IV. 10. $^{18}$FDG Uptake of the Myocardium in PET Images of Patients under Cancer Chemotherapy


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Introduction

Chemotherapy is one of the effective strategies for cancer. Many anticancer agents are in use, but various adverse effects caused by them limit their continuous use. The common side effect of the most agents is myelosuppression, and cardiotoxicity is characteristic in anthracyclines 1-5).

Myocardial damage caused by one of the anthracyclines, Doxorubicin (DXR) often, leads to irreversible and frequently fatal congestive heart failure. Then, the use of this effective agent for various cancers is sometimes ceased for the toxicity or its risk, and the therapy cannot be accomplished. Various monitoring methods have been advocated for the earlier detection of the myocardial dysfunction induced by DXR 4), such as electrocardiography (ECG), echocardiography and radionuclide ventriculography. In recent years the endomyocardial biopsy was reported to be the most reliable means to evaluate the degree of myocardial damage caused by this agent, but this invasive measurement does not seem to be popular due to its risk and cost in our country. Since sensitivity of examination of 2-deoxy-2-[18F]fluoro-D-glucose ($^{18}$FDG) uptake change in the myocardium was observed to be high 6,7), DXR-induced cardiotoxicity may be predicted in terms of change of myocardial images by positron emission tomography (PET).

This report deals with investigational studies in which cardiotoxicity induced by anticancer agents was successfully displayed on $^{18}$FDG-PET image.

Materials and Methods

A total of 18 patients were examined: 8 cases with gastric cancer, 3 with pancreatic cancer, 2 with colonic cancer, 1 with esophageal cancer, 1 with hepatocellular carcinoma, 1 with breast cancer and 2 with pancreatic cyst. The total number of PET examination was 24. Myocardial images of these patients without restricted diet were constructed by $^{18}$FDG-PET system. Following the intravenous injection of $^{18}$FDG (3-7 mCi/body) as a volus, a series of emission scans with ECAT II (EG&G, Ortec, USA) or PT 931/04 (CTI, ECAT, USA) was
carried out on the heart. Mainly 5 min.-scan was performed 40-45 min. after injection (ECAT II), and 5-7.5 min.-scan was done 22.5 min. after injection (PT 931/04). Both scanning images served the following analytic studies. 3-7 ROIs (region of interest) were determined on PET image. A ROI is 0.8 cm² in area. The quantification of ¹⁸FDG-uptake in the left ventricle of the heart was attempted and denoted as Differential Absorption Ratio [DAR = (PET count × calibration factor) / (injected dose/body weight)] ⁸,⁹. The highest DAR in ROIs was determined as the uptake of the heart in each patient. The subjects were classified into three groups by the sum of chemotherapy for the sake of convenience, namely, the first group which had not been treated by any anticancer agents, the second one insufficiently treated with a small amount of agents and the third one sufficiently treated by a large amount of agents including other anticancer agents than anthracyclines. DAR values of each group were compared statistically by Student-t test.

Results and Discussion

The myocardial DAR of non-treated group was 6.2 ± 1.4 (mean ± standard deviation), that of insufficiently treated one was 5.8 ± 2.5, and that of sufficiently treated one was 3.6 ± 1.7. A significant difference was found between the first and the third group (p < 0.02). DAR of the third group is lower than the second group, but not significant (p < 0.1).

¹⁸FDG, glucose analog labeled with ¹⁸F, is more extensively taken up by the myocardium, the brain or tumors, which demand glucose as an energy source, than by any other tissues. On the basis of this physiological property, glucose metabolism of these organs and tissues can be imaged by ¹⁸FDG-PET. This system has enabled us to clinically observe regional myocardial metabolism.

In our experiment of DXR-administered rats ⁷), myocardial uptake of ¹⁸FDG decreased, and the sensitivity to detect changes of uptake was higher than those by ECG and histological examination by light microscopy, and similar to, or higher than that by electron microscopical examination which was reported to be the most reliable method to evaluate the degree of the myocardial damage induced by DXR ¹⁰). Therefore, it is conceivable that anthracyclines-induced cardiotoxicity might be predicted in terms of changes of myocardial image by ¹⁸FDG-PET. Since the ¹⁸FDG myocardial uptake may relate to various factors, such as patient characteristics, the kind and dose of anticancer agents, period after the last administration, diet, blood sugar level, fatty-acid metabolism and so on, all the patients have to be stratified by each factor stated above. As patients in this studies were stratified only by the amount of administered agent, this clinical studies may only be the investigational trial. The results obtained, however, revealed that this ¹⁸FDG-PET system had the possibility to be a new noninvasive method for early detection and monitoring of cardiotoxicity induced by anticancer agent.

Conclusion
$^{18}$FDG myocardial uptake expressed as DAR in PET images of patients was the highest in patients without cancer chemotherapy and the lowest in patients with sufficient chemotherapy using not only anthracyclines but other agents.

We advocate that analyzing of myocardial images on $^{18}$FDG-PET may have the possibility to be a new noninvasive method to detect cardiotoxicity induced by anticancer agents including anthracyclines.

Acknowledgments

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References

Table 1. $^{18}$FDG uptake in the heart on PET image. The Differential Absorption Ratio (DAR) of patients sufficiently treated by chemotherapy (+) was the lowest. Chemotherapy (-): non-treated group. Chemotherapy (+): insufficiently treated group. Chemotherapy (++): sufficiently treated group.

<table>
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<tr>
<th>Differential Absorption Ratio (DAR)</th>
<th>Chemotherapy (-)</th>
<th>Chemotherapy (+)</th>
<th>Chemotherapy (++)</th>
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<td>O. J. E. 60 Gast. ca. 8.8</td>
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<tr>
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<td>T. S. 63 Hepatoma. 1.5</td>
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5.8±2.5 † 3.6±1.7 *

PET : Positron Emission Tomography  • : ECAT II  O : PET 931

*: p<0.02  †: p<0.1