

INDOMETHACIN IN BASAL CELL CARCINOMA

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Norri S. Al-Waili (House 34, Street 42, Section 729, Al-Mashtel, New Baghdad, Baghdad, Iraq.)

It has been suggested that prostaglandins (PGs) might be responsible for haematological disorders and impaired immunity in burns, surgical trauma, chronic infections and malignancies¹⁻⁴. Malignant cells produce excessive amounts of PGs⁵⁻⁷ - which are suppressive of T and B lymphocyte functions^{8,9}. PGs inhibit macrophage cytotoxicity¹⁰ which are considered primary antineoplastic surveillance cells¹¹. PGs cause marked suppression of antibody production against T-dependent and T-independent antigens, modulation of serum albumin and globulin and lowering of granulocytic precursor cells^{1,3,12}. Hence, for immunotherapy of cancer, it has been proposed that PGs synthesis inhibitors (PGSI) might have a place in the management of tumours by enhancing immune response to hamper the growth or even destroy the cancer cells^{1,2,13}. Accordingly indomethacin, a potent PGSI, was used successfully in the treatment of chorionic carcinoma¹³. The effect of indomethacin on basal cell carcinoma is presented.

CASE REPORT

A 55 year old lady presented with a skin lesion above the upper lip. The lesion had started ten years ago as a small nodule with itching, which increased gradually between nose and upper lip to become 3 x 4 cm in diameter. It became indurated with erosion, crusting and with a small ulcer. Occasional bleeding occurred with itching. The lesion was removed surgically five years ago and recurred in following years. Biopsy confirmed the diagnosis of basal cell carcinoma. Laboratory investigations revealed a haemoglobin of 11 g/dl, white blood cells 10000/cm with 72% neutrophils, 26% lymphocytes and 2% eosinophils, ESR 30 mm/hr, serum iron 65 mg% and serum iron binding capacity 410%. Biochemical tests were normal. The patient was given an appointment for plastic surgical removal. Meanwhile, she was treated with indomethacin after informed consent. An indomethacin suppository was used (100 mg/day) since the patient had a history of gastritis. She was advised to attend the clinic weekly for follow-up and to report any side effects. Within one month of the treatment, the lesion had decreased in size and no more bleeding or crusting was encountered. At three months, the lesion had regressed and completely disappeared and the treatment was withdrawn. Laboratory investigations showed a haemoglobin 12 g/dl, white cell count 8,900/cm with 54% neutrophils and 41% lymphocytes, ESR 15 mm/hr, serum iron 110 mg% and serum iron binding capacity 420 mg%. No side effects were reported apart from mild headache and epigastric pain which did not cause withdrawal from the study. No recurrence was noted and one year follow-up was uneventful.

DISCUSSION

PGs affect tumour growth and metastasis in a manner not fully understood. However, PGs increase cell division and DNA, RNA, protein and collagen synthesis^{14,15}. Therefore, in humans, PGSI alone or in combination with steroids was found to have some effects in the management of xeroderma pigmentosum tumours and psoriasis in which there is increased cell division and DNA synthesis^{16,17}. Moreover, PGSI could reduce tumour growth, prolong survival and enhance tumour response to radiotherapy and chemotherapy¹⁸⁻²¹. However, controversy still exists concerning the actual role of indomethacin on cell division and tumours. It has been found that indomethacin stimulated cell division and replication^{22,23} and inhibited tumour growth in vivo, whereas it stimulated tumour replication in

vitro²⁴. On the other hand, oral indomethacin caused inhibition of murine mammary tumours²⁵. Higher levels of indomethacin inhibit proliferation of Rajilymphoid cells²⁶ and Walker carcinoma²⁷.

Therefore, the mode of action of indomethacin on basal cell carcinoma could be ascribed to:

1. Indomethacin might reverse tumour-induced immunosuppression by neutralization of the excessive amount of PGs produced by cancer cells as has been suggested in the case of chorionic carcinoma treated by indomethacin.

2. Indomethacin might reduce cell division and DNA, RNA and protein synthesis.

Basal cell carcinoma is the commonest malignant tumour of the skin in the white race. It is more frequent and aggressive in patients who are immunosuppressed. The treatment consists of radiotherapy, surgery and chemotherapy. More interestingly, basal cell carcinoma can be destroyed by induction of a specific immunological response in the site of the lesions. This is performed by contact sensitization to a hapten such as DNCB with a challenge dose²⁸. The approach used in the case described was to enhance host immunity to hamper or even kill cancer cells. This was probably obtained with the use of PGSI, indomethacin. The patient showed good response to indomethacin therapy by:

1. Regression of tumour was achieved within three months.

2. No recurrence of the lesion was noticed during one year post-treatment.

3. There was obvious elevations of haemoglobin, serum iron and blood lymphocytes.

Therefore, indomethacin alone or in combination with other treatment including radiotherapy or chemotherapy might have a place in the management of basal cell carcinoma. Other controlled and extensive studies should be conducted in special centres to identify the real clinical value of this preliminary observation.

