Hormonal therapy and targeted therapy in palliative cancer care

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In patients with advanced cancer, chemotherapy, hormonal therapy and targeted therapy are common treatment modalities for systemic palliative treatment. Majority of the chemotherapeutic agents affect cells in proliferative phase (G1 to M phase of cell cycle) and differentiate cancer cells from normal cells by their higher rate of cell proliferation. Therefore normal cells with high proliferation rate are frequently affected by chemotherapy, causing adverse effects such as marrow suppression or alopecia. On the other hand, hormonal therapy and targeted therapy agents usually retain the cancer cells in quiescence state (G0 to G1 phase) and the tumour growth is halted. These two types of agents affect tumour cell through inhibition of specific receptor or the growth factor that stimulate the tumour cells. Hence they are more selective and their adverse effects are more tolerable to fragile patients.

Hormonal Therapy

Breast Cancer

Sex hormonal related cancer, such as breast cancer and prostate cancer, frequently respond to hormonal treatment. Estrogen receptor (ER) is commonly present in breast cancer, especially in the elderly. In patients with ER positive advanced breast cancer, hormonal manipulation is an effective treatment. Hormonal manipulation is achieved by either blockade of the ER in cancer cell or removal of hormone production source. Blockade of the ER by tamoxifen is the most common form of hormonal therapy in patients with advanced breast cancer. The overall response rate and duration of response of tamoxifen in patients with ER positive advanced breast cancer is 70-80% and 12-16 months.
Prostate Cancer

Prostate cancer is commonly androgen dependent. Hence hormonal treatment is also effective in patients with advanced prostate cancer. The treatment principle is similar to breast cancer. The production of androgen can be cut off by 1) surgical castration through orchidectomy; 2) medical castration by luteinizing hormone releasing hormone (LHRH) injection to abolish the surge of LHRH in the hypothalamus-pituitary axis hence reduce the stimulation to testes. Both treatment options have similar efficacy. Orchidectomy has an advantage of a relatively simple operation, free from compliance problem and quick response in symptom improvement e.g. reduction of metastatic bone pain in terms of a few days. LHRH monthly subcutaneous depot injections such as leuprorelin or goserelin are equally effective, with 80% response rate. It has an advantage of reversibility. However in the first injection of LHRH, there is an initial stimulation of testes hence increase production of androgen. The tumour may be activated (flare-up phenomenon) with an increase of symptoms (including cord compression in case of spine metastasis). Therefore patients with initial LHRH treatment have to be covered by anti-androgen for 3 days before and 3 weeks after the LHRH injection.

Anti-androgen is another alternative of hormonal treatment in prostate cancer. Drugs like flutamide, bicalutamide or cyproterone are androgen receptor blocker. Anti-androgen can be used as monotherapy, in combination with orchidectomy or medical castration, or as salvage treatment in patients initially response to surgical or medical castration.

Adverse effects of hormonal manipulation in prostate cancer patients include loss of libido, impotence, fatigue and loss of muscle bulk. The best modality of hormonal treatment in prostate cancer is difficult to define. Longer disease control time may be associated with more adverse effects on deterioration in physical capacity and sexual interest. The possibility of intermittent versus continuous hormonal treatment still need further exploration.

Targeted Therapy

Targeted therapy is a relatively new treatment modality. The medication used in targeted therapy blocks the growth of cancer cells by interfering with the specific targeted molecules needed for carcinogenesis or tumour growth. The agents used in targeted therapy are either small molecule or monoclonal antibody. The commonly used targeted therapy agents are listed in table 1.

Gefitinib is a typical example of targeted therapy agent. It is an oral medication which blocks the tyrosine kinase component in the epidermal growth factor receptor (EGFR). Stimulation of the EGFR is a key step in certain types of cancer cell such as non-small cell lung cancer (NSCLC). In early clinical trials, the efficacy of gefitinib in patients with NSCLC refractory to chemotherapy can be drastic. Majority of the responders show improvement of symptoms within 14 days after administration. In phase III clinical trials gefitinib as second line treatment demonstrates a statistically significant improvement of time-to-treatment-failure over the placebo group (3 months vs 2.6 months, p=0.0005) but only shows improvement of overall survival in non-smoker (Hazard ratio 0.67, CI 95% 0.49-0.91, P=0.011) An advantage has also been shown in Asian ethnic origin. Adverse effects of gefitinib include diarrhoea, dermatological reaction such as skin rash and acne, nausea and vomiting. Around 1.5% patients develop interstitial lung disease, which is potentially fatal.

Erlotinib is another EGFR inhibitor in NSCLC. In phase III clinical trial it shows an improvement in overall survival (median overall survival 6.7 months vs 4.7 months, p=0.001) as a second line treatment. A better response is seen in female, adenocarcinoma subtype and non-smoker. Similar response predictor has been previously identified in gefitinib as well. The phase III studies in gefitinib and erlotinib strongly suggest that proper patient selection is the key to success. In fact in the subset analysis of the two phase III studies, the overall survival in the treatment group and placebo group is very similar for smoker. Besides clinical history, the use of laboratory response predictors such as specific oncogene mutation or EGFR subtype mutation have been actively explored which will ultimately leads to better patient selection for treatment.
Besides EGFR, vascular endothelial growth factor (VEGF) is another important target. The growth of tumour must be accompanied by the growth of blood vessels in order to maintain oxygen and nutrition supplies to cancer cells. The stimulation of vascular growth by tumour cell has been noticed as early as in the 1930s. Bevacizumab is a VEGF inhibitor and its anti-tumour activity has been well demonstrated in phase III clinical trials.

Certainly more targeted therapy agents are coming through new researches and the prospect is promising. However the cost of targeted therapy is also high. The monthly cost for gefitinib and erlotinib is $14000 and $18000 respectively in this locality. Moreover these two drugs have to be administered every day indefinitely until disease progression. Fortunately, or unfortunately, a minority of patients’ disease may be controlled with the medication for more than 1 year. The financial burden can be huge. A solution to this financial and ethical problem is urgently needed.

Conclusion

Hormonal therapy and targeted therapy are two important treatment modalities in advanced cancer patients. With proper patient selection by clinical history and laboratory means, the two treatments can effectively palliate patient’s symptom as well as prolong survival. In general, their adverse effects are tolerable even in patients with poor performance status. High treatment cost in targeted therapy is a major obstacle.

Table 1

<table>
<thead>
<tr>
<th>Types</th>
<th>Name</th>
<th>Trade Name</th>
<th>Target/Mechanism</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Small Molecules</td>
<td>Imatinib (STI-571)</td>
<td>Gleevec</td>
<td>TK bcr-abl</td>
<td>CML</td>
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<td>Iressa</td>
<td>TK Her1 (ErbB-1)</td>
<td>NSCLC</td>
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<td></td>
<td>Bortezomib</td>
<td>Velcade</td>
<td>Proteosome</td>
<td>MM</td>
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<td>Monoclonal Antibodies</td>
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<td>CD20, antibody-dependent</td>
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<td>Trastuzumab (anti-HER2)</td>
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<td>cellular cytotoxicity &amp; complement-mediated cytotoxicity</td>
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References


