IL1 : 招請講演 1

Targeted Therapy of Bladder Cancer : Lessons Learned

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Urothelial cancer of the bladder is a relatively common disease in industrial nations world-wide, and accounts for approximately 13,000 deaths annually in the United States. The standard treatment for operable invasive bladder cancer is radical cystectomy, whereas patients with metastatic urothelial carcinoma are usually treated with systemic chemotherapy. For more than a decade, the standard treatment for metastatic urothelial cancer has been combination therapy with M-VAC (Methotrexate, Vinblastine, Adriamycin and Cisplatin). This regimen is consistently reported to produce a median survival in the range of 13 to 15 months. Despite considerable effort to dose-escalate or otherwise modulate the components of M-VAC, no improvement in patient survival has been observed. In the search for regimens more active than M-VAC, regimens based on gemcitabine, ifosfamide, and paclitaxel have attracted considerable interest. Although some of these newer regimens, most notably gemcitabine and cisplatin, are less toxic than M-VAC, there is as yet no compelling evidence that survival is improving. Indeed, there is a growing conviction that the cytotoxic paradigm, as we have known it, will not provide the means to qualitatively change the outcome for patients with advanced bladder cancer. Therefore, the development of novel therapeutic approaches such as targeted therapy is imperative. Unfortunately, relatively little is known about the biological properties of advanced bladder cancer that interfere with the response to treatment, but it is especially important to identify these cellular and molecular alterations that occur within the tumor cells, as well as the manner in which these alterations influence host-tumor interactions. Such knowledge is essential for the design of more effective future therapies.

Of the possible targets for therapy, the EGFR is appealing. The EGFR is expressed by more than 50% of human bladder cancers, and its expression is a function of advanced grade and stage. Clinically relevant antagonists inhibit the growth of human xenografts via effects on tumor cell proliferation as well as on tumor host interactions involved in the process of angiogenesis. However, the results of clinical trials indicate that single agent activity is low, and the prospective identification of likely responders is still not possible. Moreover, the effects of these compounds are largely cytostatic, which presents distinct challenges within the context of combination therapy. Ongoing research is directed to develop strategies that incorporate EGFR therapy into effective therapeutic approaches for bladder cancer.