

Cytotoxic Drugs and Wound Repair

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Do cytotoxic agents effect wound healing adversely, is an issue yet to be completely evaluated. As these drugs selectively suppress cell proliferation, they are likely to interfere with the healing of wound. A number of clinical and experimental studies have been performed with somewhat contradictory results.

Wound healing takes place in three phases. The first is the inflammatory or substrate stage, characterised by increase in vascular permeability of the injured area, followed by fibrin deposition and influx of neutrophils and monocytes. The second phase is composed of fibroblast proliferation and subsequent collagen and mucopolysaccharide production leading to neovascularization of the injured area due to which nutrients are provided to this region of high metabolic turnover (Im and Hoopes, 1970). This phase begins 3 days after injury and lasts for 2 weeks. The third or the final phase is the maturation phase in the third week and lasts for months. It is marked by increased collagen synthesis and degradation of old collagen, thus giving strength to the wound. The various groups of neoplastic agents can interfere with any of the stages of wound healing. Neutropenia, inhibition of early vasodilatation, fibroblast proliferation and induction of protein malnutrition are well established actions of antitumour drugs. (Desprez and Kiehn, 1960; Karpinnen and Myllarniemi, 1970; Myllarniemi and Peltokalilo, 1974). These factors have an important effect on wound healing.

The first group of the antineoplastic agents are the alkylating agents. These include nitrogen mustard, carmustine and cyclophosphamide (Chabner et al., 1975; Devita, 1980). They act by cross linking deoxyribonucleic acid strands and thus prevent cell division. Nitrogen mustard, the original of the alkylating group, is still used systemically for treating lymphomas. Animal experiments showed that the drug produced a marked reduction in granulation, tissue formation and wound collagen content when given three days after wounding (Newcombe, 1966). Clinical studies with nitrogen mustard used in the operative and post-operative periods in cases of carcinoma of the breast, colon and rectum also gave increased wound complications as infection and dehiscence (Morales et al., 1957; Mrazek et al., 1959).

Cyclophosphamide, another member of the alkylating group, acts by inhibiting deoxyribonucleic acid synthesis and also provides immunosuppression. It is largely used as a therapy for leukaemia, multiple myeloma and carcinoma of the breast, ovary and lungs. Animal experiments proved a decrease in the wound strength when the drug was administered from the third post-operative day for four days. Along with this a decreased exudate and granulation tissue and a slower rate of wound contraction was also noted (Desprez and Kiehn, 1960). Neovascularization is another process suppressed by cyclophosphamide. A single post-operative dose in rats delayed vasodilatation by twentyfour hours, whereas fibroblast proliferation was further prolonged by another twenty-four hours (Karpinnen and Myllarniemi, 1970; Myllarniemi and Peltokallio, 1974). A limited number of clinical studies carried out on patients with carcinoma of the breast, when the drug was given either a day before or from the day of operation for a week, revealed no difference in wound healing or development of complications, as compared to a control group (Finney, 1971; Nissen-Meyer et al., 1971). Carmustine, a nitro soourea, inhibits deoxyribonucleic acid and protein synthesis and is used for treating lymphomas. Animal experiments proved it to reduce wound breaking strength tested upto three weeks postoperatively (Cohen et al., 1975).

The second group of antineoplastic drugs are the antibiotics as doxorubicin hydrochloride, bleomycin, mitomycin-C and dactinomycin (Chabner et al., 1975; Devita 1980). They act by inhibiting cell division during the proliferative phase of repair. This leads to decreased fibroblast proliferation and the

wound breaking strength is thus diminished.

Dactinomycin prevents the synthesis of ribonucleic acid. A single dose given to mice post-operatively reduced wound breaking strength for a week (Cohen et al., 1975). Mitomycin-C interferes with mitosis by crosslinking deoxyribonucleic acid. Animal studies showed no effect on tensile strength, histologic features or hydroxyproline content of the intestinal anastomoses eight days post-operatively (Wiznitzer et al., 1973). Bleomycin inhibits deoxyribonucleic acid synthesis and causes its strand scission. It also has shown to decrease wound breaking strength at seven days post-operatively in mice. Doxorubicin hydrochloride, an anthracycline antibiotic again inhibits deoxyribonucleic acid and ribonucleic acid synthesis. Pre-operative or pen-operative therapy in rats lead to a decreased wound breaking strength on the fourteenth and twentyfirst post-operative day. Treatment started one week after operation had no detrimental effects (Devereux et al., 1980).

The third group of the anti-tumour drugs are the vinca alkaloids which comprise of vincristine and vinblastine. They cause mitotic arrest by binding with intracellular microtubular systems and have known to cause a reduction in wound breaking strength in mice three days post-operatively (Cohen et al., 1975).

