Cancer Chemother. Pharmacol. 1, 65–68 (1978)

Cancer Chemotherapy and Pharmacology

Editorial

Chemotherapy, a Double Agent in Respect of Immune Functions

G. Mathé

Institut de Cancérologie et d'Immunogénétique, Hôpital Paul Brousse,
Département d'Hématologie de l'Institut Gustave-Roussy,
F-94800 Villejuif, France

1. Cancer chemotherapy is generally considered to be immunosuppressive (Clarysse et al., 1976), and it was this action which led to the discovery of transplantation chemotherapy (Schwartz and Dameshek, 1959).

1.1. This side effect of cancer chemotherapy has been considered important, and in several experimental models, such as L1210 leukaemia, treatment with cyclophosphamide (CPM) alone or combined with ATS (Mathé et al., 1977), the curative effect of treatment was greatly reduced when a single chemotherapy was associated with an immunodepressive manipulation, as against being applied alone.

A modality of application of a given chemotherapy which is immunodepressive, as shown by a parallel allogeneic skin graft experiment, such as CPM in a dose of 403 mg/kg, is less effective in curing L1210 leukaemia than a smaller dose (134 mg/kg), which does not appear to be immunodepressive in the skin graft experiment (Mathé et al., 1977).

It has even been shown that some modalities of chemotherapy may decrease specific tumour immunity: studying mice carrying plasmocytoma MOPC 10^4 E and treated with CPM, Lubet and Carlson (1977) observed that high doses, although curative, left significantly less residual tumour immunity (measured by the ability to reject graded numbers of viable cells) than low doses.

1.2. In man, all authors agree on the fact that cancer chemotherapy, even without corticosteroids, can diminish immune responses (Clarysse et al., 1976).

Lymphopenia, or its aggravation by chemotherapy, has been found by most authors, including Jones et al. (unpublished).

Humoral immunity has been shown to decrease after chemotherapy in Hodgkin's disease, in contrast to that measured in untreated patients, in whom it was normal (Weitzman et al., 1977). According to Leventhal et al. (1974), B-lymphocyte function is almost constantly depressed during chemotherapy, but this depression has no significant effect.

For this author, T-lymphocyte depression is, on the contrary, important: a decrease of T-cell response in the phase of induction chemotherapy of acute leukaemia is associated with a poor prognosis.

T-lymphocyte depression under chemotherapy has been shown with many tests.

Delayed hypersensitivity has very often been shown to be decreased (Schneider, 1968; Simmler et al., 1976).

Several workers (Hersh and Oppenheim, 1967; Cheema and Hersh, 1971; Cardozo, 1970; Al Sarraf et al., 1972; Schneider, 1968; Simmler et al., 1976) have mentioned depression of PHA responses in patients subjected to different types of chemotherapy for different neoplasias.

Monocyte functions, especially phagocytosis and bactericidal capacity, have been shown to be impaired by chemotherapy (McVie et al., 1977).

The total number of null cells has been shown to be decreased in our acute lymphoid leukaemic patients subjected to post-remission induction chemotherapy (Joseph et al., 1976).

2. Despite many reports, immunosuppression caused by cancer chemotherapy may have been too generalized, and overestimated.

2.1. Many chemotherapies reported as immunosuppressive included corticosteroids, and Hersh and Oppenheim (1967) noted that the inclusion of these hormones makes immunosuppression more severe.

2.2. There are differences with different tumours, not only between leukaemias and solid tumours, but between different neoplasias within these two groups (Bolton et al., 1975).

0344-5704/78/0001/0065/$ 1.00

2.3. The time factor plays an important role, as we have shown and emphasized (Mathé et al., 1970): intermittent chemotherapies, even with high doses, are less immunosuppressive than continuous chemotherapies, even at low dose levels. However, the immunosuppressive effect of continuous cyclophosphamide was shown to be dose-related (Winkelstein et al., 1972).

2.4. There are differences according to the drugs used. We have seen that corticosteroids, particularly, are strongly immunosuppressive (Hersh and Oppenheim, 1967). There are cytostatics, such as 6-mercaptopurine, methotrexate, cyclophosphamide, adriamycine, and BCNU, that are often strongly immunosuppressive, and there are some that, with certain modes of application and under certain conditions, might not be immunosuppressive, such as imidazole carboxamide, bleomycine, vincristine, 5-fluorouracil, and cytosine arabinoside (Hersh, 1978).

