

PSORIASIS IN THE ONCOLOGIC SETTING: THERAPEUTIC CHALLENGES AND INTEGRATED CLINICAL DECISION-MAKING

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Summary

Psoriasis management in patients with cancer history or active malignancy poses challenges due to concerns about immunosuppressive therapies exacerbating cancer progression. This review synthesizes current evidence on treatment safety and efficacy, highlighting IL-17/IL-23 inhibitors as low-risk options, and the role of multidisciplinary care. Key findings support individualized risk-benefit assessments, with newer biologics offering favorable safety profiles. Future research should address long-term outcomes and refine consensus recommendations.

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Introduction

Psoriasis, a chronic immune-mediated disease, has seen transformative therapeutic advances, particularly with biologics targeting IL-17, IL-23, and TNF- α . However, managing patients with concurrent or prior neoplasia remains complex due to theoretical risks of immunosuppression and cancer recurrence.

Cancer survivors and patients with active malignancies often face limited psoriasis treatment options. Traditional systemic therapies (e.g., methotrexate, cyclosporine) and older biologics raise concerns about immune interference, while newer agents lack long-term safety data in this population.

This review evaluates therapies for psoriasis in patients with neoplasia, summarizes clinical

guidelines, and provides a framework for personalized decision-making.

Cancer Risk in Psoriasis Therapy

Topical Therapies

Although research on the link between topical psoriasis treatments and cancer is limited, current data do not show a significant connection between the use of topical corticosteroids or vitamin D analogs and cancer development [1-4].

Tazarotene is a topical retinoid that is metabolized to tazarotenic acid, which binds selectively to RAR- β and RAR- γ receptors, regulating keratinocyte proliferation and differentiation. Although its direct impact on cancer risk has not been extensively studied, tazarotene has demonstrated efficacy in the

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treatment of basal cell carcinoma, squamous cell carcinoma, and mycosis fungoides. Its anti-neoplastic effect is thought to involve up-regulation of the tumor suppressor gene TIG-3, commonly downregulated in both psoriasis and certain skin malignancies, thereby inhibiting cell proliferation and promoting apoptosis [5].

Phototherapy

Phototherapy, a standard treatment for psoriasis, reduces inflammation by inhibiting dendritic cell function and suppressing effector T-cell activation [6].

However, phototherapy can also raise cancer risk by causing DNA damage. These DNA lesions can disrupt replication and, if not repaired, may contribute to skin cancers development. UV radiation impairs the p53 tumor suppressor pathway, compromising genomic stability and increasing the risk of carcinogenesis [7].

PUVA therapy (oral 8-methoxypsoralen combined with UVA light) is linked to an increased risk of non-melanoma skin cancers, particularly squamous cell carcinoma, even in sun-protected sites [8]. This increased risk persists after stopping treatment, and patients who undergo more than 350 PUVA sessions have a much higher risk of SCC [9]. The risk of basal cell carcinoma is lower than that for SCC, even at high doses, and people who have more than 250 PUVA sessions also face an increased risk of melanoma [10]. Importantly, a large follow-up study found no significant link between PUVA and internal cancers [11].

Narrowband UVB (NB-UVB) is another common type of phototherapy used for psoriasis. Research generally shows that NB-UVB carries a lower skin cancer risk than PUVA, with no significant increase in basal cell carcinoma or squamous cell carcinoma rates [12]. However, very high cumulative doses (over 300 sessions) may slightly raise SCC risk, especially when combined with PUVA [13]. Evidence for an increased melanoma risk with NB-UVB is limited and not conclusive [13].

Conventional Systemic Therapies

Methotrexate, an analog of folic acid, is widely used in moderate to severe psoriasis. It inhibits DNA replication by blocking dihydro-

folate reductase, slowing the growth of skin cells. The cancer risk associated with methotrexate is debated. A meta-analysis found a 1.2% malignancy rate in methotrexate-treated psoriasis patients [14], and a Korean study found no significant difference in cancer rates between these patients and those without psoriasis [15]. This aligns with findings in rheumatology, where methotrexate does not seem to greatly increase overall cancer risk [16-18].

However, methotrexate has been linked to a higher risk of basal cell carcinoma and squamous cell carcinoma, especially with long-term use or when combined with PUVA or cyclosporine [19,20]. Prolonged use (over two years) is considered an independent risk factor for squamous cell carcinoma [9]. The evidence regarding melanoma risk is inconsistent, with some studies suggesting a small increase and others finding no association [21-23]. There have also been case reports of lymphomas, particularly Epstein-Barr virus-associated, in patients on long-term methotrexate [24-27].

Cyclosporin is a traditional systemic therapy for severe psoriasis, generally used for short-term treatment [28]. Long-term use is associated with an increased risk of cancer, particularly non-melanoma skin cancers like SCC [29]. The risk is higher with prolonged treatment or in patients previously treated with PUVA [30]. Cyclosporin has also been linked to lymphoproliferative disorders, especially in transplant patients who receive higher doses, but there are rare reports in psoriasis patients as well [31,32].

