Short Report

Mechanism of the Development of Resistance to Mitomycin C in Hirosaki Sarcoma

ISAMU USUBUCHI, TATSUSKE SATO and HAJIME KUDO

Department of Pathology, Hirosaki University School of Medicine, Hirosaki 036

USUBUCHI, I., SATO, T. and KUDO, H. Mechanism of the Development of Resistance to Mitomycin C in Hirosaki Sarcoma. Tohoku J. exp. Med., 1980, 132 (2), 237-238 — In the peritoneal cavity of the rat, Hirosaki sarcoma, an ascites tumor of the rat, acquired a resistance to the essentially effective dose of 100 \( \mu g \)/kg of mitomycin C by means of the daily treatment with the ineffective dose of 10 or 1 \( \mu g \)/kg of mitomycin C. It is considered that most of Hirosaki sarcoma cells may have gradually acquired a hereditary resistance to mitomycin C in the course of the contact with the drug. —— drug resistance of tumor; development of resistance

Although many studies on the drug resistance of tumor cells have been reported, its mechanism has not usually been elucidated (Sakurai 1964). We carried out experiments on the development of resistance to mitomycin C and found out that the mechanism is difficult to explain by the concept "mutation and selection".

Non-inbred rats of both sexes of Gifu strain, weighing 150 to 180 g, were used in all experiments. Tumor cells employed were those of Hirosaki sarcoma previously reported in detail (Usubuchi and Abe 1956). The minimum effective dose of mitomycin C to Hirosaki sarcoma in vivo is 50 \( \mu g \)/kg/day (Usubuchi et al. 1958).

(1) A clonal cell line of Hirosaki sarcoma was established. Four groups, each consisting of 10 rats, were i.p. inoculated with \( 1 \times 10^7 \) cells of the clonal line. Forty-eight hr after the inoculation, the dose of 100, 10 or 1 \( \mu g \)/kg of mitomycin C was i.p. injected to the respective groups. One group received no treatment. The injection was done once a day for 5 days. All rats that received 100 \( \mu g \)/kg were cured after having shown marked degeneration of tumor cells distinguished by polymorphonuclear giant cells (Fig. 1). On the other hand, mean survival time of two groups injected with 10 or 1 \( \mu g \)/kg was 7.0±0.8 (mean±S.D.) or 6.8±1.2 days respectively, without showing the characteristic degeneration of tumor cells. Mean survival time of the control was 7.2±0.8 days. No statistically significant differences were found by analysis of variance (p<0.005).

(2) Immediately after the i.p. transplantation of \( 1 \times 10^7 \) cells of the clonal cell line, rats were treated daily with i.p. administration of mitomycin C, 10 or 1 \( \mu g \)/kg. Tumor cells treated were serially transplanted to the next passage before the host dies and the similar treatment was repeated in the new host. After 24 administrations (24 days) in the case of 10 \( \mu g \)/kg/day or 44 administrations (44 days) in the case of 1 \( \mu g \)/kg/day, the tumor cells acquired a complete resistance to 5 daily administrations of 100 \( \mu g \)/kg of mitomycin C, and the rats died without showing the characteristic degeneration of tumor cells (Fig. 2).

(3) The similar treatment as described above was continued in the experimental group treated with 1 \( \mu g \)/kg and stopped when 100 administrations (100 days) were done. In the examination after 6 months, the tumor cells showed a complete resistance to 100 \( \mu g \)/kg. Moreover, each of 10 clonal cell lines derived from this mitomycin C-resistant Hirosaki sarcoma was also resistant to 100 \( \mu g \)/kg.

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Fig. 1. Mitomycin C-sensitive Hirosaki sarcoma cells treated daily with 100 $\mu$g/kg of mitomycin C for 5 days, showing the characteristic degeneration. Giemsa staining. $\times$ 720.

Fig. 2. Mitomycin C-resistant Hirosaki sarcoma cells treated daily with 100 $\mu$g/kg of mitomycin C for 5 days, without showing the characteristic degeneration. Giemsa staining. $\times$ 720.

These results showed that Hirosaki sarcoma acquired a resistance to the essentially effective dose of 100 $\mu$g/kg of mitomycin C by means of the daily treatment with the ineffective dose of 10 or 1 $\mu$g/kg of mitomycin C. On the mechanism of the development of resistance to mitomycin C, it is difficult to consider that a few resistant cells having appeared in cell population of Hirosaki sarcoma were selected in the course of the contact with the drug, because the treatment was done throughout with the ineffective dose which did not make the selection. We think, as the mechanism, that most of Hirosaki sarcoma cells may have gradually acquired a hereditary resistance to mitomycin C in the course of the contact with the drug.

References

