Studies on Resistant of Cancer Cells to Nitrogen-Mustard-N-Oxide

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At the present time Nitrogen-Mustard-N-Oxide (NMO) is being widely used clinically in the treatment of cancer. The trouble is that with continued use, cancer becomes resistant to an anticancer agent. We have studied both clinically and experimentally the problem of NMO resistance, especially with regard to tumor DNA, on which we report here.

We cite here as the first clinical case that of a seventeen year old youth with mediastinal tumor. A thoracotomy was done but resection of the tumor was found to be impossible. After the operation, this patient was given 125 mg THM and 700 mg NMO and we could see by x-ray film that these alkylating agents were most effective. Thereafter, 25 mg TEM and 1600 mg NMO were added but up to the present time the tumor has been increasing and it is thus proved that...
the tumor has acquired resistance against NMO. During application of the agents, depolymerase in patient's serum against DNA has been gradually reduced.

The second case is that of a fifty-five year old woman having reticulosarcoma of the maxillary bone. After resection of the tumor, a metastasis appeared in the posterior mediastinum. By x-ray film we could see that the metastasis was comparatively large but after application of 420 mg NMO it was considerably reduced. We used 240 mg NMO thereafter but the tumor began to increase and we knew then that the tumor had become resistant to NMO.

As stated above, we clarified clinically that tumor acquires resistance against alkylating agents and we studied this problem experimentally from the standpoint of DNA.

Using a rat, we first formed a Yoshida ascites tumor resistant to NMO by injecting 50 µg—1 mg every day during nine consecutive tumor transplantations. When we inject 1 mg NMO intraperitoneally, the mitotic rate reduction is evidently weak in cases of resistant tumor as compared with sensitive tumors. When we begin injections of NMO at the time of transplantation and continue them every day, the resistant tumor grows in spite of NMO injections, but under the same conditions the sensitive tumor does not grow. Thus we ascertained the acquisition of resistance by tumors, and studied the problem with the following results:

Depolymerase found in serum of a Yoshida ascites tumor rat has a stronger action against DNA than that found in a normal rat; but the enzyme found in the serum of NMO-resistant tumor rat is weaker than that found in NMO-sensitive rat, although still stronger than in a normal rat. When NMO is injected into rats, the serum of the sensitive tumor rat shows decreased depolymerization but there is a tendency toward an increase in the resistant tumor rat serum.

When we observe the ability of tumor cells to dephosphorylate DNA after loading with NMO, we can see their remarkable increase in cases of sensitive tumor, but in cases of resistant tumor, there is a decreasing tendency which is the same as a deamination effect. This same relationship is also seen in the liver cells of the animals.

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