The fourth group of cytotoxic agents are the antimetabolites, which include 5-Fluorouracil and methotrexate. These interfere with the normal metabolic pathway in the deoxyribonucleic acid synthesis phase of the cell. They inhibit the proliferative phase of wound healing as they disrupt the kinetics of protein synthesis. Methotrexate, a folic acid antagonist, is used in treating leukaemias, head and neck tumours and carcinoma of the breast and testicle. Breaking strength of wounds has again found to be reduced in rats when administered five days after wounding (Calnan and Davies, 1965). 5-Fluorouracil, a pyrimidine analogue antimetabolite is used in carcinoma of the gastrointestinal tract and breast. A few clinical studies with this drug gave conflicting results. When administered one week after operation in the treatment of carcinoma of the breast, it increased wound complications (Cohn et al., 1968). When it was given two weeks after surgery in colon carcinoma, no deleterious effects were seen on the wound (Higgins et al., 1971). Also perioperative and post operative parenteral doses of 5-Fluorouracil in these cases showed no wound or anastomotic complications (Rousselot et al., 1967). Another group of drugs used in anticancer therapy are the hormones. Steroids are widely used in treating leukaemias, lymphomas, carcinoma of the breast and multiple myeloma; gonadal hormones are given in cases of breast carcinoma and endometrial and renal cell carcinoma. Adrenal steroids are also administered to reduce oedema of the brain and spinal cord especially during radiation therapy. As has been well established, all steroids delay wound healing (Hunt and Van Winkle, 1976), by prolonging the substrate phase of repair. Methylprednisolone and Dexamethasone have been studied in animals showing a delay in the maturation phase by the former, (Lence et al., 1975), and practically no adverse effect by the latter (Mc Namara et al., 1969). Progesterones which are also immunosuppressives were found to have similar effect on wound healing as methylprednisolone (Lence et al., 1975). The other gonadal steroids have not been evaluated extensively.

The local reaction at the site of injection of these antineoplastic drugs, is tissue necrosis, produced especially by those agents which are vesicants. The drugs most known for this effect are the anthracyclines, particularly doxorubicin hydrochloride (Bowers and Lynch, 1978; Reilly et al., 1977), and to a lesser extent mitomycin-C, dactinomycin and mithramycin. The clinical signs appear one week after extravasation and the mechanism of damage is vascular obliteration and collagen necrobiosis. The course of the injury extends from one to four months. There is continued tissue destruction due to depression of mitosis which inhibits local repair and release of offending agents from the dying cells, which gets bound to the surrounding viable cells (Chait and Dinner, 1975). The vinca alkaloids do not produce such severe local reactions, and those occurring are short lived. The cause of these regional effects is probably the antimitotic properties of the drugs (Ignoffo and Friedman, 1980). The alkylating agents produce local effects occasionally which are usually of a milder nature. These are probably due to the diluent used in the drug. They appear rapidly and last for a short period (Harris and Thomas,

1961; Ignoffo and Friedman, 1980).

Animal experiments prove that antineoplastic agents delay wound healing. Clinical studies, which are still limited, were performed in different conditions. Some authors also believe that the presence of a malignant tumour in the body causes delay in wound healing (Finn et al., 1980) and the concomitant use of antitumour drugs would further aggravate the wound complications. Other studies failed to show any adverse effects on wound repair (Finney, 1971; Higgins et al., 1971; Karrar 1972; Morales et al., 1957; Mrazek et al., 1959; Nissen-Meyer et al., 1971; Rousselot et al., 1967). As delay in postoperative chemotherapy does not have any unfavourable results on tumour recurrence, it would be advisable to delay the initiation of cytotoxic drugs, after major surgery, until the first two phases of wound healing are complete.