Differences have also been demonstrated in animals with the use of different drugs, even different drugs of the same chemical family: a) we found that (chloro-2-ethyl)-1-ribofuranosylisopropylidene-2′-3′-paranitrobenzoate-5′-3 nitrosourea or RFCNU, a sugar derivative of nitrosourea, is less immunosuppressive in the hemolytic plaque-forming test than BCNU, and has a longer maximally efficient dose interval in L1210 leukaemia in mice (Imbach et al., 1975). b) Adriamycin (ADM) was found to affect antitumour immune effector mechanisms in an allogeneic system less than daunorubicin (DRB) (Mantovani et al., 1976), and to be less toxic for macrophages than DRB (Mantovani, 1977); these differences, according to the authors, could explain the superiority of ADM over DRB in antitumour effectiveness.

According to Ezdinli et al. (1977), the combination chemotherapies most often used cause a more profound and persistent depression of both T and B lymphocytes than single drug treatment.

2.5. Chemotherapies do not always inhibit all immune functions, and dissociation of alterations in different tests occurs frequently.

For Simmler et al. (1976), delayed skin hypersensitivity responses are more often decreased than in vitro mitogen-stimulated lymphocyte transformation in patients subjected to chemotherapy.

Jones et al. (unpublished) observed in breast cancer patients that a chemotherapy combining cyclophosphamide, methotrexate, vincristine or vinblastine, and 5-fluorouracil, when administered for 1 year or more, causes further lymphopenia but no increased depression of responsiveness in the remaining lymphocytes.

3. Chemotherapy-induced immunosuppression may be followed by a rebound, which might be the equivalent of immunostimulation. Such a rebound was described by Harris et al. (1973) in chemotherapy responses, and it could be interpreted as the consequence of the favourable effect of chemotherapy on the tumour. Jones et al. (unpublished) found that it was not related to clinical response but occurred in a random fashion.

The two mechanisms might be effective together or separately. As a matter of fact, such a rebound has been seen after a maintenance chemotherapy applied for the minimal residual disease left by remission-induction chemotherapy in acute lymphoid leukaemic patients (Borella et al., 1972).

4. Moreover, chemotherapy may, in contrast to its usual immunosuppressive action, restore depressed immunity in cancer patients. We have observed an effect of this type in patients in whom chemotherapy was strongly effective in the reduction of the tumour volume; immunorestoration was detectable before chemotherapy was stopped, and we attributed this effect to the action of chemotherapy on the neoplastic disease (Mathé, 1976).

But this mechanism might not be the only one. In fact, it has been shown that tumour-bearing animals (Fujimoto et al., 1976a and b; Kirchner et al., 1974; Gorczynski and Norbury, 1975; Geffard and Orbach-Arbouys, 1976; Lespinats and Poupon, 1976) and cancer patients (Goodwin et al., 1977) may present an increase of suppressor cells, and it was shown by Polak and Turk (1974), Mitsuoka et al. (1976), and Sy et al. (1977) that cyclophosphamide, and by Orbach-Arbouys et al. (1978), in our laboratory, that methotrexate may block the effect of suppressor cells.

This may be a similar phenomenon to that observed in animals by Maguire (1977), who showed that CPM administration can enhance T cell-mediated immunity to tumours.

5. Agents used in cancer chemotherapy may not act only as direct cytostatics on tumour cells; they may also increase their sensitivity to immune reactions by increasing immunogenicity. This mechanism of action has been suggested for imidazole carboxamide (DTIC) (Bonmassar et al., 1975; Campanile et al., 1975), which seems to select more immunogenic cells. This hypothesis is not incompatible with that suggesting that they increase immunogenicity by a haptenic process. According to Houchens et al. (1976), tumour cells treated with DTIC not only retain their original antigenicity, but acquire antigenic properties during treatment.

Another purine precursor, 3(or 5)-aminopyrazole-4-carboxamide, which is not active against L1210 leukaemia, was shown to alter the immunogenicity of L1210 cells (Nicolin et al., 1973).

Mustards containing haptenic functional groups

were synthesized by Wright et al. (1977), and these may be bound covalently to cell surfaces. The preliminary results of their study in the treatment of tumours with such agents are promising.

