III. 8 Changes in Growth and 18FDG(2-Deoxy-2-[18F]Fluoro-D-Glucose) Uptake of Rat Hepatomas by Anticancer Drugs

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Introduction

The diagnosis of tumors by positron CT using 18FDG has been applied recently.1-6) We have been both experimentally and clinically exploring the possibility of utilizing this diagnosis system not only for diagnosing tumors but also for evaluating the efficacy of cancer chemotherapy.7,8) Furthermore, we have experimentally investigated the relationship between the growth change of tumors and the change in 18FDG uptake rate, particularly in terms of the sequence of the changes in order to detect the applicability of this system to the field of cancer chemotherapy. It seems to be clinically of great importance that we should try a comparative study detecting the sensitivity of the growth change of tumors expressed by weight, area and volume, and that of 18FDG uptake rate of tumors to cancer chemotherapy.

Materials and Methods

Male Donryu rats weighing 120-160 g were used in this experiment. 490-550 x 10⁴ hepatoma(AH272) cells were subcutaneously implanted in the backs of the rats. Anticancer drugs(Adriamycin(ADR) 4 mg/kg, Mitomycin(MMC) 0.25 mg/kg or MMC 2.5 mg/kg) were injected into the tail veins of the rats on the 9th day after the implantation, respectively. At the specified intervals of 7, 9, 11, 12, 13, 15, 17 and 20 days after the implantation, 18FDG(19-33μci/body) supplied by the Cyclotron and Radioisotope Center, Tohoku University, was intravenously injected into the rats, which were sacrificed by cervical dislocation one hour after the administration. The excised tumors were weighed, the area of tumors was measured directly in the long axis x the longest diameter vertical to the long axis, the volume of tumors was measured and the radioactivity of tumors was counted by an automate NAI well counter. The volume of tumors was defined by difference of weight measured before and after they were soaked in 10 % formalin solution of which specific gravity had been measured. The uptake of 18FDG in tumors was expressed as % injected dose/g tissue.
Results

Control group (Fig. 1)

On the 9th and 10th days after the implantation the weight, the area and the volume of the tumors increased, respectively. On the 11th and 12th days they slightly decreased. The increase followed on the 17th and 20th days, which was the peak of the course of the experiment.

Meanwhile, 18FDG uptake rate indicated the peak on the 10th day and the decrease on the 12th day after the implantation, then on the 13th day it resumed a slight increase, but on the 20th day it decreased again, while the tumor growth values increased. That is, in the first half of the experiment (until the 12th day after the implantation), the change of the tumor growth values (the weight, the area and the volume of the tumors) as well as that of 18FDG uptake rate are almost correspondent, however, in the latter half of the experiment (17th and 20th days), the increase of tumor growth values was observed, although 18FDG uptake rate reduced.

ADR-administered group (Fig. 2)

The tumor growth values reduced on the 13th day after the implantation, but they increased on the 15th, 17th and 20th days in the latter half of the experiment. Those values were lower than those of the control group. Regarding the change with the lapse of time, the 18FDG uptake rate of this group was almost similar to that of the control one and the difference between the 18FDG uptake of the control group and this group was minor.

MMC(0.25 mg/kg)-administered group (Fig. 3)

The tumor growth values with the lapse of time of this group took the similar form of change to that of the control and the ADR-administered group. The values in the latter half of the experiment were lower than those of the control one. 18FDG uptake rate was relatively higher on the 10th day after the implantation (first day after MMC-administration), but went down thereafter.

MMC(2.5 mg/kg)-administered group (Fig. 4)

The tumor growth values were high on the 10th day after the tumor implantation (first day after MMC administration) but went down thereafter. In the latter half of the experiment the values were markedly lower than those of the control group and also lower than those of the ADR-administered and MMC(0.25 mg/kg)-administered group, and 18FDG uptake rate was lower than that of the control, ADR-administered and MMC(0.25 mg/kg)-administered groups.