References

1. Bowers, D.G. Jr. and Lynch, J.B. (1978) Adriamycin extravasation. *J. Plast. Reconsti. Surg.*, 61:86.
2. Calnan, J. and Davies, A. (1965) The effect of methotrexate (amethopterin) on wound healing; an experimental study. *Br. J. Cancer*, 19:505.
3. Chabner, B.A., Myers, C.E., Coleman, C.N. and Johns, D.G. (1975) The clinical pharmacology of antineoplastic agents. *N.Engl.J.Med.*, 292:1107.
4. Cohen, S.C., Gabelnick, H.L., Johnson, R.K. and Goldin, A. (1975) Effects of antineoplastic agents on wound healing in mice. *Surgery*, 78:238.
5. Cohn, IJr., Slack, N.H. and Fisher, B. (1968) Complications and toxic manifestations of surgical adjuvant chemotherapy for breast cancer. *Surg. Gynecol. Obstet.*, 127:1201.
6. Desprez, J.D. and Kiehn, C.L. (1960) The effects of cytoxan (cyclophosphamide) on wound healing. *Plant. Reconstr. Surg.*, 26:301.
7. Devereux, D.F., Kent, H. and Brennan, M.F. (1980) Time dependent effects of adriamycin and X-ray therapy on wound healing in the rat. *Cancer*, 45:2805.
8. Devita, V.T. Jr. Principles of cancer therapy, in Harrison's principles of internal medicine. 9th.ed Edited by K.J. Isselbacher, R.J., Adams, Braunwald, E. and others. 9th ed. New York, McGraw-Hill, 1980, p. 1597.
9. Finn, D., Steels, GJr., Osteen, R.T. and Wilson, R.E. (1980), Morbidity and mortality after surgery in patients with disseminated or locally advanced cancer receiving systemic chemotherapy. *J. Surg. Oncol.*, 13:237.
10. Finney, R. (1971) Adjuvant chemotherapy in the radical treatment of carcinoma of breast; a clinical trial. *Am.J. Roentgenol. Rad. Ther. Nuc. Med.*, 111:137.
11. Harris, F.L., and Thomas, C.G. Jr. (1961) The effects of topical nitrogen mustard on wound healing. *Surg. Gynecol. Obstet.*, 112:684.
12. Higgins, G.A., Dwight, R.W., Smith, J.V. and Keehn, R.J. (1971) Fluorouracil; as an adjuvant to surgery in carcinoma of the colon. *Arch. Surg.*, 102:339.
13. Hunt, T.K. and Van Winkle, WJr. Wound healing; disorders of repair. *Chirurgecom*, 1976.
14. Ignoffo, R.J., and Friedman, M.A. (1980) Therapy of Local toxicities caused by extravasation of cancer chemotherapeutic drugs. *Cancer Treat. Rev.*, 7:17.
15. Im, M.J. and Hoopes, J.E. (1970) Metabolism in healing skin wounds. *J. Surg. Res.*, 10:459.
16. Karpinnen, V., and Myllarniemi, H. (1970) Vascular reactions in the healing laparotomy wound under cytotoxic treatment. *Acta. Chir. Scand.*, 136:675.
17. Karrar, K. (1972) Importance of dosage schedules in adjuvant chemotherapy. *Cancer Chemother. Rep.*, 56:35.
18. Lenco, W., Mcknight, M. and MacDonald, A.S. (1975) Effects of cortisone acetate, methylprednisolone and medroxyprogesterone on wound contracture and epithelialization in rabbits.

Ann. Surg., 181:67.

19. McNamara, J.J., Laznborn, P.J., Mills, D. and Abby., G.V. (1969) Effect of short-term pharmacological doses of adrenocorticosteroid therapy on wound healing. Ann. Surg., 170:199.
20. Morales, F., Bell, M., McDonald, G.O. and Cole, W.H. (1957) The prophylactic treatment of cancer at the time of operation. Ann. Surg., 146:588.
21. Mrazek, R., Economou, S., McDonald, G.O., Slaughter, D.P. and Cole, W.H. (1959) Prophylactic and adjuvant use of nitrogen mustard in the surgical treatment of cancer. Ann. Surg., 150:745.
22. Myliarniemi, H. and Peltokallio, P. (1974) The effect of high dose cyclophosphamide therapy in the abdominal cavity of the rat; adhesions and their vascular pattern. Ann. Chir. Gynaecol. Fenn., 63:238.
23. Newcombe, J.F. (1966) Effect of intra-arterial nitrogen mustard infusion on wound healing in rabbits; formation of granulation tissue and wound contraction. Ann. Surg., 163:319.
24. Nissen-Meyer, R., Kjellgren, K. and Mansson, B. (1971) Preliminary report from the Scandinavian adjuvant chemotherapy study group. Cancer Chemother. Rep., 55 :561.
25. Reilly, J.J., Neifeld, J.P. and Rosenberg, S.A. (1977) Clinical course and management of accidental adrlaznycin extravasation. Cancer, 40:205 3.
26. Rousselot, L.M., Cole, D.R., Grossi, C.E. and others. (1967) Intraluminal chemotherapy (HN2 or 5-FU) adjuvant to operation for cancer of the colon and rectum. II. Follow-up report of 97 cases. Cancer, 20:829.
27. Wiznitzer, T., Orda, R., Bawnik, J.B. and others. (1973) Mitomycin and the healing of intestinal anastomosis. Arch. Surg., 106 :314.