine models, hypofractionated RT (8 Gy x 3 fractions) increased PD-L1 expression on tumour cells, enhancing the response to anti-PD-1 (Goh et al., 2016). These findings suggest that RT may "prime" the tumour for a more effective response to immunotherapy. Furthermore, RT promotes the release of tumour antigens, which are captured by dendritic cells and presented to T cells, amplifying the specific immune response against the tumour (Harms et al., 2018). This process is essential for the induction of long-term immunological memory, which can prevent relapses.

Another important aspect observed in preclinical models is the role of RT in reducing local immunosuppression. Radiation can decrease the presence of Tregs and TAMs, which inhibit the activity of cytotoxic T cells (Jain, 2005). This modulation of the tumour microenvironment creates a more favourable environment for the action of immunotherapy, increasing the efficacy of the treatment. Furthermore, studies in MCC models have shown that RT can induce the formation of normal vascular pathways in the tumour, a process known as vascular normalisation, which improves the delivery of oxygen and nutrients, in addition to facilitating the infiltration of immune cells (Jain, 2005). Vascular normalisation also reduces tumour hypoxia, which is associated with resistance to RT and immunotherapy. RT can modulate the expression of costimulatory molecules, such as CD80 and CD86, on tumour cells, increasing antigen presentation and T cell activation (Coggshall, Tello, North, & Yu, 2018). A phase II study with avelumab (anti-PD-L1) demonstrated an ORR rate of 33% and an overall survival (OS) of 11.3 months in patients with advanced MCC (Tang & Toker, 1978). These results represented a significant advance in the treatment of the disease, especially considering that many patients do not respond to conventional chemotherapy. However, resistance to immunotherapy alone remains a challenge, highlighting the need for combination strategies. Furthermore, the study showed that PD-L1 expression in the tumour was correlated with a higher response rate, suggesting that this biomarker may be useful for selecting patients who benefit most from combination therapy.

Another phase I/II study with pembrolizumab (anti-PD-1) and RT reported an ORR of 56%, with evidence of an abscopal effect in non-irradiated lesions (Yarchoan et al., 2019). This study demonstrated that RT can enhance the response to immunotherapy, not only at the irradiated site but also in distant metastatic lesions. The abscopal effect was observed in patients with multiple metastases, suggesting that combination therapy may be an effective approach for systemic disease control. Furthermore, the combination was well tolerated, with toxicity similar to that observed with immunotherapy alone. However, the occurrence of RT-related adverse events, such as dermatitis and fatigue, was more frequent in elderly patients, highlighting the need for careful monitoring.

Retrospective studies have also demonstrated that adjuvant RT can improve outcomes in patients with localised MCC. A retrospective study of 112 patients showed that adjuvant RT reduced the risk of local recurrence and increased progression-free survival (PFS) compared with surgery alone (Nghiem et al., 2019). These findings suggest that RT may play an important role in local disease control, even in early stages. However, toxicity associated with the combination of RT and immunotherapy is still a concern, especially in elderly patients, who account for the majority of MCC cases (Nghiem et al., 2019).

Identifying predictive biomarkers is crucial for selecting patients who benefit most from combination therapy. PD-L1 expression has been widely studied as a biomarker of response to immunotherapy. In MCC, PD-L1 expression is associated with a higher response rate to treatment with immune checkpoint inhibitors (Villani et al., 2019). Furthermore, the presence of MCPyV in MCC may influence response to treatment, since the expression of viral antigens may increase tumour immunogenicity (Kaufman et al., 2018). Studies suggest that patients with MCPyV-positive tumours may have a more robust response to immunotherapy, due to the greater expression of viral antigens recognised by the immune system.

Another promising biomarker is tumour mutational burden. Tumours with a high mutational burden tend to have a greater response to immunotherapy, due to the greater production of neoantigens, which are recognised by the immune system (Kaufman et al., 2018). In MCC, the mutational burden varies significantly between MCPyV-positive and MCPyV-negative subtypes, with the latter having a higher mutational burden and potentially greater response to immunotherapy (Kaufman et al., 2018). Furthermore, mutational profiling can identify specific mutations that predict response to treatment, such as mutations in genes involved in the DNA repair pathway.

Analysis of the tumour microenvironment can also provide valuable insights into response to combination therapy. The presence of tumour-infiltrating T cells (TILs) has been associated with improved clinical outcomes in MCC patients treated with immunotherapy (Kaufman et al., 2018). Furthermore, the presence of Tregs and TAMs can inhibit the immune response, suggesting that modulation of these cell populations may improve treatment efficacy (Kaufman et al., 2018).