This antigenic alteration of tumour cells might, according to Goldin and Houchens (1978), be related to so-called collateral sensitivity, a phenomenon in which the origin of tumour-cell resistance to a drug leads to increased response to a second therapeutic agent (Venditti and Goldin, 1964). The increase of antigenicity induced by a given drug seems to be related to resistance to it as shown by antibody studies (Nicolin et al., 1972) and by cell-mediated cytotoxicity assays (Nicolin et al., 1974).

6. Hence, one should no longer envisage chemotherapy solely as a cancer treatment working to the patient's good by its toxicity against the tumour target cells, but should bear in mind that at the same time, it exerts an unfavourable effect by the inhibition of the immune machinery largo sensu.

Not only can one avoid the strong immunodepressive effect that some chemotherapies induce, by careful selection of agents and combinations, but one can restore immunity by reducing the tumour volume and possibly by an action on suppressor cells; in certain circumstances, one can induce a kind of immunotherapy by realizing an immune rebound after interrupting chemotherapy. Moreover, the knowledge of these notions might lead to a double manipulation by chemotherapy: direct destruction of tumour target cells on one hand, and enhanced immunity on the other. This knowledge will lead to a more scientific approach to the combination of chemotherapy and immunotherapy, which has been shown to be efficient in man and now has an experimental basis (Mathé, 1977a). We even know that one of the side effects of active immunotherapy may be immunosuppression (Mathé, 1977b) via the possible induction of suppressor cells in certain conditions, as shown in our laboratory by Orbach-Arbouys and Poupon (1978). We may be able to kill suppressor cells with chemotherapy when they appear (Orbach-Arbouys et al., 1978). Thus, not only may immunotherapy amplify the effect of chemotherapy, but chemotherapy appears to be able to amplify that of immunotherapy. Hence the interest in developing immunological as well biochemical pharmacology in cancer therapy, which is necessary not only for immunotherapy, but also for chemotherapy.

Finally, the possibility of increasing tumour cell immunogenicity with certain cytostatics should be the object of further studies with other compounds and models, as should attempts to induce immunogenicity in the tumour cells which, it is suspected, do not carry tumour-associated antigens, especially in metastases (Fidler, 1978, in press).

References

Al-Sarraf, M., Sardesai, S., Vaitkevicius, V. K.: Clinical immunologic responsiveness in malignant disease. (2) In vitro response to phytohemagglutinin and the effect of cytotoxic drugs. Oncology **26,** 357 (1972)

Bolton, P. A., Mander, A. M., Davidson, J. M., James, S. L., Necombre, R. G., Hughes, L. E.: Cellular immunity in cancer: comparison of delayed hypersensitivity skin tests in three common cancers. Brit. med. J. **1975 II,** 18

Bonmassar, E., Testorelli, C., Franco, P., Goldin, A., Cudkowicz, G.: Changes of the immunogenic properties of a radiation-induced mouse lymphoma following treatment with antitumor drugs. Cancer Res. **35,** 1957 (1975)

Borella, L., Green, A. A., Webster, R. G.: Immunologic rebound after cessation of long-term chemotherapy in acute leukemia. Blood **40,** 42 (1972)

Campanile, F., Gaston, M., Bonmassar, E., Goldin, A.: Increased immunogenicity of two lymphomas following treatment with dimethyl trizeno-imidazole-carboxamide (TIC) in athymic-nude mice. Proc. Amer. Ass. Cancer Res. **16,** 36 (Abstract 142) (1975)

Cardozo, E. L.: The effect of cytostatic therapy with cyclophosphamide alone or in combination with methotrexate on the PHA lymphocyte culture and on the immunoglobulins. Oncology **24,** 261 (1970)

Cheema, A. R., Hersh, E. M.: Patient'survival after chemotherapy and its relationship to in vitro lymphocyte blastogenesis. Cancer **28,** 851 (1971)

Clarysse, A., Kenis, Y., Mathé, G.: Cancer chemotherapy. Its role in the treatment strategy of hematologic malignancies and solid tumors. Berlin-Heidelberg-New York: Springer 1976

Ezdinli, E., Simonson, K., Icli, F., Kerman, R.: Effects of single versus multiple agent therapy on cell-mediated immunity. Proc. Amer. Soc. Oncol. **18,** 355 (Abstract C-353) (1977)

Fidler, I. J.: Experimental basis for immunotherapy of metastatic disease. In: Immunotherapy of Human Cancer. 22nd Annual Clinical Conference, Houston (in press, 1978)

