1. INTRODUCTION

Although numerous anticancer agents have been developed, solid tumors in general respond poorly to treatment. Many people do not accept the current situation concerning cancer chemotherapy, especially in the field of gastrointestinal cancer. Is chemotherapy for gastrointestinal cancer meaningless?

My answer to that is no, even in the current situation.

Several GI oncology groups have conducted randomised control studies in which they have compared some combination chemotherapy with the best supportive care (BSC) alone in cases of advanced gastric cancer or advanced colorectal cancer\(^1,3\). As one such examples, in comparison with BSC, a regimen consisting of 5-FU, adriamycin and methotrexate appears to prolong survival in patients with advanced gastric cancer\(^1\). Similar results have been reported in a randomised study of advanced colorectal cancer by other groups\(^3\).

Therefore current conventional chemotherapy for gastrointestinal cancer is not always useless. However, the situation is still far from satisfactory. In fact the median overall survival time of the treated group in the study for advanced gastric cancer was only 9 months\(^1\).

Recently we have also obtained a similar median survival time, that is about 8 months, in advanced gastric cancer after the treatment with 5-FU and cisplatin\(^4\).
1.1 Why can we not eradicate solid tumors with anticancer agents?

Generally drugs can give patients proper benefits by adjusting a functional disorder. On the other hand, the target of an anticancer agent is cancer cells themselves, which originate from the patient’s own cell. Unfortunately cancer cells are almost identical genetically to their corresponding normal cells. Although there are numerous reports concerning genetic and phenotype changes in tumors, there is as far as I know no pivotal change in tumor cells which distinguishes them from normal cells. I suppose that a subpopulation of dramatically changed tumors could be eradicated by the patients own immune system and then that subpopulation of tumors would be out of the question clinically. In general drugs, toxicity occurs at concentrations well above those needed to achieve maximum desired effect. So these drugs have a wide therapeutic window. On the other hand, in the case of anticancer agents, the therapeutic window is quite narrow because of a high degree of overlap between efficacy and toxicity.

1.2 We need DDS in cancer chemotherapy

Recently the concept of the molecular target has come into fashion in the development of new anticancer agents. I do not oppose the movement. However, people must be cautious, because they could possibly meet the same problems as with the current conventional cancer chemotherapy, even after exhaustive efforts for development. In the development of anticancer agent used conventionally, the drug was usually synthesized or extracted from a plant or bacteria and then screened using several cell lines, checked in in vivo systems and finally introduced into clinical trials. During the procedure, the macroscopic characteristics were not usually considered. On the other hand, the agents categorized in DDS have been developed with the macroscopic features of solid tumors in mind even in the manufacturing procedure.

1.3 EPR effect in solid tumor tissue

Figures 1 and 2 explain some examples of macroscopic derangement of solid tumor, which are now generally accepted as an effect named EPR (Enhanced Permeability and Retention) effect\(^5,6\). In the experiment shown in Figure 1, a blue dye, Evans blue was injected into the tail vein of tumor-bearing mice at a dosage of 10mg/kg. At this dose level there was no free dye in the plasma; it was mostly bound to albumin, as confirmed by molecular sieve chromatography. These four pictures illustrate tumor tissue...