Lesionalized Therapy beyond Personalized Therapy in Cancer Management

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Personalized therapy which specifically focuses on targeting cancer cells is now considered as a standard therapy in cancer management. Though personalized therapy can reduce side effects of normal cell damages by specific targeting, most tumors eventually acquire resistance to target specific drugs by genetic or epigenetic changes. Thus, additional efforts have been made to overcome the limitations of personalized therapy.

Tumor heterogeneity induces characteristic changes in their therapeutic responses. Local factors such as blood supply and tissue acidosis differently influence the tumor cells and cells in the tumor microenvironment. Previous therapies have focused on only tumor cells, but tumor cells and their microenvironmental cells should be considered as therapeutic targets (1). Since malignant progression followed by distal dissemination can reflect either genetic or epigenetic cellular heterogeneity or both, cellular heterogeneity between primary and metastatic lesions could be also considered in the design of more efficient cancer therapies (2).

Cell-to-cell copy number variation of oncogenes such as MET and PDGFR can confer altered characteristics to subspecialized cell populations. Epigenetic heterogeneity can also contribute to differentiation-related or drug resistance-related changes in cancer cells, in which DNA is hypomethylated to generate genetic instability and disturb gene expression. Cellular heterogeneity can even occur within one tumor lesion. In deeper area of the tumor, most cells exit from the cell cycle, and only cancer cells located on the exterior of the tumor mass undergo cell cycling. Most conventional chemotherapies affect the dividing cells, and non-dividing cells are relatively resistant to chemotherapy.

Because different clinical presentations subsequently affect therapeutic response and prognosis, successful tumor therapy requires deep understanding of tumor heterogeneity. Thyroid carcinoma is a good example to discuss tumor heterogeneity and different clinical presentations in each patient, or even in the different lesions from same patient.

Thyroid cancer is the most common cancer in Korean women, and almost cases are differentiated thyroid cancer (DTC). Radioiodines have been widely used for the management of DTC and the molecular mechanism of iodine selectivity is related to the sodium iodide symporter (NIS). Accumulation of radioiodine is dependent on the expression of membrane NIS, which is a molecular target of radioiodine whole body scans and 131I therapy.

NIS expression is quite variable among tumors, and is an important factor in 131I therapy response of residual DTC. Response rate of 131I treatment was 80% and 33% in NIS positive and negative tumor, respectively (3). Moreover, different NIS expression was observed in different tumor lesions even in one patient. Only 40% of DTC patients showed similar NIS activity between primary tumors and metastatic lymph nodes (4). Half of patients with multiple lymph node metastases showed different NIS expression between the different lesions.

We found that tumor detectability of radioiodine scan is higher in relatively well differentiated tumor than in less differentiated tumor, but tumor detectability of 18F-FDG PET is reversed (5). Radioidine scan and 18F-FDG PET can visualize the functional level of NIS molecule in DTC tissues (6). This kind of molecular imaging can characterize the heterogeneity of DTC tumor in different lesions, and guide the most proper management.

Though in vitro molecular diagnostics can analyze the differences in tumor lesions, most of them require tissue sample and are difficult for direct application in clinic. However, molecular imaging modalities easily visualize the heterogeneous features of different tumor lesions. According to different characteristics among tumor lesions in one patient, more efficient treatment and suitable management should be taken. We would like to name it as “lesionalized therapy.” Lesionalized therapy beyond personalized therapy should be applied for more effective and successful cancer management.
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