Discussion

The combination of immunotherapy and RT represents a promising strategy in the treatment of advanced or metastatic MCC. The synergistic mechanisms between these modalities, such as the potentiation of the antitumor immune response and the abscopal effect, justify the conduct of additional clinical studies. However, challenges persist, such as the heterogeneity of treatment protocols and the need to identify robust predictive biomarkers. Immunotherapy with immune checkpoint inhibitors, such as anti-PD-1/PD-L1, has revolutionised the treatment of MCC, but primary or acquired resistance to these therapies remains a significant obstacle (Harms et al., 2015). RT, in turn, modulates the tumour microenvironment, increasing PD-L1 expression and promoting the release of tumour antigens, which can partially overcome resistance to immunotherapy (Harms et al., 2015). One of the most intriguing aspects of combination therapy is the abscopal effect, in which radiation applied to a primary lesion induces an antitumor response in distant metastatic lesions (Harms et al., 2015). This phenomenon is mediated by systemic activation of the immune system, which recognises and attacks tumour cells in non-irradiated sites. Clinical studies have shown that the combination of RT and immunotherapy can amplify the abscopal effect, making this approach particularly promising for the treatment of patients with metastatic disease (Akaike et al., 2024). However, the occurrence of the abscopal effect remains variable among patients, highlighting the need to identify predictive factors that can predict which patients are most likely to benefit from this approach.

In addition, toxicity associated with combination therapy should be carefully monitored, especially in elderly patients, who account for the majority of MCC cases (Villani et al., 2019). RT can cause local adverse effects, such as dermatitis and fibrosis, while immunotherapy is associated with systemic adverse events, such as hepatic and endocrine toxicity. Combining these modalities may increase the risk of cumulative toxicity, which requires close monitoring and implementation of toxicity management protocols.

Another challenge is the molecular heterogeneity of MCC, which may influence the response to combination therapy. MCPyV-positive and MCPyV-negative tumours have distinct molecular characteristics, with implications for treatment (Kaufman et al., 2018). For example, MCPyV-positive tumours tend to have higher PD-L1 expression and greater T-cell infiltration, which may predict a better response to immunotherapy (Kaufman et al., 2018). On the other hand, MCPyV-negative tumours have a higher mutational burden, which may increase neoantigen production and, consequently, immune response (Nghiem et al., 2019).

Identification of predictive biomarkers is another crucial aspect for the advancement of combination therapy in MCC. In addition to PD-L1 expression and mutational burden, other biomarkers, such as the presence of TILs and the composition of the tumour microenvironment, have been associated with treatment response (Nghiem et al., 2016). Analysis of the tumour immune profile, including the presence of Tregs and TAMs, may provide additional insights into the response to combination therapy. Furthermore, the integration of multi-omics data, including genomics, transcriptomics, and proteomics, may allow a more personalised approach, identifying subgroups of patients who benefit most from this therapeutic strategy.

Finally, exploring new therapeutic combinations is essential to overcome the current limitations of MCC treatment. In addition to the combination of immunotherapy and RT, other approaches, such as the addition of targeted therapies targeting specific molecular pathways (e.g., PI3K/AKT/mTOR inhibitors) or the use of therapeutic vaccines targeting MCPyV, may expand treatment options (Nghiem et al., 2016).

Table 1: Clinical and Preclinical Studies on Combination Therapy in Merkel Cell Cancer (MCC).

Study	Study Type	Intervention	Key results
Nghiem, et al., 2016	Phase II	Avelumab (anti-PD-L1)	ORR: 33%; OS: 11.3 months; greater response in PD-L1 positive tumors.
Topalian, et al., 2020	Phase I/II	Pembrolizumab (anti-PD-1) + Radiation therapy	ORR: 56%; Abscopal effect observed in non-irradiated lesions.
Deng, et al., 2014	Preclinical	Hypofractionated radiotherapy + anti-PD-1	Increased PD-L1 expression and systemic antitumor response (abscopal effect).
Golden, et al., 2014	Preclinical	Radiotherapy + immunotherapy	Release of tumor antigens and activation of dendritic cells.
Paulson, et al., 2018	Clinical	Biomarker analysis	MCPyV-positive tumors have a greater response to immunotherapy.
Goh, et al., 2016	Genomics	Mutational Load Analysis	MCPyV-negative tumors have a higher mutational load and neoantigen production.

The results presented in Table 1 highlight the potential of combined immunotherapy and RT in the treatment of MCC. The synergy between these modalities, mediated by mechanisms such as tumour antigen release, dendritic cell activation, and the abscopal effect, offers a promising approach for local and systemic control of the disease. However, the molecular heterogeneity of MCC and the variability in the occurrence of the abscopal effect highlight the need for a personalised approach based on predictive biomarkers of response. Future studies should focus on optimising treatment protocols and identifying subgroups of patients who benefit most from this therapeutic strategy.

