Psoriasis and cancer. An Australian/New Zealand narrative.

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Abstract

Patients with psoriasis have an increased risk of cancer, which may be due to impaired immune surveillance, immune-modulatory treatments, chronic inflammation, and/or co-risk factors such as obesity. The increase in treatment-independent solid cancers, including urinary/bladder cancers, oropharynx/larynx, liver/gallbladder, and colon/rectal cancers seem to be linked to alcohol and smoking. Lung cancer and non-melanoma skin cancer are also increased in patients with psoriasis. The risk of non-melanoma skin cancer increases with age and severity of psoriasis. It is also higher in men, particularly for squamous cell carcinoma, which may reflect previous exposure to PUVA and/or ciclosporin. The risk of cutaneous T-cell lymphoma is substantially higher in patients with moderate-to-severe psoriasis.

Biologic therapies are independently associated with a slight increase risk of cancer, but this is less than ciclosporin, with the risk confounded by disease severity, and other co-risk factors. The risk of cancer from low-dose methotrexate, is likely minimal. In contrast, acitretin is likely protective against a variety of solid and haematological malignancies. The data on small molecule therapies such as apremilast is too immature for comment, other than no signal has yet been identified.

The decision whether to stop psoriasis immune-modulatory treatments following a diagnosis of cancer, and when to resume, needs to be considered in the context of the patients' specific cancer. However, there is no absolute need to stop any treatment other than possibly ciclosporin, unless

there is a concern over an increased risk of serious infection or drug-drug interaction with cancer-directed therapies, including radiotherapy.

Learning points

- Patients with psoriasis have a slight increase in the relative risk of developing solid organ malignancies, which increases with the severity of psoriasis, but this predominantly reflects the co-risk factors of obesity, smoking and alcohol consumption.
- Patients with psoriasis have a moderate increase in the relative risk of developing haematological malignancies, in particular lymphoma, but the absolute risk remains very low.
- The risk of squamous cell carcinoma is increased in psoriasis, but melanoma risk may be lower
- Reduction in common risk factors such as obesity, smoking and alcohol consumption have a much greater effect on reducing cancer burden in patients with psoriasis, than stopping or avoiding a systemic immune-modulatory agent

Introduction

The general aging of the population, and the consequent relative increase in the prevalence of cancer, has increased the awareness over a potential association between psoriasis and cancer, in particular the contribution of long-term use of biologic and immune-modulatory therapies. The Australasian Psoriasis Collaboration^{1,2} held a round table discussion to address a number of questions in an Australian/New Zealand context:

- Does psoriasis increase the risk of developing cancer?
- Do systemic immune-modulatory treatments increase the risk of developing cancer in patients with psoriasis?
- Do immune-modulatory treatments, in a patient who develops cancer, need to be stopped?
- Should any specific detection/screening programs or cancer prevention strategies, be recommended for patients with psoriasis?

The following narrative makes a number of clinical observations and recommendations based on the published literature and expert clinical opinion. The epidemiological data is variably presented as hazard ratios (HR), adjusted-HR (aHR), relative risks (RR), odds ratio (OR) or standardised incidence ratios (SIR), usually with 95% confidence intervals (95%CI).

Psoriasis and risk of cancer

Chronic inflammation is associated with an increased risk of cancer, as demonstrated by the increased tumorigenesis seen in a variety of medical conditions (e.g. gastritis, cystitis, bronchitis, ulcerative colitis, rheumatoid arthritis, etc.). Inflammatory mediators are thought to contribute to neoplasia by inducing pro-neoplastic mutations, adaptive responses, resistance to apoptosis, and environmental changes such as stimulation of angiogenesis.³ However, it is difficult to tease out the role of confounding co-morbidities, particularly smoking, alcohol, diabetes and obesity, which have all been shown to independently increase the risk of cancer.⁴⁻⁸

Solid organ malignancies

Multiple studies have now shown an increase in the relative risk of some solid organ cancers in patients with psoriasis, particularly those linked to alcohol consumption and cigarette smoking.⁹⁻¹² A Taiwanese study found that cancer risk was higher in male than in female patients with psoriasis (aHR: 1.86 vs. 1.14), including cancer of the urinary bladder and skin, followed by oropharynx/larynx, liver/gallbladder, and colon/rectum.¹³ The hazard ratio for cancer varies by age, with younger adult patients at the greatest risk. The risk of cancer in children with psoriasis, on the other hand, was not increased in a retrospective cohort study of biologic-naïve children compared with a matched paediatric population.¹⁴ Interestingly, phototherapy with UVB appeared to reduce the risk of cancer in patients with psoriasis (aHR: 0.52).¹³