To summarize the above results, tumor growth was seen in the control group in the latter half of the experiment, while it was prevented in the following three groups: ADR group, MMC(0.25 mg/kg) group and MMC(2.5 mg/kg)-administered group. The similar decrease of 18FDG uptake rate was observed in
the ADR group and the MMC(0.25 mg/kg) group, but in the MMC(2.5 mg/kg) group, it was extremely low. The change of 18FDG uptake rate did not precede that of tumor growth.

Discussion

We have both experimentally and clinically studied in tumor imaging by positron CT, using 18FDG which has a high uptake in tumors, particularly, in terms of efficacy evaluation of cancer chemotherapy.7,8)

The current efficacy evaluation method of cancer chemotherapy basically depends on whether or not morphological change exists. The evaluation of CR(Complete Response), PR(Partial Response), MR(Minor Response), NC(No Change) or PD(Progressive Disease) was done according to the diminishment rate of tumors after chemotherapy.9) Among the groups evaluated as above, sufficient diminishment of tumors was not observed in the NC group and it is not recognized as responsive to cancer chemotherapy. However, the survival period of the NC group is significantly prolonged compared to that of PD group.10) The results would suggest that some beneficial change has occurred except morphological change of tumors by chemotherapy in the tumor tissue or the tumor cells. Cancer patients with morphologically unmeasurable lesions are not involved in efficacity evaluation of cancer chemotherapy. Therefore, the feasibility of utilizing pathophysiological change of hosts and tumors as the parameter of treatment results has currently been investigated. In fact, CEA in case of colon cancer and α-fetoprotein in case of hepatoma are adopted as parameter for efficacy evaluation of chemotherapy. It is generally recognized that there is the correlation between morphological change of tumors and CEA values,11) and, it is reported that the change in CEA values was seen several weeks to several months prior to the tumor change.12-14) These reports imply that studies in this field have clinical significance for evaluation and prediction of efficacy of cancer chemotherapy.

The significance of diagnosing system by positron CT imaging using physiological substance labeled as short-life positron emitter is that it enables us to know the metabolic state of target organs.

Consequently, the method by which glucose uptake in tumors is examined by positron CT system with 18FDG as tracer may be defined as method between evaluation method of morphological change in tumors and that of change in pathophysiological parameters. Then, we here report the results of our experimental studies on the difference between the morphological change and 18FDG uptake of tumors with the lapse of time. As far as subcutaneous implantation of hepatome(AH272) and ADR/MMC administration concern, the change of 18FDG uptake rate did not precede that of tumor growth. Further experimental and clinical studies are expected in the future.
Conclusion

We experimentally studied the correlation between the change of tumor growth and that of 18FDG uptake rate in tumors in cancer chemotherapy. Suppression of tumor growth by the administration of anticancer drugs seems to relate to reduction of 18FDG uptake rate, but the difference with the lapse of time caused changes was not observed at all. The change of 18FDG uptake rate could not be defined as a promising means for predicting efficacy of cancer chemotherapy at an earlier stage with the AH272 subcutaneously implanted rats. Further studies are expected with other experimental as well as clinical subjects in this field.

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References

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Fig. 1. Changes of tumor growth and 18FDG uptake in s. c. implanted hepatomas (AH272) in rats. Mean values of 6 rats at each point. ×: weight, g. △: area, cm². ○: volume, cc. ●: % injected dose/g tissue.

Fig. 2. Changes of tumor growth and 18FDG uptake in s. c. implanted hepatomas (AH272) in rats following ADR 4 mg/kg administration. Mean values of 5 or 6 rats at each point. ×: weight, g. △: area, cm². ○: volume, cc. ●: % injected dose/g tissue.
Fig. 3. Changes of tumor growth and 18FDG uptake in s. c. implanted hepatomas (AH272) in rats following MMC 0.25 mg/kg administration. Mean values of 6 rats at each point. ×: weight, g. △: area, cm², ○: volume, cc. •: % injected dose/g tissue.

Fig. 4. Changes of tumor growth and 18FDG uptake in s. c. implanted hepatomas (AH272) in rats following MMC 2.5 mg/kg administration. Mean values of 6 rats at each point. ×: weight, g. △: area, cm², ○: volume, cc. •: % injected dose/g tissue.