Acitretin, a synthetic retinoid, regulates keratinocyte proliferation and differentiation [28]. Although data on its oncologic risk are limited, some studies indicate that acitretin may reduce the incidence of squamous cell carcinoma, particularly when used in combination with PUVA. This combination appears to reduce the toxicity of PUVA, which is known to increase the risk of SCC [33]. Acitretin has also been studied for its prophylactic role in preventing skin cancers in post-transplant patients, further underscoring its potential to lower skin cancer risk [34,35]. Current evidence does not support an increased risk of internal malignancies with acitretin use [15].

Biologic Agents

Biologic therapies have revolutionized psoriasis management, providing targeted options such as TNF inhibitors (adalimumab, etanercept, infliximab, certolizumab), IL-12/23 antagonists (ustekinumab), IL-17 inhibitors (ixekizumab, secukinumab, bimekizumab, brodalumab), and IL-23 inhibitors (risankizumab, tildrakizumab, guselkumab).

While the introduction of biologics has raised concerns about increased malignancy risk, particularly regarding limited real-world data on IL-17/IL-23 inhibitors, emerging evidence supports their potential [36]. Several studies, including a meta-analysis, have not demonstrated a heightened cancer risk with long-term biologic exposure [37]. However, ongoing investigation is needed.

TNF-alpha's dual role in mediating apoptosis and promoting carcinogenesis raises concerns that TNF inhibitors, by suppressing this dual role, may compromise immune surveillance, promote tumor cell survival, and elevate the risk of neoplasia [38].

Studies evaluating the cancer risk associated with TNF inhibitors (TNFi) show inconsistent results. Although most studies do not show a significant increase in overall cancer risk, some have reported a higher incidence of non-melanoma skin cancer, particularly squamous cell carcinoma, potentially influenced by prior treatments like cyclosporine or PUVA [39-41]. The association between basal cell carcinoma (BCC) and TNF inhibitors remains inconclusive, although some studies suggest an increased risk [42]. Evidence regarding melanoma risk is similarly inconsistent, with studies reporting mixed results [43-48].

TNF inhibitors have also been linked to an increased risk of lymphoproliferative disorders, such as non-Hodgkin and Hodgkin lymphomas, with case reports describing lymphomas, including cutaneous T-cell lymphomas (CTCL), in patients treated with TNFi [49,50]. Additionally, a case of gastric mucosa-associated lymphoid tissue lymphoma has been reported in a psoriasis patient treated with infliximab [51]. Another case described the development of myelodysplasia progressing to acute myeloid leukemia following

TNF inhibitor therapy in a patient with psoriasis [52].

IL-12 enhances antitumor activity primarily through IFN- γ activation, whereas IL-23 exerts pro-tumorigenic effects. Given these opposing roles, anti-IL-12/23 therapies targeting the shared p40 subunit may alter the tumor microenvironment and potentially increase malignancy risk by diminishing IL-12-mediated antitumor responses [53].

Ustekinumab, an IL-12/23 antagonist, has shown a reduced overall cancer risk in a Korean study, and long-term safety studies have not demonstrated increased risk of skin cancers [54]. Though rare, some cases of cutaneous T-cell lymphoma have been associated with ustekinumab use, but the overall cancer risk remains similar to placebo [53].

IL-17 exhibits a dual role in cancer, promoting or suppressing tumors depending on the context [55]. This raises concerns about the oncogenic risks of anti-IL-17 therapies. However, studies suggest that IL-17 inhibitors do not significantly increase malignancy risk and may even be associated with a reduced risk of certain cancers, including lymphoproliferative disorders, solid organ cancers, and BCC, compared to TNF inhibitors [56]. The risk of melanoma remains an area of ongoing investigation, with existing data being limited and underscoring the necessity for further long-term research.

A large international study indicated a decreased risk of non-Hodgkin lymphoma in patients treated with IL-17 inhibitors. However, there have been a few case reports of cutaneous T-cell lymphoma (CTCL) associated with IL-17 inhibitors [50].

IL-23 promotes T-helper 17 (Th17) differentiation and suppresses natural killer cell-mediated tumor surveillance [57-58]. Limited studies suggest that IL-23 inhibitors may offer a favorable safety profile regarding cancer development [56].

Small molecule therapies

Apremilast is a small-molecule inhibitor that targets phosphodiesterase 4 (PDE4), an enzyme responsible for breaking down cyclic adenosine monophosphate (cAMP). By inhibiting PDE4, apremilast raises intracellular cAMP levels,

helping to balance pro-inflammatory and anti-inflammatory mediators. This action decreases the production of key inflammatory cytokines like TNF- α , IL-17, and IL-23, which play a crucial role in the development of psoriasis [59].

Apremilast appears to be a safe therapeutic option for psoriasis patients, even those with a history of cancer. In a review of 841 patients with severe comorbidities, including cancer, apremilast was not linked to a significant increase in cancer progression or recurrence, suggesting it may be a low-risk choice for these patients [60].