A large cohort study of 198,366 patients with psoriasis (186,076 with mild psoriasis, 12,290 moderate-to-severe psoriasis) found the aHR (95% CI) for any incident cancer, excluding non-melanoma skin cancer, was 1.06 (1.02-1.09). For lung cancer, the aHR was 1.12 (1.01-1.25) for patients with mild psoriasis and 1.62 (1.16-2.28) for moderate/severe disease. However, no significant association was seen with cancer of the breast, colon, or prostate in this study.¹¹

A smaller study of 32,910 women, 719 with psoriasis, over the age of 65 years, found the aHR (95% CI) of lung cancer was 1.9 (1.2-3.0), colon cancer 1.6 (1.1-2.5), and any cancer 1.2 (1.0-1.4) in patients with psoriasis, compared to no psoriasis.¹⁵ When adjusted for smoking, body mass index, education, physical activity, and hormone therapy use, only the association for colon cancer remained with an aHR of 1.6 (1.0-2.4) and was stronger for patients with severe psoriasis.¹⁵

In a follow-up study of 9,773 Swedish patients who had been admitted to hospital with a diagnosis of psoriasis over the period 1965-1983, 789 of these patients went on to develop a malignancy at least 1 year after their discharge from hospital. The SIR (95% CI) for all cancers was 1.37 (1.28-1.47), with an increased SIR of cancers of the penis (4.66), vulva (3.24), the oral cavity and pharynx (2.8), lung (2.13), liver (1.91), pancreas (1.56), kidney (1.56), bladder (1.43) and female breast (1.27).¹⁶ This data needs to be interpreted with caution as the number of male/female genital cancers was quite low. A large Swedish cohort study of 56,235 breast cancer patients, demonstrated they had an aHR (95%CI) for developing psoriasis of 1.17 (1.07–1.28), with the risk of being diagnosed with psoriasis being highest shortly after diagnosis, but the risk remained for up to 12 years after their breast cancer.¹⁷

Data from the Australasian Psoriasis Registry (1,122 patients with 5,195 patient years of follow up), shows a cancer rate (excluding non-melanoma skin cancer) of 0.5/100 patient years, which is similar to the 0.49 and 0.68/100 patient years from the PsoBest and PSOLAR registries respectively (personal communication, Australasian Psoriasis Registry, Apr 2018).

The data on cancer survival in psoriasis patients, compared to individuals without psoriasis, is mixed. In a case-control study of 8,161 psoriasis patients with an aHR (95% CI) of cancer of 1.53 (1.21-1.96), there was no difference in cancer survival compared to patients without psoriasis.¹⁸ However, in a population-based Swedish study of 1,746 psoriasis cancer patients, the HR (95%CI) for cancer death was 1.26 (1.18-1.35) compared to over a million non-psoriasis cancer patients. Younger cancer patients with psoriasis (< 65 years), and those who had been treated for alcohol-related diseases had a worse prognosis.¹⁹ In a further cohort study using the UK General Practice Research Database, the HR (95%CI) for dying from a malignancy was 1.41 (1.07-1.86), in 3,603 patients with severe psoriasis, compared to age-matched control without psoriasis.¹⁰ This equates to an absolute risk of cancer deaths of 39/1,000 patient years, with the excess risk of death from cancer being 1.6 deaths/1,000 patient-years. To put this into perspective, the excess risk of death from cardiovascular disease in patients with psoriasis was calculated as 3.5/1,000 patient-years (absolute risk 61.9/1,000 patient-years).¹⁰

