SKIN

IN-DEPTH REVIEW

Non-Steroidal Anti-Inflammatory Drugs in the Chemoprevention of Non-Melanoma Skin Cancer

Hanan Al-Lawati, PhD[1]

[1] Pharmacy Program, Department of Pharmaceutics, Oman College of Health Sciences, Muscat, Oman

ABSTRACT

Skin cancer, which includes melanoma and non-melanoma cancer types (basal cell and squamous cell carcinomas), is the most common type of neoplasia worldwide with massive calls for exploring chemoprevention strategies. Research suggests that chronic inflammation is a critical component of cancer progression in which over expression of COX-2 has been reported in many cancer studies. Non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit COX enzymes have been investigated for skin cancer chemoprevention both in vitro and in vivo. We have searched the association between NSAIDs and non-melanoma skin cancer in Pub-Med and Embase database in particular for animal, cell lines, and human studies. In animal and skin cancer cell line research studies, NSAIDs have been shown to have a chemoprotective role in non-melanoma skin cancer through various reported mechanisms. However, clinical data results with regards to non-melanoma cancer has been controversial due to the absence of large scale randomised clinical trials. To sustain the idea for NSAIDs role as chemo-preventative agents, further robust investigations with large trial number are required in order to consolidate epidemiological findings with the in vitro data results.

INTRODUCTION

Skin cancer which includes melanoma and non-melanoma (basal cell and squamous cell carcinomas) is the most common type of neoplasia in the world with more new skin cancer cases been seen each year than the new incidences of breast, prostate, lung, and colon cancers combined.[1,2] According to the Skin Cancer Foundation, 20% of Americans will develop this condition in their life time.[3] Skin cancer carries a huge health burden, which brings the need for exploring chemoprevention strategies as a mean of combating this type of cancer.

One approach of chemoprevention that has been explored for various cancers is controlling the associated inflammation. Chronic inflammation is a critical component of cancer progression, and there is epidemiological evidence that supports the theory that there is an extrinsic inflammatory pathway that promotes and in certain cases initiates cancer.[4] The prolonged exposure to inflammatory mediators including the metabolites of arachidonic acid, chemokines, cytokines, and free radicals leads to elevated cellular proliferation and mutagenesis, and the activation of oncogenes, which have the potential to cause cancer. On the other hand, cancer can also cause inflammation by promoting the over expression of the

cyclooxygenase (COX)-2 enzyme and pro-inflammatory mediators, which at later stages of tumor growth become controlled by the tumors themselves.[5] The over expression of COX-2 due to solid malignancies has been reported in many studies for colon, prostate, breast, pancreas, and other types of cancer, which suggests a role for COX-2 inhibitors in the treatment plan for cancer patients.[6]

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medication that have antipyretic, analgesic, and anti-inflammatory properties. NSAIDs exert their pharmacological effects through their inhibitory action on the COX enzymes (COX-1, COX-2), which are responsible for biosynthesis of both prostaglandin and prostanoids.[7] NSAID can be classified according to the degree of COX inhibition into non-selective NSAIDs such as aspirin, naproxen, or diclofenac, and selective COX-2 inhibitors like celecoxib, meloxicam, etc. Moreover, NSAIDs can be categorized from chemical perspective such as propionic acid derivatives, acetic acid derivatives, enolic acid derivatives and so on.[8]

The chronic use of most of these agents has been linked to increase in gastrointestinal (GI) and cardiovascular risks, which seem to be related to the extent of COX-2 selectivity of the different agents, as well as the doses used.[9] Nevertheless, given that their GI and cardiovascular toxicities are modest especially when compared to other chemotherapeutic agents, NSAIDs have been investigated for chemoprevention. In fact, various epidemiologic studies have provided evidence of protective effect for these agents in various cancers which include cancers of the breast, colon, esophageal, stomach, prostate and lung.[10-15] In this report, we provide a review of the role of these agents in the chemoprevention of non-melanoma skin cancers.