Fujimoto, S., Greene, M. I., Sehon, A. H.: Regulation of the immune response to tumor antigens. I. Immunosuppressor cells in tumor-bearing hosts. J. Immunol. **116,** 791 (1976a)

Fujimoto, S., Greene, M. I., Sehon, A. H.: Regulation of immune response to tumor antigens. II. The nature of immunosuppressor cells in tumor-bearing hosts. J. Immunol. **116,** 800 (1976b)

Geffard, M., Orbach-Arbouys, S.: Enhancement of T suppressor activity in mice by high doses of BCG. Cancer Immunol. Immunother. **1,** 41 (1976)

Goldin, A., Houchens, D. P.: Chemotherapy modalities and immune condition of the host. In: Antibiotics Chemotherapy. Bâle: Karger (in press, 1978)

Goodwin, J. S., Messner, R. P., Bankhurst, A. D., Peake, G. T., Saiki, J. H., Williams, R. C., Jr.: Prostaglandium-producing suppressor cells in Hodgkin's disease. New Engl. J. Med. **297,** 963 (1977)

Gorczynski, R. M., Norbury, C.: Suppressor cells in murine sarcoma virus induced tumors. Cells in immunity. International Symposium, London, p. 149. Ontario: University of Western Ontario Press 1975

Harris, J. K., Bagai, R. C., Stewart, T. H. M.: Serial monitoring of immune reactivity in cancer patients receiving chemotherapy as a means of predicting anti-tumor response. Proc. 7th Leucocyte Culture Congress. Daguillard, F. (ed.), p. 433. New York: Academic Press 1973

Hersh, E. M.: Clinical rationale for immunotherapy and integration of immunotherapy into the strategy of cancer treatment. In: Im-

munotherapy of human cancer. 22nd Annual Clinical Conference. Houston, 1977 (in press, 1978)

Hersh, E. M., Oppenheim, J. J.: Inhibition of in vitro lymphocyte transformation during chemotherapy in man. Cancer Res. **27,** 98 (1967)

Houchens, D. P., Bonmassar, E., Gaston, M., Goldin, A.: Drug-mediated immunogenic changes of virus-induced leukemias in vivo. Cancer Res. **36,** 1347 (1976)

Imbach, J. L., Montero, J. L., Moruzzi, A., Serrou, B., Chenu, E., Hayat, M., Mathé, G.: The oncostatic and immunosuppressive action of new nitrosourea derivatives containing sugar radicals. Biomedicine **23,** 410 (1975)

Jones, K. D., Whitehead, R. H., Grimshaw, D., Hughes, L. E.: Lymphocyte response to chemotherapy in breast cancer (unpublished)

Joseph, R. R., Belpomme, D., Mathé, G.: Increase in "null" cells in acute lymphocytic leukaemia in remission on long-term immunotherapy. Brit. J. Cancer **33,** 567 (1976)

Kirchner, H., Chused, T. M., Herberman, R., et al.: Evidence of suppressor cell activity in spleen of mice bearing primary tumors induced by moloney sarcoma virus. J. exp. Med. **139,** 1473 (1974)

Lespinats, G., Poupon, M. F.: Données récentes sur l'immunologie des tumeurs. Mécanismes d'échappement au contrôle immunologique. Rôle des cellules suppressives. Bull. Cancer (Paris) **63,** 269 (1976)

Leventhal, B. G., Cohen, P., Triem, S. C.: Effect of chemotherapy on the immune response in acute leukemia. Israel J. med. Sci. **10,** 866 (1974)

Lubet, R. A., Carlson, D. E.: Tumor immunity directed against MOPC 104E: Effect of various therapeutic regimens. Cancer Immunol. Immunother. **2,** 267 (1977)

Maguire, H. C.: Increased tumor immunity with cyclophosphamide. Proc. Amer. Ass. Cancer Res. **18,** 185 (Abstract 738) (1977)

Mantovani, A.: In vitro and in vivo cytotoxicity of adriamycin and daunomycin for murine macrophages. Cancer Res. **37,** 815 (1977)

Mantovani, A., Tagliabue, A., Vecchi, A., Spreafico, F.: Effects of adriamycin and daunomycin on spleen cell populations in normal and tumor allografted mice. Europ. J. Cancer **12,** 381 (1976)

