Radiol Oncol 2002; 36(1): 33-40.

Modulation of radiotherapy- and chemotherapy-induced normal tissue response as prophylaxis of their side effects

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Background. *Ionising radiation and cytostatic agents used in cancer therapy induce an immune response in normal tissues mediated by cytokines and adhesion molecules. Strategies modulating this response may downregulate cancer therapy side effects. The data published on the given topic have been reviewed.*
Conclusions. *The strategies influencing the tissue immune response with the aim to reduce the side effects of chemotherapy and radiotherapy are conflicting. Some of them inhibit this response supposing that an exaggerated reaction may have a damaging effect (e.g. corticosteroids, nonsteroidal anti-inflammatory drugs (NSAID), lisofylline, anti-cytokine antibodies, anti-sense oligonucleotides, sialyl Lewis X analogues), others promote this reaction by inducing endogenous production of cytokines (AS101) or use recombinant forms of appropriate cytokines involved in this response in order to intensify the physiologic tissue response. In clinical practice, corticosteroids and NSAID are widely used to modulate this response, while other agents are still experimental.*

Key words: radiotherapy – adverse effects; antineoplastic agents; antineoplastic agents – adverse effects; adjuvant, immunologic

Introduction

Ionising radiation and cytostatic agents used in cancer therapy exert damaging effects on normal tissues and induce there a complex response at the cellular and molecular levels. Cytokines and adhesion molecules are released during this response and mediate intercellular interactions among the effectors of immune and other systems.[1,2] Medical strategies that modulate this response in order to reduce chemotherapy- and radiotherapy-induced side effects are contradictory. Some of them inhibit this reaction, and their use is based on the hypothesis that exaggerated or persisting inflammatory response enhances the tissue damage; others stimulate this response in order to enhance physiological protective processes.

Received 25 February 2002
Accepted 11 March 2002

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Acknowledgements: The author is indebted to Pavel Vodvářka for his helpful comments and Lenka Zivčáková for technical assistance.

a) Inhibition of the tissue response

Glucocorticoids exert strong anti-inflammatory effects including inhibition of pro-inflammatory cytokine production.[1-5] The molecular mechanism of their effects is not completely understood, but they inhibit the activity of some transcription factors.[3] In clinical practice, corticosteroids are used to prevent or treat chemotherapy-induced nausea and vomitus[6] and to prevent radiation- and chemotherapy-induced pneumonitis and fibrosis.[7,8] Although corticosteroids suppressed radiation pneumonitis in an experimental model they were not able to reduce pulmonary fibrosis development.[9] In another study, short-term use of dexamethasone suppressed temporarily radiation-induced pro-inflammatory cytokine gene expression in the mouse lung, but a rebound was observed after the drug withdrawal and the drug did little to change the essence and course of the pneumonitic process.[10] Dexamethasone is widely used in the prophylaxis of radiation-induced brain oedema and inflammation; this effect was demonstrated on an experimental model.[7,11] Dexamethasone significantly reduces the incidence of the somnolence syndrome after prophylactic cranial irradiation in children with leukemia.[12] Betamethasone was beneficial in radiation-induced oral mucositis in a few patients.[13] Dexamethasone delays the development of experimental radiation nephropathy; it does not stop the progression of injury.[14,15] Captopril, an angiotensin convertase enzyme inhibitor, enhanced the beneficial effect of dexamethasone in radiation nephropathy.[15] Corticosteroids suppress cytokine secretion in irradiated animal skin.[16] They reduce hematotoxic effects of 5-fluorouracil and methotrexate, but not of other cytostatic agents in an experimental model.[17]

Nonsteroidal anti-inflammatory drugs (NSAID) inhibit the prostaglandin synthesis through cyclooxygenase blockade,[18] activation of the transcription factor of nuclear factor κB (NF-κB)[19] and adhesion of neutrophils as a result of a decreased expression of L-selectine.[18] In clinical practice, they are used in the treatment of fever, pain, and fatigue associated with chemotherapy and radiotherapy. Mesalazine has been studied in the prevention of oral mucositis;[20] however, the result of this non-randomised study lacks clinical relevance. Indomethacine did not influence the survival of lethally irradiated mice.[21]

Lisofylline is a xanthine derivative able to inhibit the release of various cytokines, such as TNF-α, TGF-β, MIP-1α, IFN-γ, Il-1β, IL-6, IL-10.[22,23] Its mechanism of action is thought to involve inhibition of acyl-substituted unsaturated phosphatidic acid, a second messenger lipid implicated in pro-inflammatory cytokine cellular activation.[24,25] It also decreases white cell adhesiveness.[26] Lisofylline inhibited 5-fluorouracil-induced release of TGF-β and maybe also other hematopoiesis inhibiting cytokines and thus enhanced trilineage hematopoietic recovery after 5-fluorouracil treatment in mice.[27]

Pentoxifylline is a xanthine derivative with profound immunomodulatory properties in vitro, including inhibition of TNF-α, Il-1β and IL-10 release.[23,28] Elevated levels of TNF-α have been shown to correlate with both the development and severity of transplantation-related complications.[29] Although pentoxifylline reduced these complications in a study,[30] these results were not reproduced in others including the one focused on 5-fluorouracil-induced oral mucositis.[31-33]

The results of a study with a TNF-α neutralising monoclonal antibody in transplant patients lack clinical significance.[34]