REVIEW

Non-Melanoma Skin Cancer

Non-melanoma skin cancers (NMSC) includes basal cell Carcinomas (BCCs) and squamous cell carcinomas (SCCs) both of which account for around 80% and 16% of all skin cancers, respectively.[16] Epidemiological data suggest solar UV radiation to be a major causative factor of both BCCs and SCC, and chronic sun exposure is considered to be the leading environmental risk factor for the development of NMSC.[17] In addition to its role in causing oxidative DNA damage and initiating p53 mutations, UV radiation is an inflammatory stimuli which leads to the cutaneous production of various inflammatory mediators including prostaglandins and other metabolites of arachidonic acid.[18]

NMSC Studies in Experimental Animal Models and Skin Cell Lines

There is growing evidence that there is an extrinsic inflammatory pathway, involving COX enzymes which promotes and in certain cases initiates NMSC. The association between COX-2 and carcinogenesis was investigated by Marks *et al*, who used a mouse skin model for multistage carcinogenesis and identified COX-2 as an endogenous tumor promoter and found its overexpression to be a risk factor for cancer development.[19] This association for the two types of NMSC was further studied by An *et al* who used immunohistochemical staining of COX-2 and observed an overexpression of COX-2 in human and murine actinic keratosis, SCC and BCC samples as well as during UVB irradiation of mice.[20] Similar overexpression of COX-2 with UV exposure

was observed by Buckman *et al*, who found an increase in COX-2 and prostaglandin PGE_2 expression in human keratinocytes after an in-vitro irradiation with UVB, with the COX-2 levels showing a sixfold increase.[21] Higashi *et al* found an enhanced expression of COX-2 as well as PGE_2 in two human skin cancer cell lines, a cutaneous SCC, HSC-5, and eccrine carcinoma, ErCa, compared to that in a non-cancerous immortalized human keratinocyte cell line, HaCaT.[22] PGE_2 inhibits apoptosis and therefore is thought to play a central role in tumorigenesis. They further experimented with a COX-2 antisense oligonucleotide and a selective COX-2 inhibitor and found two possible signal pathways that involve COX-2 in regulating cell transformation, one of which depends on PGE_2.

In addition to upregulating COX-2, UV exposure is also linked with the activation of the transcription activator protein-1 (AP-1), a transcription factor known to be constitutively activated in SCC and has a functional role in skin cancer promotion.[18] This was demonstrated for UVA by Silvers *et al* who found that irradiation of the immortalized keratinocyte cell line, HaCaT, with UVA resulted in an increase in AP-1 transactivation and the expression of c-Fos, which is found to be overexpressed in a variety of cancers.[23] Chen *et al* showed an increase in AP-1 in the same cell line during irradiation with UVB.[24] The inhibition of AP-1 medicated activity has been demonstrated to reduce carcinogenesis in mouse epidermal cells, making inhibition of AP-1 a target for therapy.

These findings warranted exploring the effect of NSAIDs, including their COX-2 inhibitory effect and their effect on AP-1, on the development of NMSC cancer. A study on the COX-2 related effect was considered by Pentland *et al*, who used an animal model to understand the effect of COX-2 inhibition on the reduction of NMSC induced by UV light in hairless mice.[25] Their results showed that COX-2 inhibition with celecoxib was effective in preventing new tumor formation. Fischer *et al* also showed a dose dependent decrease in UV-induced skin tumor yield with the use of celecoxib or indomethacin in SKH:HR-1-hrBr hairless mice. They observed a reduction in prostaglandin synthesis with both agents, but failed to observe any alteration in the COX-2 expression.[26] In another study, Orengo *et al* showed that, both a low dose of celecoxib (equivalent to 200 mg human dose) and a high dose (equivalent to 400 mg human dose) were effective in lengthening the tumor latency period and in reducing its multiplicity in SK-HR-1 female hairless mice.[27] Other NSAIDs have also shown similar promising results in animal models. Mikulec *et al* found that Sulindac at a dose of 25 and 150 ppm were effective in reducing UV-induced tumor multiplicity by 50% and 94%, respectively, in SKH-1 hairless mice. In the same study, Naproxen at 100 and 400 ppm caused a reduction of tumor multiplicity by 26% and 63%, respectively.[28]

NSAIDS were also shown to have a chemoprotective role in NMSC through their effect on AP-1. Ma *et al* demonstrated that aspirin inhibited AP-1 activity through the inhibition of the activation of JNK in JB6 cells.[29] This marked block of UV induced AP-1 in murine epidermis establishes a role for aspirin in the chemoprevention of NMSC.