REFERENCES

1. Al-Waili, N., Al-Azzawi, H. The effects of prostaglandin E2 on serum iron following acute and chronic blood loss. *Clin. Exp. Pharma. Physiol.*, 1985; 12:443-446.
2. Al-Waili, N., Al-Azzawi, H., and Al-Niami, M. Bone marrow cellular elements and peripheral blood indices following acute haemorrhage and prostaglandin E2 treatment. *Saudi Med.* 3., 1983; 4:236.
3. Al-Waili, N., Thewani, A., and Al-Azzawi, H. The effect of PGA, on antibodyproduction. *The World Conference on Clinical Pharmacology and Therapeutics*, London, Macmillan, 1980; p. 0246.
4. Al-Waili, N., Thewani, A., and Al-Azzawi, H. The effect of prostaglandin on antibodyproduction during primary and secondary immune responses. *3. Facul. Med. (Baghdad)*, 1980 22:330.
5. Bennett, A., Berstock, D.A., Raja, B., and Stamford, I. Survival time after surgery is inversely related to the amount of prostaglandins extracted from human breast cancer. *Br. J. Pharmacol.*, 1979; 66:451.
6. Bennett, A., Charlier, E., MacDonald, A., Stamford, L Bone destruction by breast cancer. *Prostaglandin*, 1976;11:261.
7. Karim, S., and Rao, B. Prostaglandins and turnouts. *Prostaglandin, physiological, pharmacological and pathological aspects*. Edited by Karim, S. Lancaster, MTP Press, 1976; p.106.
8. Baray, M. Prostaglandins; fine tuning the immune system *Immun. Today*, 1980; 1:65.
9. Goodwin, J.S., and Webb, D. Regulation of the immune response by prostaglandins. *Gin. Immunol. Immunopathol.*, 1980; 15:106.
10. Taffet, S.M. and Russell, S. Macrophages-mediated tumour cell killing; regulation of expression of cytolytic activity by prostaglandin. *E.J. Immunol.*, 1981.,126:424.
11. Hibbs, J., Chapman, H., and Weinberg, J. The macrophage as an antineoplastic surveillance cell; biological perspectives. *J. Reticul. Society*, 1978; 24:549.
12. Al-Azzawi, H., Al-Waili, N., Al-Sammarrai, H., and Thewani, A. The effects of prostaglandin A1

- on serum protein components during primary and secondary immune response. J. Fac. Med(Baghdad), 1981; 23:233.
13. Al-Waili, N., Al-Azzawi, H., Al-Rawi, Z. Treatment of advanced chorionic carcinoma by indomethacin and steroids. Saud Med. J., 1984; 5:81.
 14. Kischer, C. The epidermal response of developing skin to PGBi, mitochondrial alterations obtained in vitro. Exp. Cell Res., 1973; 81:393.
 15. Lupulescu, A. Cytolytic and metabolic effects of prostaglandins on the skin of the rat. J. Invest. Dermatol., 1977; 68:136.
 16. Al-Saleem, T., Ali, Z.S., Qassab, M. Skin cancers in xeroderma pigmentosum; response to indomethacin and steroids. Lancet, 1980; 2:264.
 17. Al-Waili, J. Two cases of psoriasis and high dose of indometacin. Amer. Med. J., 1987; 5:150.
 18. Strausser, H.R., and Humes, 3. Prostaglandin synthesis inhibition effect on bone changes and sarcoma tumour induction in BALBC mice. Int. 3. Cancer, 1975; 15:724.
 19. Bennett, A., Houghton, J., Leaper, DJ. and Stamford, I.F., Tumour growth and response to treatment beneficial effect of the prostaglandin synthesis inhibitor Ourbiprofen. Br. 3. Pharmacol., 1978; 63:356.
 20. Berstock, V.A., Houhton, J., Bennett, A. Improved anticancer effect by combining cytotoxic drugs with an inhibitor of prostaglandin synthesis. Cancer Treat. Rev., 1979; 6(suppl):69.
 21. Bennett, A., Berstock, D.A., and Carroll, M. Enhanced anti-cancer effect by combining cytotoxic drugs with an inhibitor of prostaglandin synthesis inhibitor flubiprofen. Br. 3. Pharmacol., 1981; 75:208.
 22. Thomas, D., Philpott, O., and Jaffe, B. The relationship between concentrations of prostaglandin E and rates of cell replication. Exp. Cell Res., 1974; 84:40.
 23. Hammarstroms, J. Prostaglandins production in cell culture. Eur. 3. Biochem., 1977; 27:7.
 24. Fulton, A.M. Effects of indomethacin on the growth of cultured mammary tumours. Int. 3. Cancer, 1984; 33:375.
 25. Fulton, A., and Heppner, G.H. Murine mammary tumour growth inhibition with indomethacin. Proc. Am. Assoc. Cancer Res., 1983; 24:21.
 26. Karmali, R., Horrobin, P., Menezs, 3., and Patel, P. The relationship between concentrations of PGA1, E1, E2, F2 and rate of cell proliferation. Pharmacol. Res. Commun., 1979; 11:69.
 27. Tisdale, M., Gibbs, J., Dobrzanski, F. Effect of chloambucil and indomethacin on growth and prostaglandin level in sensitive and resistant Walker carcinoma. Chem. Biol. Interact., 1982; 39:221.
 28. Sanderson, K., and Mackie, R. Tumours of skin, In, Root, A., Wilkinson, D., Ebling, F., in textbook of dermatology, Edited by Arthur Rook et al. 4th ed. Oxford Blackwell, 1984, p.2129.