Haematological cancers

Haematological malignancies are also increased in patients with psoriasis. Using the General Practice Research Database²⁰ which includes 153,197 patients with psoriasis, the aRR (95%CI) for lymphoma and its subtypes for mild and severe disease were 1.34 (1.16-1.54) and 1.59 (0.88-2.89) respectively. In patients with severe psoriasis this was 3.18 (1.0-10.0) for Hodgkin lymphoma, and 10.75 (3.9-29.8) for cutaneous T-cell lymphoma. In a subsequent study using a different United Kingdom database, the aHR (95%CI) for incident lymphoma in mild psoriasis was 1.31 (1.15-1.49), and 1.89 (1.25-2.86) in severe disease.¹¹ Similar results have also been found in other cohort studies,²¹⁻²³ although there may have been some inadvertent misdiagnosis of T-cell lymphoma as psoriasis. Brauchli et al, in a nested case-control study,²⁴ documented an OR (95%CI) of 2.12 (1.45–3.10) for lymphohaematopoietic cancers, which was higher in patients who had not received oral anti-psoriasis treatment, or had a disease duration of greater than 2 years (aOR 1.31).²⁴ The risk of lymphoma is also elevated in children with psoriasis; a retrospective cohort study in biologic-naïve children with psoriasis found an SIR (95%CI) for lymphoma of 5.42 (1.62–12.94), compared to a matched population of children without psoriasis.¹⁴

However the absolute risk of haematological cancers attributable to psoriasis is low, with an estimated excess risk of 0.079/1,000 psoriasis patient-years.²⁰ The attributable risk for lymphoma has been calculated at 0.17/1000 person-years, meaning one extra lymphoma per 5,823 patients with psoriasis.²⁵

Skin cancer

Patients with psoriasis have a higher risk of non-melanoma skin cancer (keratinocytic carcinoma), in particular squamous cell carcinoma (SCC), but this is thought primarily due to previous treatment with photochemotherapy (PUVA) and possibly ciclosporin.²⁶ Based on two prospective cohorts, with close to 5 million person-years of follow-up, the RR (95%CI) of SCC was 1.51 (1.11-2.05). There was no association between psoriasis and the risk of basal cell carcinoma.²⁷ A cohort study showed the aHR (95%CI) for non-melanoma skin cancer increased from 1.09 (1.05-1.13) in mild psoriasis to 1.61 (1.42-1.84) for severe psoriasis.¹¹ This has been confirmed in a number of other studies.^{16,22,27-28} Despite the increased risk of non-melanoma skin cancer in patients with psoriasis, there is little evidence to show that such skin cancers are either more aggressive, or associated with an increase in mortality.

Interestingly the risk for melanoma in patients with psoriasis may be lower than in individuals without psoriasis; one Swedish cohort study reported an SIR (95%CI) of melanoma as 0.32 (0.10-0.74) compared to non-psoriasis controls.¹⁶ This is supported by a study comparing 72,739 psoriasis patients with 25,956 non-dermatological controls; the RR (95%CI) for melanoma was 0.40 (0.31-0.51).²⁹ There is no immediate explanation for this observation.

Key points:

- There is a slight increase in the relative risk of developing solid organ malignancies, which increases with the severity of psoriasis, but this predominantly reflects the co-risk factors of obesity, smoking and alcohol consumption.
- Patients with psoriasis have a moderate increase in the relative risk of developing haematological malignancies, in particular lymphoma, but the absolute risk remains very low.
- The risk of squamous cell carcinoma is increased in psoriasis, but melanoma risk may be lower.

Effect of immune-modulatory treatment

There is on-going speculation as to whether immune-modulatory treatment of psoriasis adds to any cancer burden.^{9,18,30} The difficulty arises with confounding of prescribing immune-modulatory therapies for patients with more severe disease, who consequently have more co-morbidities, which themselves increase the risk of cancer (e.g. obesity, smoking, alcohol, etc.).

The association between PUVA and a substantial increase in the risk of non-melanoma skin cancer, in particular SCC, is well established. A systematic review of 46 PUVA studies has identified that SCC can develop with relatively low UVA exposure, and the risk increases linearly with the number of treatments.³¹ The risk of non-melanoma skin cancer is higher in studies from the United States, compared to European studies; this may partly be explained by the more aggressive PUVA dosage protocols and lighter skin phototypes of the treated patients in the United States. Disturbingly, the increased risk of SCC persists after cessation of PUVA therapy.