Population-Based NMSC Studies

The role of NSAIDs in the chemoprevention of various cancers has been investigated and promising results have been found for certain type of cancers; however clinical data on the role of these agents with regards to non-melanoma cancers has been mixed. In the

absence of large scale randomised clinical trials which assess the risk of NMSC with NSAID use, evidence from other studies including population based case control or cohort studies have been examined.

The chemoprevention effects of celecoxib have been examined in a randomized clinical trial which included 240 actinic keratosis patients.[30] Celecoxib, at a daily dose of 400 mg for 9 months resulted in a reduction in the risk of developing NMSC (RR = 0.41, 95% CI 0.23-0.72) in this patient group, and in particular a reduction in the risk of developing BSC (RR = 0.40, 95% CI 0.18-0.93) and SCCs (RR = 0.42, 95% CI 0.19- 0.93). Thus, the study showed great potential for celecoxib in the chemoprevention of high risk individuals with extensive actinic damage. Similar risk reduction was observed with the long use of other NSAIDS in the prevention of recurrent NMSC.

A meta-analysis which included 8 case-control studies with 21,356 patients and 187,037 controls and 5 cohort studies with a population of 294,377 found aspirin at a range of doses (50-400 mg) to have a significant effect on skin cancer risk reduction; in particular, a continual use of low doses below 150 mg resulted in a reduced risk of non-melanoma skin cancers (OR, 0.97; CI, 0.95-0.99).[31] Another meta-analysis which examined 11 studies including a randomized controlled trial, 5 cohort studies, and 5 case control studies, found a reduction of about 10% among users of any NSAID (RR, 0.93 [95% CI, 0.86-1.02]).[32] The association, however was not significant for either of aspirin users or the non-aspirin NSAIDs users. Another meta-analysis of 8 studies also found NSAID use not to be significantly associated with a risk reduction of either SCC or BCC.[33]

A case control within a community based cohort of 1621 people in Australia which included 86 SCC patients and 187 matched controls found that patients of SCC were less likely to have used full dose of an NSAID at least twice per week for at least a year. Among the participants without SCC, the regular use of an NSAID of at least twice per week significantly lowered counts of AK compared to non-users (rate ratio of 0.52; 95% CI, 0.30-0.91).[34]

In a population based case control in the UK which examined 65,398 patients with BCC and 7,864 patients with SCC, the authors could not find a statistically significant relation between the use of NSAIDs and the risk off BCC.[35] This was also true for the subgroups which included users of aspirin or non-aspirin NSAIDs. The long use of Ibuprofen, on the other hand, was associated with a risk reduction of BCC (OR 0.85, 95% 0.77-0.94) which was more pronounced when limited to patients who used ibuprofen as the only NSAID (OR: 0.61, 95% CI: 0.48–0.78). The long term use of aspirin as the only NSAID was associated with a slight risk reduction of BCC, while that of selective cox-II inhibitors seems to have increased the risk of BCC (OR 2.52, 95% CI, 1.05–6.02).

CONCLUSION

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used to control pain and inflammation in various conditions and several NSAID agents are on the world health organization's list of essential medicine for several countries. Their activity in chronic inflammation, especially their role in the inhibition of the synthesis and activities of several key inflammatory mediators have posed them as candidates to research in the prevention and treatment of various cancers. As a matter of fact, NSAID use for

chemoprevention have been explored for various cancer types, and good promising results have been found. In particular, several in vitro studies and in vivo studies using experimental animal models have shown a chemoprotective role for these agents in NMSC through their role in the reduction of COX-2 activities and PGE_2 expression and their effect on AP-1. Furthermore, several population-based studies have revealed a role for these agents in the risk reduction of NMSC when taken at the approved range of doses. Further large scale randomised clinical trials are needed to further explore this role.