Deucravacitinib is approved for treating moderate to severe psoriasis [61]. It selectively inhibits tyrosine kinase 2 (TYK2), preventing its activation while preserving the activity of other Janus kinase (JAK) family members. TYK2 mediates signaling for cytokines such as IL-23 and type I interferons, which are both critical in psoriasis. By selectively inhibiting TYK2, deucravacitinib reduces IL-23-mediated Th17 cell activation and the downstream inflammatory cascade, leading to decreased keratinocyte proliferation and inflammation [62].

Clinical trials have demonstrated a favorable safety profile, with low rates of malignancy. Over a 52-week study, the incidence of malignancies in patients treated with deucravacitinib was similar to those treated with placebo or apremilast, suggesting no increased cancer risk associated with its use [63,64].

Psoriasis Management in Patients with Malignancy

Therapeutic Approaches for Psoriasis in Oncologic Patients

Management of psoriasis in individuals with a current or prior cancer diagnosis requires careful consideration. Biologic agents, particularly those targeting TNF- α , are frequently avoided due to apprehension regarding their potential to influence cancer recurrence or progression. Recent research indicates that therapies inhibiting IL-17 or IL-23 may be safer alternatives in this context. According to the EuroGuiDerm guidelines, preferred options for oncologic patients include topical treatments, narrowband UVB phototherapy (excluding those

with elevated skin cancer risk), acitretin or low-dose methotrexate [65]. Furthermore, the European guidelines for the systemic management of moderate-to-severe psoriasis vulgaris advocate for the use of anti-TNF α agents, ustekinumab, and IL-17 and IL-23 inhibitors in patients with a history of malignancy, with treatment decisions guided by individualized assessments that account for patient preferences and the duration of cancer remission [65].

Apremilast has emerged as a favorable systemic option for patients with malignancy concerns. Unlike other systemic drugs and biologics, apremilast does not exert significant immunosuppressive effects, making it suitable for those with active or previous cancers. Its use is not restricted in patients with a cancer history, and it does not necessitate ongoing laboratory monitoring, offering both safety and convenience. This profile makes apremilast particularly advantageous for oncology patients with psoriasis, allowing effective symptom management without increasing the risk of cancer progression or interfering with oncologic care [60].

Deucravacitinib, a selective TYK2 inhibitor, provides another promising option for patients with malignancy risk. Its targeted mechanism avoids the broader immunosuppressive effects seen with other JAK inhibitors, potentially lowering the chance of cancer recurrence or progression. Clinical studies have shown that deucravacitinib delivers substantial improvement in psoriasis symptoms and quality of life, with a safety profile comparable to placebo and apremilast [63,64].

Timing Considerations for Psoriasis Therapy Following Cancer Diagnosis

The initiation of psoriasis treatment in relation to a cancer diagnosis is a critical consideration. At present, no consensus exists regarding the optimal timing, due to variations in cancer types, prognostic outcomes, and the timing of oncologic treatment, which has ranged from one to ten years post-diagnosis. In general, for patients with a history of malignancy, a minimum interval of five years before commencing biologic therapies is advised [66]. Nevertheless, increasing evidence supports the

earlier introduction of IL-17 and IL-23 inhibitors, given their favorable safety profiles in oncology settings.

Simultaneous Administration of Anti-Psoriatic and Oncologic Treatments

Oncologic therapies, particularly chemotherapy and targeted therapies, exert profound immunomodulatory effects that can impact psoriasis activity. Agents such as topoisomerase inhibitors and antimicrotubule agents can enhance antigen presentation and induce immunogenic cell death, leading to variable effects on psoriasis, including both improvement and exacerbation during cancer therapy [67].

Immune checkpoint inhibitors (e.g., anti-PD-1 and anti-PD-L1 agents), widely used in the management of solid tumors, are known to precipitate psoriasis flares. Managing these flares is essential to ensure the continuation of oncologic treatment. In such cases, agents like apremilast, which downregulates proinflammatory cytokine production, and acitretin are frequently employed to control psoriatic activity during immunotherapy [68,69]

Managing psoriasis in cancer patients demands a multidisciplinary strategy, taking into account the oncologic prognosis. In individuals with a favorable cancer outlook, systemic

therapies for psoriasis are generally expected to have outcomes comparable to those in patients without malignancy. Conversely, in patients with a poorer prognosis, therapeutic goals shift toward optimizing quality of life, where the benefits of psoriasis control may outweigh potential oncologic risks [70].

Conclusions

The management of psoriasis in patients with a history of malignancy or active cancer remains a complex and evolving field. Balancing effective disease control with minimizing oncologic risks necessitates individualized, multidisciplinary approaches. Emerging evidence supports the use of IL-17 and IL-23 inhibitors as safer biologic options, while non-immunosuppressive agents like apremilast and deucravacitinib offer additional therapeutic avenues for patients at higher oncologic risk. Although current data are reassuring regarding the oncologic safety of newer treatments, long-term surveillance and larger, prospective studies are required to further refine clinical guidelines. Personalized treatment decisions, grounded in careful risk-benefit analysis, patient preference, and cancer prognosis, are essential to optimize outcomes for this unique patient population.

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Conflict of interest
NONE DECLARED

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