An increased risk of basal cell carcinomas has been observed in patients receiving > 100 PUVA treatments. The data for PUVA triggered melanoma is less clear, with most European studies finding no association, but several studies in the United States indicating a 2-fold increase in both invasive and in-situ melanoma after > 200 PUVA treatments.³¹

Reassuringly, patients undergoing treatment with narrow band (nb)UVB, who had not had PUVA, do not appear to have a significant increase in skin cancers.^{28,32} However, there are few published long term follow-up studies of large cohorts who have received >200 treatments. Patients who have received both nbUVB and PUVA, have more basal cell carcinomas than the general population.²⁸

Whilst ciclosporin-induced skin cancers are well documented in the organ transplant literature, the association is less clear when ciclosporin is used in otherwise healthy individuals with psoriasis. A small nested cohort crossover study of 28 patients on ciclosporin, who were part of a large PUVA follow-up database,³³ estimated that ciclosporin increased the risk of squamous cell carcinoma 7-fold. They equated any use of ciclosporin as the equivalent of 200 PUVA treatments. A European study however found a lower risk; in 1,252 patients with psoriasis treated with ciclosporin, the SIR was 2.1 as compared to the general population, with the risk increasing with longer continuous use (>2 years), exposure to PUVA and/or other immune-modulatory agents.³⁴ A subsequent review of 60 studies, which included over 1,700 psoriasis patients treated with ciclosporin, found no skin cancers when ciclosporin had been used for less than 6 months continuously or less than 2 years if used intermittently.³⁵

With respect to solid organ malignancies, studies on methotrexate and ciclosporin in patients with psoriasis have found no consistent increased risk of non-cutaneous solid tumours.^{9,18,30,36} An Australian study has reported a 50% excess risk of malignancy among methotrexate-exposed patients with rheumatoid arthritis relative to the general population with an SIR (95%CI) of 1.5, (1.2-1.9), with a 3-fold increase in melanoma (3.0, 1.2-6.2), a 5-fold increase in non-Hodgkin's lymphoma (5.1, 2.2-10.0), and an almost 3-fold increase in lung cancer (2.9, 1.6-4.8).³⁷ The evidence for methotrexate and haematological malignancies is mixed. Earlier studies^{20,21,38} did suggest a slight relative increase in lymphoma in patients treated with methotrexate but, unlike studies in rheumatoid arthritis, subsequent studies have generally not found an association.^{9,18,30,39} Once again, confounding by severity and duration of disease needs to be taken into account.

Hydroxyurea is anecdotally associated with an increased risk of non-melanoma skin cancer when used for a variety of haematological indications (e.g. polycythaemia),⁴⁰ but it is difficult to tease out the effect of the underlying disease from any immune-modulatory effect of hydroxyurea.

There is no evidence of increased risk of solid cancers with acitretin. Acitretin is beneficial in the management of both non-melanoma skin cancer⁴¹⁻⁴² and cutaneous T-cell lymphoma,⁴³ so there are advantages in using acitretin, either as monotherapy, or in combination with biologics, phototherapy or traditional systemic therapies.

There does not appear to be an increased risk of malignancy from fumaric acid esters used to treat psoriasis⁴⁴ although there have been anecdotal reports of treatment emergent melanoma and non-melanoma skin cancer.⁴⁵

The evidence-base for a potential association between biologic treatments for psoriasis and subsequent development of solid cancers is immature, but so far largely reassuring.^{9,18,30} A systematic review of eight prospective cohort studies, mostly of anti-tumour necrosis factor- α (TNF α), found no evidence for increased risk of cancers (reported as all cancers, lymphoma, melanoma, prostate, colorectal and breast cancer), other than non-melanoma skin cancer.⁴⁶ There are important limitations to this review, as the length of follow-up of the various studies was relatively short, and rigorous inclusion/exclusion criteria were applied. However, the PSOLAR registry did find an increased risk of cancer.³⁸ Out of 12,090 patients, 252 malignancies (excluding non-melanoma skin cancer) were detected. The OR (95%CI) for any cancer (except non-melanoma skin cancer), for any patients who had received more than 12 months treatment with an anti-TNF- α agent, was 1.54 (1.10-2.15).³⁸

There does appear to be an increased risk of non-melanoma skin cancer in patients who have received prolonged treatment with anti-TNF- α agents. The aHR (95%CI) among individuals ever exposed to a biologic (mostly anti-TNF- α) was 1.42 (1.12-1.80), but it is difficult to correct for comorbidities, disease severity and duration of treatment.³⁰ Patients treated with anti-TNF- α will have had more severe disease with more prolonged or extensive exposure to non-biologic therapies, as compared with patients started more recently on newer biologics. TNF- α plays a vital role in immune-surveillance and has both anti-tumour (apoptosis induction, gene suppression) and pro-tumour (angiogenic, pro-inflammatory immunosuppressant) effects.