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:
Hanan Al-Lawati
Oman College of Health Sciences, P.O. Box 393, Postal Code 113, Muscat, Oman
Email: allawati@ualberta.ca

References:

1. H. W. Rogers, W. M. A, F. S. R and C. B. M, "Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the US population, 2012," JAMA Dermatol, vol. 151, no. 1, pp. 1081-1086, 2015.
2. R. L. Siegel, K. D. Miller and A. Jemal, "Cancer statistics, 2016," CA: A cancer journal for clinicians., 2015.
3. J. K. Robinson, "Sun exposure, sun protection, and vitamin D," JAMA, vol. 294, pp. 1541-43., 2005.
4. L. M. Coussens and Z. Werb, "Inflammation and cancer," Nature, vol. 420, no. 6917, pp. 860-867, 2002.
5. E. Shacter and S. A. Weitzman, "Chronic inflammation and cancer," Oncology, vol. 16, no. 2, pp. 217-232, 2002.
6. Rakoff-Nahoum, "Why cancer and inflammation," Yale Journal of Biology and Medicine, vol. 79, pp. 123-130, 2006.
7. B. Kay and P. Paola, "New Insights into the use of Currently Available Non-steroidal Anti-inflammatory Drugs," J Pain Res, vol. 8, pp. 105-118, 2015.
8. L. J. Crofford, "Use of NSAIDs in treating patients with arthritis," Arthritis Research & Therapy, vol. 15 Suppl 352, 2013.
9. S. Harirforoosh, W. Asghar and F. Jamali, "Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications," Journal of Pharmacy & Pharmaceutical Sciences, vol. 16, no. 5, pp. 821-847, 2014.
10. M. J. Thun, M. M. Namboodiri and H. C. W. Jr, "Aspirin use and reduced risk of fatal colon cancer," N Engl J Med, vol. 325, p. 1593–6, 1991.
11. E. Giovannucci, E. B. Rimm, M. J. Stampfer, G. A. Colditz, A. Ascherio and W. C. Willett, "Aspirin use and the risk for colorectal cancer and adenoma in male health professionals," Ann Intern Med, vol. 121, p. 241–6., 1994.
12. M. J. Thun, M. M. Namboodiri, E. E. Calle, W. D. Flanders and &. H. C. W, " Thun MJ, Namboodiri MM, Calle EE, Flanders WD, et al. Aspirin use and risk of fatal cancer," Cancer Res, vol. 53, p. 1322–7, 1993.
13. S. A. Khuder and A. B. Mutgi, "Breast cancer and NSAID use: a metaanalysis," Br J Cancer, vol. 84, p. 1188–92.
14. A. E. Norrish, R. T. Jackson and M. C. U, "Non-steroidal anti-inflammatory drugs and prostate cancer progression," Int J Cancer, vol. 77, pp. 511-5, 1998.
15. J. E. Muscat, S. Q. Chen, J. P. Richie, N. K. Altorki, M. Citron, S. Olson, A. I. Neugut and S. D. Stellman, "Risk of lung carcinoma among users of of nonsteroidal antiinflammatory drugs," Cancer, vol. 97, p. 1732–6., 2003.
16. A. C. Halpern and L. J. Hanson, "Awareness of, knowledge of and attitudes to nonmelanoma skin cancer (NMSC) and actinic keratosis (AK) among physicians," International journal of dermatology, vol. 43, no. 9, pp. 638-642., 2004.
17. J. e. Reichrath, Sunlight, vitamin D and skin cancer., New York, NY, USA: Springer, 2014.
18. J. K. Kundu and Y. J. Surh, "Inflammation: gearing the journey to cancer," Mutation Research/Reviews in Mutation Research, vol. 659, no. 1, pp. 15-30, 2008.
19. F. Marks, G. Furstenberger, G. Neufang and K. Muller-Decker, "Mouse skin as a model for cancer chemoprevention by nonsteroidal anti-inflammatory drugs," Recent Results Cancer Res, vol. 163, pp. 46-57, 2003.
20. K. P. An, M. Athar, X. Tang, K. S. K. J. Russo, J. Beech, M. Aszterbaum, L.

Kopelovich, E. H. Epstein, H. Mukhtar and D. R. Bickers, "An KP, Athar M, Tang X, Katiyar SK, et al. Cyclooxygenase-2 expression in murine and human nonmelanoma skin cancers: implications for therapeutic approaches," Photochem Photobiol, vol. 76, p. 73–80, 2002.

