Edited by
K. Hellmann and T. A. Connors

CHEMOTHERAPY

Volume 8

Cancer Chemotherapy II

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Preface

The International Society of Chemotherapy meets every two years to review progress in chemotherapy of infections and of malignant disease. Each meeting gets larger to encompass the extension of chemotherapy into new areas. In some instances, expansion has been rapid, for example in cephalosporins, penicillins and combination chemotherapy of cancer - in others slow, as in the field of parasitology. New problems of resistance and untoward effects arise; reduction of host toxicity without loss of antitumour activity by new substances occupies wide attention. The improved results with cancer chemotherapy, especially in leukaemias, are leading to a greater prevalence of severe infection in patients so treated, pharmacokinetics of drugs in normal and diseased subjects is receiving increasing attention along with related problems of bioavailability and interactions between drugs. Meanwhile the attack on some of the major bacterial infections, such as gonorrhoea and tuberculosis, which were among the first infections to feel the impact of chemotherapy, still continue to be major world problems and are now under attack with new agents and new methods.

From this wide field and the 1,000 papers read at the Congress we have produced Proceedings which reflect the variety and vigour of research in this important field of medicine. It was not possible to include all of the papers presented at the Congress but we have attempted to include most aspects of current progress in chemotherapy.

We thank the authors of these communications for their cooperation in enabling the Proceedings to be available at the earliest possible date. The method of preparation does not allow for uniformity of typefaces and presentation of the material and we hope that the blemishes of language and typographical errors do not detract from the understanding of the reader and the importance of the Proceedings.

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Contents

ON THE CYTOGENETIC CRITERIA OF RATIONAL TUMOR CHEMOTHERAPY

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SUMMARY

Tumor cells are characterized by high variability and it is possible, as a rule, to isolate from a tumor some stem cell lines with various numbers of chromosomes and with chromosome markers. Studies were carried out on transplantable ascites tumors in mice (NK/Ly, L5178 and Sarcoma 37 strains). Only hypertetraploid cells remained in a nitrosomethylurea-resistant tumor strain. Sarcoma 37 and leukemia L5178 which were also resistant to chemotherapy, differed from the initial sensitive tumors by the presence of new stem cell lines with a definite number of marker chromosomes. It is suggested that the variety of tumor karyotypes within a strain is a result of cell selection in the course of tumor progression. This fact must be taken into consideration by cancer chemotherapy whether by single agents or by combinations.

Recent achievements of cytogenetic methods permit the establishment of some strictly quantitative criteria for the control of tumor cell populations, both in the course of tumor progression, and in the course of chemotherapy. One of such criteria is the change of tumor cells karyotype with marker chromosomes.

Tumor cells are characterized by high variability and therefore, tumor cell populations are usually heterogenous. As a rule, it is possible to isolate from a tumor some stem cell lines of different cytogenetic features. These lines differ by the chromosome number and by the presence

of structurally changed (marker) chromosomes. Since one or several chromosomes could be lost while preparing slides, the presence of marker chromosomes is a more reliable feature of karyotype than the total chromosome number.

Karyotypes of the ascitic forms of NK/Ly and L5178 leukemias and of Sarcoma 37 have been studied. These tumors are sensitive to alkylating compounds, to antimetabolites and to supermutagens. We found pronounced aneuploidy and marker chromosomes, namely: a large telocehtric chromosome with a secondary constriction almost in the midst of it (A chromosome); a big metacentric chromosome (B chromosome); a very small one, 2 to 3 times smaller than the smallest chromosome of the standard mouse karyotype (C chromosome); a large submetacentric chromosome which is the longest of all the other mouse chromosomes, and it has a marked secondary constriction in the middle of its long arm (D chromosome).

Combinations of these 4 types of marker chromosomes produce various lines of cells: for instance, there is a cell line with A + B + 2C marker chromosomes, with D + B + 2C, A + B + C, A + B + 3C, D + B + 3C and A + 2B + 2C chromosomes. Each of these lines is found both in diploid and in tetraploid variants. Single polyploid cells were also found.

Depending on the conditions of tumor growth, one or another cell line prevails. For instance, an increase in number of tetraploid metaphases was observed during the first 4 days after tumor transplantation and also in the final stages of its growth.

The cell line with A + B + 2C marker chromosomes is a model line for tumor growth in the peritoneal cavity of random bred albino mice, whereas the line with D + B + 2C marker chromosomes is a characteristic of the development of the same tumor in the peritoneal cavity of BALB mice.

Such increase of the number of tetraploid metaphases in the population of tumor cells during the first 4 days and by the 16th day of its growth suggests that tetraploid cells are more resistant to the action of different unfavourable factors. High stability of tetraploid cells to such effects was confirmed by the fact that NK/Ly strain becaomes completely tetraploid and contains some new stem cells after 20 passages with the treatment with N-nitrosomethylurea; the same was observed in Sarcoma 37 after 23 passages and Sarcolysin (Melphalan) and in