Mathé, G.: Cancer active immunotherapy. Immunoprophylaxis and immunorestoration. An introduction. Berlin-Heidelberg-New York: Springer 1976

Mathé, G.: Immune status and cancer chemotherapy. Cancer Immunol. Immunother. **2,** 81 (1977a)

Mathé, G.: Immunopharmacology and immunotherapy of residual disease in cancer patients. In: Medicinal Chemistry, Vol. V. Amsterdam: Elsevier 1977b

Mathé, G., Schneider, M., Schwarzenberg, L.: The time factor in cancer chemotherapy. Europ. J. Cancer **6,** 23 (1970)

Mathé, G., Halle-Pannenko, O., Bourut, C.: Effectiveness of murine leukemia chemotherapy according to the immune status. Reconsideration of correlations between chemotherapy, tumor cell killing and survival time. Cancer Immunol. Immunother. **2,** 139 (1977)

McVie J. G., Logan, E. C. M., Kay, A. B.: Monocyte function in cancer patients. Europ. J. Cancer **13,** 351 (1977)

Mitsuoka, A., Baba, M., Morikawa, S.: Enhancement of delayed hypersensitivity by depletion of suppressor T-cells with cyclophosphamide in mice. Nature (Lond.) **262,** 77 (1976)

Nicolin, A., Vadlamudi, S., Goldin, A.: Antigenicity of L1210 leukemic sublines induced by drugs. Cancer Res. **32,** 653 (1972)

Nicolin, A., Vadlamudi, S., Goldin, A.: Increased immunogenicity of murine lymphatic tumors by parazole-4-carboxamide, 3 (or 5)-amino (NSC-1402; PCA). Cancer Chemother. Rep. **57,** 3 (1973)

Nicolin, A., Bini, A., Franco, P., Goldin, A.: Cell-mediated response to mouse leukemic sublime antigenically altered following drug treatment in vivo. Cancer Chemother. Rep. **58,** 325 (1974)

Orbach-Arbouys, S., Poupon, M. F.: Active suppression of in vitro reactivity of spleen cells by BCG treatment. Immunology **13** (in press, 1978)

Orbach-Arbouys, S., Castes, M., Berardet, M.: Enhancement of immunological responses by methotrexate pretreatment as a result of an eventual elimination of suppressor cells. In: Experimental Hematology To-day. Heidelberg-Berlin-New York: Springer 1978

Polak, L., Turk, J. L.: Reversal of immunological tolerance by cyclophosphamide through inhibition of suppressor cell activity. Nature (Lond.) **249,** 654 (1974)

Schneider, M.: Effets des chimiothérapies antimitotiques sur une réaction d'hypersensibilité retardée. Rev. franç. Étud. clin. biol. **13,** 877 (1968)

Schwartz, R., Dameshek, W.: Drug induced immunological tolerance. Nature (Lond.) **183,** 1682 (1959)

Simmler, M. C., Rameau, G., Chou, M. J., Mathé, G.: Monitoring of nonspecific cell-mediated immunity in cancer patients. I. Frequent dissociation between the responses of skin tests to recall antigens and in vitro lymphocyte transformation. Israel J. med. Sci. **12,** 472 (1976)

Sy, M. S., Miller, S. D., Claman, H. N.: Immune suppression with supraoptional doses of antigen in contact sensitivity. I. Demonstration of suppressor cells and their sensitivity of cyclophosphamide. J. Immunol. **119,** 240 (1977)

Venditti, J. M., Goldin, A.: Drug synergism in antineoplastic chemotherapy. In: Advances in Chemotherapy, Vol. 1, p. 397. New York: Academic Press 1964

Weitzman, S. A., Aisenberg, A. C., Siber, G. R., Stossel, T. P., Smith, D. H.: The treatment of Hodgkin's disease (HD) and humoral immunity. Proc. Amer. Ass. Cancer Res. **18,** 24 (Abstract 95) (1977)

Winkelstein, A., Mikulla, J. M., Pollack, B. H., Stolzer, B. L.: Altered PHA responses in rheumatoid arthritis patients receiving cyclophosphamide. J. Lab. clin. Med. **80,** 506 (1972)

Wright, J. E., Soloway, A. H., Subramanyam, V., Gozzo, J. J.: Mustard haptens for chemoimmunotherapy of cancer. Proc. Amer. Ass. Cancer Res. **18,** 233 (Abstract 932) (1977)