The cancer risk of the newer interleukin (IL)-12/23, IL-17, Janus kinase 1/3, and phosphodiesterase-4 inhibitors remains to be determined, but no specific flags have yet been raised.^{9,18,30}

Key points:

- PUVA (>200 treatments) and/or >6 months continuous ciclosporin significantly increase the risk of squamous cell carcinoma in patients with psoriasis.
- Immune-modulatory treatment has minimal, if any, significant additional effect on the risk of developing solid cancers in patients with psoriasis.
- Immune-modulatory treatment has minimal, if any, significant additional effect on the risk of developing lymphoma in patients with psoriasis.
- It is possible that early control of moderate/severe psoriasis with appropriate immune-modulatory therapies will significantly reduce the inflammatory burden, which may in turn reduce the relative cancer risk in patients with psoriasis.

Management of psoriasis in a patient with cancer

Little has been published on the need to stop, or alter, immune-modulatory treatment when a patient with psoriasis is diagnosed with a sporadic cancer. It was the opinion of the expert group that there is no specific requirement to stop psoriasis therapy, with the possible exception of ciclosporin. However, drug-drug (including radiotherapy) interactions must be considered, and any additional increase in infection risk should be taken into account.

There is currently no specific contraindication to starting any of the psoriasis immune-modulatory treatments for patients who have had cancer, who subsequently develop severe psoriasis, with the exception of ciclosporin. As acitretin may reduce the risk of cancer, it may be worthwhile considering co-prescribing acitretin when appropriate.

Key points:

- There is no specific need to stop immune-modulatory treatment of psoriasis after the diagnosis of sporadic cancer, with the possible exception of ciclosporin.
- Be conscious of the potential for drug interactions with any specific cancer therapy.

Screening programmes and chemoprevention.

There is no data to recommend any specific cancer screening programmes in patients with psoriasis. Although the relative risk for solid organ and haematological cancers is elevated in patients with psoriasis, the absolute risk remains low, particularly in the majority of patients who have mild/moderate disease. Other co-morbidities and risk factors including obesity, smoking and alcohol

consumption should be considered when assessing need for age-specific cancer screening programmes. The one exception is patients who have received >100 treatments of PUVA, particularly if they have also received ciclosporin; additional regular skin cancer surveillance is strongly recommended.

For a patient with psoriasis and significant sun exposure, but no previous skin cancers, clinicians should encourage year-round sun protection, regular skin checks, weight loss (if BMI>25), topical retinoid, and possibly oral nicotinamide. There is no specific data on chemoprevention of skin cancer in patients with psoriasis, but data can be extrapolated from high-risk organ transplant patients; this would recommend that nicotinamide and low-dose systemic retinoids be considered,⁴⁷⁻⁵⁰ particularly for patients who have received >200 treatments of PUVA, > 6 months continuous ciclosporin or > 1 year of an anti-TNF- α . There is also a theoretical role for vaccination against human papilloma virus, although studies on skin cancer prevention are lacking. In patients with psoriasis and active non-melanoma skin cancer, nicotinamide and standard dose systemic retinoids may be considered.

Conclusion

Whilst the relative risk of cancer is elevated in psoriasis it would be necessary to treat over 1,500 patients with psoriasis to see an extra non-melanoma skin cancer, and over 5,000 patients with psoriasis for an additional case of lymphoma.²⁵ PUVA, ciclosporin and possibly prolonged administration of anti-TNF- α do contribute to a slight increase in non-melanoma skin cancers. The evidence of immune-modulatory treatments contributing to an increased risk of solid organ malignancies is evolving, but seems reassuring.

Reduction in common risk factors such as obesity, smoking and alcohol consumption have a much greater effect on reducing cancer burden in patients with psoriasis, than the stopping or avoidance of a systemic immune-modulatory agent. It is possible that early control of moderate/severe psoriasis with appropriate immune-modulatory therapies may actually reduce the relative cancer risk in patients.

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