Intravenous immunoglobulin, especially in high doses, has profound immunomodulatory effects, including the inhibition of anti-inflammatory cytokine release;[35,36] in addition, high TGF-β concentrations have been detected in intravenous immunoglobulin preparations.[37] Intravenous or intramuscular immunoglobulin has been studied sporadically in the prophylaxis or therapy of irradiation or

chemotherapy-induced oral mucositis and radiation pneumonitis. It is not possible to make a definite conclusion of its effects from these results.[38-41]

As TGF-β plays an important role in the pathogenesis of fibrosis development, its inhibition might reduce the risk of this complication. Neutralising antibodies to both TGF-β_1 and TGF-β_2 significantly reduced the bleomycin-induced increase in the accumulation of lung collagen in an experimental model;[42] However, fibrosis was ameliorated only partially.[43] TGF-β antisense oligonucleotides, short synthetic deoxyribonucleotide oligomers complementary to DNA, prevent protein production.[44] They have been investigated in the prevention of experimental peritoneal fibrous adhesions.[45] There are no reports on their use in association with chemotherapy or radiotherapy.

IL-4 has been shown to be able to downregulate radiation-induced production of mediators of inflammation, including IL1β in the lung, suggesting its anti-inflammatory potential in regulating the radiation-induced response.[46]

Interferon γ, taurine, and niacin reduced bleomycin-induced pulmonary fibrosis in an animal model via TGF-β inhibition and subsequent procollagen expression downregulation.[47-49]

The endothelial selectins (E-selectin and P-selectin) bind to sialylated tetrasaccharide sialyl Lewis X and A counter receptors on neutrophils, monocytes and lymphocytes, mediating their emigration into the tissue.[50,51] The analogues of sialyl Lewis X such as glycyrrhizin and carminic acid bind to E-selectin on irradiated endothelial cells and thereby inhibit adhesion of leukocytes and inflammatory response in vitro.[52]

b) Stimulation of the tissue response

It has been known for more than forty years that immunomodulators stimulating the cells of the reticulo-endothelial system can protect against deleterious effects of radiation.[53]

AS 101 (ammonium trichloro (dioxyethylene-0,0′) tellurate) stimulates some subpopulations of white cells and increases the release of various cytokines, including IL-1, IL-2, IL-6, TNF-α, GM-CSF, stem cell factor (SCF), and IFN-γ.[54-57] AS 101 reduces hematotoxic effects of cyclophosphamide, 5-fluorouracil, doxorubicine, lomustine, carboplatin and etoposide,[56-59] and alopecia after carboplatin and etoposide.[57] It also has been shown to exert radioprotective effects.[60]

The physiological role of cytokines in the immune response and tissue regeneration has led to experiments studying the effectiveness of recombinant forms of cytokines in the protection of normal tissues from damaging effects of chemotherapy and radiotherapy. The results of these experimental studies were successful, depending on the schedule and the dose of the cytokine used.[61,62]

Recombinant IL-1α, TNF-α, INF-γ administered before treatment reduced hematotoxic effects of both irradiation and chemotherapy with various agents.[21,62-70] G-CSF, GM-CSF, SCF act as radioprotectors both in vitro and in vivo;[71-75] on the contrary, their concomitant administration with chemotherapy increases the sensitivity of hematopoietic cells to its cytotoxic effects.[76] MIP-1α exerts chemoprotective effects on bone marrow cells.[77] IL-1α also reduced small gut and lung toxicity of radio- or chemotherapy.[78-80]

The combination of IL-1 and TNF-α had synergistic effects.[66] Both cytokines are relatively toxic due to their physiological roles in inflammation, especially after systemic application.[81] G-CSF and GM-CSF are well tolerated and potentiate radioprotective effects of IL-1.[66]

Local application of TGF-β3 on oral mucosa significantly reduced the 5-fluorouracil-induced oral mucositis in hamsters.[82,83] IL-1, EGF, FGF have been shown to protect mice against ARA-C-induced alopecia.[84,85]

The mechanism of the protective effects of cytokines might be explained by the following hypothesis: 1) Exogenous cytokines activate the physiological pathways of immune response through their receptors, thus activating and amplifying the defence of the organism. The induction of enzymes with antioxidant effects[86,87] could be a part of this response. 2) Some cytokines, such as IL-1 or SCF, may directly or indirectly, through release of other cytokines, stimulate hematopoietic progenitor cells.[61,62,74] 3) Cytokines might inhibit the cell proliferation, thus reducing the sensitivity to proliferation-inhibiting agents or inducing the cell-cycling so that the cells enter into the relatively radio- or chemoresistent phases of the cell cycle, the S and G1 ones.[61,77] 4) Certain cytokines, such as IL-6, IFN-γ, GM-CSF, inhibit cell apoptosis including its cytotoxic agents- and irradiation-induced activation.[88-91]

Conclusions

The modulation of the tissue response to the damaging effects of radiotherapy and chemotherapy may reduce toxic effects of these treatment modalities. Only corticosteroids and NSAID are used in clinical practice to reduce acute toxicity of cancer therapy. The agents that could affect late sequels are studied experimentally; AS101 is being tested at the clinical level. The response-modifying use of recombinant cytokines to reduce toxicity of radiotherapy or chemotherapy did not progress into clinical usage. The local use of TGF-β in association with chemotherapy-induced oral mucositis is promising.

The suppression of the inflammatory response must be used with caution in the clinical practice, however. Although corticosteroids are beneficial in the modulation of acute side effects, this effect results from inhibition of the protective response that is of pivotal importance in the maintenance of organism integrity and whose suppression might have detrimental end-effects as has been demonstrated by reduced survival of mice that were administered dexamethasone after irradiation.[92,93]

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