Conclusion

Combined immunotherapy and RT have the potential to improve clinical outcomes in MCC, overcoming the limitations of isolated treatment. The synergy between these therapeutic modalities, mediated by mechanisms such as the potentiation of the antitumor immune response and the abscopal effect, offers a promising approach for local and systemic control of the disease, especially in advanced or metastatic cases. This combination can increase the ORR and OS rate, in addition to reducing the risk of local and metastatic recurrence. However, the molecular heterogeneity of MCC and the variability in the occurrence of the abscopal effect highlight the need for a personalised approach, based on predictive biomarkers of response.

The identification of robust biomarkers is essential to select patients who most benefit from combined therapy. The integration of multi-omics data can provide a more comprehensive view of the mechanisms of response and resistance to treatment, allowing the personalisation of therapeutic strategies. The exploration of new therapeutic combinations can expand treatment options and improve outcomes.

Finally, optimising protocols is essential to ensure the safety and efficacy of combination therapy. Strict monitoring of adverse events is essential to minimise the risks associated with treatment.

Abreviations

MCC - Merkel Cell Carcinoma, **CD8+ -** Cytotoxic T Cells, **HIV -** Human Immunodeficiency Virus, **MCPyV -** Merkel Cell Polyomavirus, **ORR -** Objective Response, **OS -** Overall Survival, **PFS-** Progression Free Survival,

RT - Radiotherapy, **TAMs -** Tumor Associated Macrophages, **TILs -** Infiltrating T Cells, **Tregs -** Regulatory T Cells.

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Declaration of Conflict of Interest

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What do we already know about this topic?

Recent research suggests that the combination of immunotherapy and radiotherapy may be a promising approach for the treatment of Merkel cell carcinoma (MCC). Studies suggest that radiotherapy may help overcome primary and secondary resistance to immunotherapy, especially in patients who experience limited disease progression while receiving avelumab. In a retrospective study, patients treated with this combination showed response rates of 75% at the first post-radiotherapy assessment, with 60% of patients free of recurrence at 6 months and 1 year.

In addition, immunotherapy has emerged as an effective alternative to traditional chemotherapy, with new agents such as retifanlimab receiving accelerated approval for advanced MCC. The combination of immunotherapy with local therapies, such as radiotherapy, is increasingly being explored to improve patient outcomes.

What is the main contribution to evidence-based practice in this article?

The main contribution to evidence-based practice of this article is the demonstration of the synergistic potential between immunotherapy and radiotherapy in the treatment of Merkel cell carcinoma (MCC). The study highlights that radiotherapy can be an effective strategy for patients with limited disease progression while receiving avelumab, helping to overcome primary and secondary resistance to immunotherapy.

The results indicate that 75% of patients treated with this combined approach had an objective response at the first post-radiotherapy assessment, and 60% of patients were free of recurrence after 6 months and 1 year. In addition, the study reinforces the importance of personalizing treatment for patients with advanced MCC, considering radiotherapy as an adjunct to immunotherapy to improve progression-free survival.

What are the implications of the article for theory, practice, or policy?

The article on combination therapies in Merkel cell carcinoma highlights the synergistic interaction between immunotherapy and radiotherapy, showing how this approach can improve patient outcomes. The research suggests that radiotherapy can help overcome primary and secondary resistance to immunotherapy, especially in patients treated with avelumab. The results indicate that 75% of patients showed an objective response after the therapeutic combination, and 60% of them had no recurrence after six months and one year.

In the theoretical context, the article reinforces the hypothesis that radiotherapy can enhance the immune response, making the tumor environment more favorable to the action of checkpoint inhibitors. For clinical practice, the research suggests that this combined approach can be an effective strategy for patients with advanced MCC, promoting higher response rates and better progression-free survival. In the sphere of health policies, the study findings emphasize the need for more clinical trials to validate this combination on a large scale and influence treatment guidelines.

This study provides important insights to personalize therapies and expand treatment options for patients with MCC, promoting an evidence-based approach for better outcomes.

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Vianna, Alberto Pereira de Lima participated as the main author, helping to write the introduction, methodology, results and discussion of the article. Uyeda, Mari participated as a co-author writing part of the introduction, discussion and results. Maluf, Gabriel participated as a co-author writing the results, discussion and conclusion. Kenupp, Maria Graziela de Fátima Alvarez participated as a co-author writing the introduction and discussion

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