Immunomodulation of Antitumour Response by Drugs: Is This Related to Their Selective Effect on Suppressor T Cells?

The use of chemotherapy to eradicate an experimentally established tumour has been associated under certain conditions with the immunomodulation of the host's antitumour response by the drug. The requirement for "cooperation" between the drug's effect and the host's antitumour immune response to achieve tumour eradication was well established in a system based on therapy with alkylating drugs in treatment of mice bearing large MOPC-315 plasmacytoma tumour.[1,2] The main initial finding was that low-dose therapy with cyclophosphamide (CY)[1] or melphalan (L-PAM: L-phenylalanine mustard)[2] was curative for mice bearing a late, large tumour, whereas it was not effective when given to mice at an early non-palpable tumour stage. The effectiveness of low-dose therapy in mice bearing a large MOPC-315 tumour was associated with the development and participation of the host's antitumour immune response on the basis of the following findings:

a. Ineffectiveness of low-dose therapy in tumour-bearing mice immunosuppressed by the administration of antithymocyte serum;[2,3]

b. Marked resistance to challenge with an otherwise highly tumourigenic dose of MOPC-315 tumour cells from mice cured by low-dose therapy;[1,2]

c. Effectiveness of adoptive immunotherapy of spleen cells from mice cured by low-dose therapy when the "immune" spleen cells were injected in conjunction with, but after, the administration of the drug;[4,5]

d. Development of strong antitumour cytotoxic immune potential in immunosuppressed spleen cells of tumour-bearing mice[1] following low-dose therapy at an advanced stage of MOPC-315 tumour growth;[1,2,6] and

e. Restoration and augmentation of antitumour responsiveness by *in vitro* exposure of immunosuppressed tumour-bearing spleen cells to a low concentration of L-PAM.[6]

It is worth mentioning that therapy with a high dose of CY[4] or L-PAM[2] – "high-dose therapy" – cured mice bearing MOPC-315 tumours at an early stage as well as at a late stage of development, but the cure of the mice was not accompanied by the occurrence of antitumour immune response. Thus, high-dose therapy was equally effective in tumour-bearing mice not treated with antithymocyte serum as well as in tumour-bearing mice immunosuppressed by the administration of antithymocyte serum. Moreover, mice cured by high-dose therapy were susceptible to challenge with a highly tumourigenic dose of MOPC-315 tumour cells and their spleen were not able to generate, *in vitro*, a cytotoxic reponse against MOPC-315 tumour cells.[4,6]

Facilitation of the development of antitumour immune response *in vivo* or *in vitro* by CY or L-PAM raised the possibility that these drugs may affect selectively certain suppressor-cell populations present in the spleen of the tumour-bearing host. This assumption was strengthened by previous findings showing that CY can, under certain conditions, potentiate various immune responses such as IgE response,[7] delayed – type hypersensitivity,[8] contact sensitivity[9] and autoimmune response.[10]

Extensive studies were done on the possible role of suppressor T cells in immunoregulation and inhibition of various cell-mediated type immune responses including immune response against tumour cells. Accordingly, the possibility should be considered that immunomodulation of antitumour response by certain chemotherapeutic drugs is due to their selective effect on suppressor T cells. It was shown in this respect, that CY has a selective effect on human[11,12] and murine[13] suppressor T cells as expressed by selective inhibition of suppressor T cells acting in humoral and cell-mediate immune responses and by prevention of the induction of suppressor T cells by Con A. With regard to L-PAM, we have shown that L-PAM treatment *in vitro* prevented the induction of suppressor T cells by Con A in human peripheral blood lymphocytes[14] and in murine[15] spleen-cell populations.

The connection between the depletion of suppressor T cells by CY

and the augmentation of specific antitumour response was shown in various experimental systems. Thus, when CY was administered to mice before their immunisation with syngeneic SV-40-transformed cells, the specific immune response elicited was stronger when compared with the response generated in non-CY-treated mice.[16] The interpretation that the immuno-augmenting effect of CY is due to the elimination of suppressor T cells was based on the finding that the transfer of T cells from normal syngeneic mice to drug-treated animals abolished the CY-induced augmentation.[16] We found also[17,18] that combined chemotherapy (with CY) and immunotherapy (with glutaraldehyde-treated MOPC-315 cells) were more effective than CY alone or GA-MOPC-treated cells only in promoting the antitumour immune response, as expressed by resistance to challenge with a tumourigenic dose of MOPC-315 tumour cells. The synergy between CY therapy and immunity against a mouse tumour was also described in a system of CBA/T6T6 mice inoculated with C3H-derived fibrosarcoma BP8.[19] It was found that CBA mice cured of BP8 ascites by CY treatment developed an antitumour immune response as shown by rejection of challenge with BP8.

The possibilities put forward for explaining this synergistic effect of CY were induced changes in the length of antigen exposure, modification of the antigenicity of the tumour cells by CY and the modification of antigen processing or inhibition of homeostatic mechanisms.[19]

A selective effect of CY on suppressor T cells was indicated by findings that mice with advanced disseminated syngeneic tumours can be successfully treated with a combination of chemotherapy and adoptively transferred syngeneic immune cells.[20,21] Tumour regression caused by combined chemo-immunotherapy was inhibited by the intravenous infusion of spleen T cells from donors with established tumours but not by spleen cells from normal donors. Suppressor T cells from tumour-bearing donors were eliminated from the spleen by treatment of donors with cyclophosphamide.[20]

The results reported up to now have shown a certain parallelism between the immunomodulation of antitumour response by chemotherapeutic response and their selective effect on suppressor T-cell population(s). Thus, L-PAM and CY both were able to immunomodulate the antitumour response and to affect selectively suppressor T cells. However, the question of whether the immunomodulation of antitumour response by chemotherapeutic drugs is due to their selective effect on suppressor T cells still remains unsolved for the following reasons:

a. Mouse plasmacytoma is one of the main experimental systems in which immunomodulation of antitumour response by CY or L-PAM was reported.[1-4,6,24,25] In this system, the suppressor cells described were macrophages[6,22-24] and viable tumour cells[6,25] present in the spleen. Moreover, L-PAM *in vitro* affected selectively these two types of glasswool-adherent populations and was without effect on the glasswool-non-adherent spleen-cell population (depleted of macrophages and tumour cells).[6] It is, of course, still possible that L-PAM affects a glasswool-adherent suppressive T-cell population or that the drug renders immune cells unresponsive to the inhibitory activity of the glasswool-adherent cells.[6]

b. The participation of suppressor T cells in the prevention of antitumour immune response was shown mainly in systems based on immunisation with syngeneic tumour cells[16] or on adoptive immunotherapy with immune spleen cells.[20,21] The relationship between these systems and the induced regression of an established tumour by low-dose chemotherapy is not yet clear.

c. The selective effect of a drug such as cyclophosphamide on suppressor T cells was shown to occur in a wide variety of experimental systems.[7-10,13] It is not yet clear whether the same population of suppressor T cells is affected in all the systems nor has the mechanism(s) of selective inhibition of suppressor T-cell activity been determined. It should also be mentioned that in the case of induction of suppressor T cells by Con A, cyclophosphamide and melphalan prevented the induction of suppressor T cells but were not effective against already induced suppressor T cells.[11,12,14,15]

Conclusion

It seems that the role of the selective effect of chemotherapeutic drugs on suppressor T-cell activity in the process of immunomodulation of antitumour response by drugs has not yet been well established. It might also be that this is not the only effect involved in immunomodulation of antitumour response by chemotherapy. At least two other suppressive cell populations, namely macrophages and tumour cells, might be affected by the drugs.

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