15. Combination Chemotherapy of Cancer. I

Combination Chemotherapy of Yoshida Sarcoma with Azulenoid and Imino Compound

By Shigetsugu KATSURA, Kō SATŌ, Kenichi AKAISHI,
Kazuhiro HARADA, and Rintarō SATŌ

Department of Surgery, Faculty of Medicine, Tōhoku University

(Comm. by T. KUMAGAI, M.J.A., Jan. 13, 1958)

In 1951¹⁾⁻³⁾ we reported the effect of tropolone and related compounds on Yoshida sarcoma in cooperation with Prof. Nozoe's Chemical Institute in Tōhoku University. Since then anticancer activity of the compounds with unsaturated seven membered ring structure has been studied in our Department.

Recently, 73% of Yoshida sarcoma was completely cured in a state of pure culture of tumor cells by subcutaneously repeated injections with combination chemotherapy of 1-thia-3-azaazulane-2-one (Az.) and *p*-phenylene-diphosphoric acid tetraethyleneimid (RC4).

According to Miura⁴⁾ in 1956, Az. with unsaturated seven membered ring structure interfered with P³² incorporation in rat liver slice at a low concentration of 10⁻⁵ M. Despite continuous subcutaneous injections of Az. (1/40 M.L.D.) on Yoshida sarcoma, no special cytomorphological changes were recognized and prolongation of life was not observed.

On the other hand now the significance of ethyl-enimine derivatives such as TEM, TEPA, and thio-TEPA has been recognized. We had the opportunity first to examine RC4⁵⁾ synthesized in the Takamine Laboratory in Japan. The anticancer mode of RC4 is similar to

TEM, TEPA, and thio-TEPA but it is much less toxic than the latter on Yoshida sarcoma. The survival time lengthened only 2.4 times in the group of the repeated subcutaneous injections of RC4 in animals inoculated intraperitoneally 4-5 days previously. The tumor cells decreased markedly 7 days after the treatment, but a few resistant tumor cells were not controlled by the successive subcutaneous injections of this substance alone.

We have observed an interesting finding by a combined use of Az. and RC4 which have an entirely different mode of action from

1-Thia-3-azaazulane-2-one

p-Phenylene-diphosphoric acid tetraethyleneimid

each other. The animals were divided into 4 groups: Group 1. The experiment by combined subcutaneous injection of RC4 (1/10 M.L.D.) and Az. (1/40 M.L.D.) every 24 hours, only 8% survived. Group 2. Combined subcutaneous injection of RC4 and Az. was carried out every 12 hours in the following mode; the first dosis 1/20-1/10 M.L.D. of RC4 and 1/40 M.L.D. of Az., the second dosis 1/25-1/20 M.L.D. of RC4 and 1/100 M.L.D. of Az., and followed with 1/33 M.L.D. of RC4 and 1/100 M.L.D. of Az. as maintenance dosis. The cytomorphological changes were not remarkable as that in Group 1. Mitosis decreased 12-48 hours after injection. Abnormal cell divisions, such as stickness and scattering of chromosome in metaphase, bridge formation, and delayed chromosome in anaphase were seen sporadically. Cell divisions

Cytomorphological changes after combination chemotherapy with 1-thia-3-azaazulane-2-one and *p*-phenylene-diphosphoric acid tetraethyleneimid

were hardly observed 72-96 hours later. On the other hand, degenerating process as vacuolar degeneration and cytolysis in the resting cells appeared, which were accompanied with inflammatory cells, such as leucocytes, monocytes, etc., while the appearance of macrophage was not remarkable. 73% (25 cases) survived after the 27th-28th injection

when all tumor cells died. These survivals did not show any recurrence during 6 month's observation. Group 3. This group received 20 injections. Most of them died due to recurrence of tumor cells from the rest of resistant cells after termination of injections. Group 4. The same therapy as above was carried out on animals in terminal stage, i.e. 7-8 days after transplantation. All died around the 12th day after the transplantation of tumor cells.

From the above 4 experiments, the therapy shown in the 2nd group showed the best result. The reason is that the combined use of 2 materials which had entirely different mode of action from each other prevented the growth of resistant tumor cells. No deteriorated effect was noticed on the body. The effective treatment with a small amount of long term continuous injections on tumor cells was substantiated. Therapeutically, in case of administrating these substances, the time interval of injection was found out to play an important role on the tumor cells.

References

- 1) Katsura, S-T., Satō, K., Akaishi, K., Nozoe, T., Seto, S., and Kitahara, Y.,: Proc. Japan Acad., **27**, 31 (1951).
- 2) Katsura, S-T., Satō, K., Akaishi, K., Nozoe, T., Seto, S., and Ebine, S.,: Proc. Japan Acad., **27**, 36 (1951).
- 3) Katsura, S-T., Satō, K., Akaishi, K., Nozoe, T., and Kitahara, Y.,: Proc. Japan Acad., **27**, 250 (1951).
- 4) Miura, Y., Noguchi, T., and Nozoe, T.,: Bull. Soc. Chim. Biol., **38**, 1441 (1956).
- 5) Sunagawa, G., Satō, Y., and Nakao, H.,: In press.