21. S. Y. Buckman, A. Gresham, P. Hale, G. Hruza, J. Anast, J. Masferrer and A. P. Pentland, "COX-2 expression is induced by UVB exposure in human skin: implications for the development of skin cancer," Carcinogenesis, vol. 19, no. 5, pp. 723-729, 1998.
22. Y. Higashi, T. Kanekura and T. Kanzaki, "Enhanced expression of cyclooxygenase (COX) ‐ 2 in human skin epidermal cancer cells: Evidence for growth suppression by inhibiting COX ‐ 2 expression," International Journal of Cancer, vol. 86, no. 5, pp. 667-671, 2000.
23. A. L. Silvers and G. T. Bowden, "UVA irradiation-induced activation of activator protein-1 is correlated with induced expression of AP-1 family members in the human keratinocyte cell line HaCaT," Photochem Photobiol, vol. 75, pp. 302-310, 2002.
24. C. W and G. T. Bowden, "Role of p38 mitogen ‐ activated protein kinases in ultraviolet ‐ B irradiation‐induced activator protein 1 activation in human keratinocytes," Molecular carcinogenesis, vol. 28, no. 4, pp. 196-202, 2000 .
25. A. P. Pentland, J. W. Schoggins, G. A. Scott, K. K. N. and R. Han, "Reduction of UV-induced skin tumors in hairless mice by selective COX-2 inhibition," Carcinogenesis, vol. 20, pp. 1939-44, 1999.
26. S. M. Fischer, H. H. Lo, Gordon, G. B, K. Seibert, G. Kelloff, R. A. Lubet and C. J. Conti, "Chemopreventive activity of celecoxib, a specific cyclooxygenase ‐ 2 inhibitor, and indomethacin against ultraviolet light‐induced skin carcinogenesis.," Molecular carcinogenesis, vol. 25, no. 4, pp. 231-240, 1999.
27. I. F. Orengo, J. Gerguis, R. Phillips, A. Guevara, A. T. Lewis and H. S. Black, "Celecoxib, a cyclooxygenase 2 inhibitor as a potential chemopreventive to UV-induced skin cancer: a study in the hairless mouse model," Archives of dermatology, vol. 138, no. 6, pp. 751-755, 2002.
28. C. D. Mikulec, J. E. Rundhaug, M. S. Simper, R. A. Lubet and S. M. Fischer, "The chemopreventive efficacies of nonsteroidal anti-inflammatory drugs: the relationship of short-term biomarkers to long-term skin tumor outcome," Cancer Prevention Research, vol. 6, no. 7, pp. 675-685, 2013.
29. W. Y. Ma, C. Huang and Z. Dong, "Inhibition of ultraviolet C irradiation-induced AP-1 activity by aspirin is through inhibition of JNKs but not erks or P38 MAP kinase," International journal of oncology, vol. 12, no. 3, pp. 565-573., 1998.
30. C. A. Elmets, J. L. Viner, A. P. Pentland, W. Cantrell, H. Y. Lin, H. Bailey, S. Kang, K. G. Linden, M. Heffernan, M. Duvic and E. Richmond, "Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial," J Natl Cancer Inst, vol. 102, pp. 1835-1844, 2010.
31. Y. Zhu, Y. Cheng, R. C. Luo and A. M. Li, "Aspirin for the primary prevention of skin cancer: A meta-analysis," Oncology letters, vol. 9, no. 3, pp. 1073-1080, 2015.
32. C. Muranushi, C. M. Olsen, A. C. Green and N. Pandeya, "Can oral nonsteroidal antiinflammatory drugs play a role in the prevention of basal cell carcinoma? A systematic review and metaanalysis," Journal of the American Academy of Dermatology, vol. 74, no. 1, pp. 108-119, 2016.
33. B. Zhang, X. Liang, L. Ye and Y. Wang, "No chemopreventive effect of nonsteroidal anti-inflammatory drugs on nonmelanoma skin cancer: Evidence from meta-analysis," PloS one, vol. 9, no. 5, p. e96887, 2014.
34. G. Butler, R. Neale, A. C. Green, N. Pandeya and D. C. Whiteman, "Nonsteroidal anti-inflammatory drugs and the risk of actinic keratoses and squamous cell cancers of the skin," Journal of the American Academy of Dermatology, vol. 53, no. 6, pp. 966-972, 2005.
35. D. Reinau, C. Surber, S. S. Jick and C. R. Meier, "Nonsteroidal anti ‐ inflammatory drugs and the risk of nonmelanoma skin cancer," International Journal of Cancer, vol. 137, no. 1, pp. 144-153, 2015.