To Optimise Myeloma Treatment in the Era of Targeted Therapy

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Multiple myeloma is a cancer with multifocal proliferation of plasma cells in the bone marrow. Plasma cells are important in normal immune defence because of its ability to produce immunoglobulin, which is responsible for defence against offensive microorganisms. Patients with myeloma often present with bone pain, fractures and high blood calcium levels, resulting in impairment of kidney function, anaemia and infection.

Diagnosis of myeloma is based on the demonstration of excessive (>10%) plasma cells in the marrow, presence of monoclonal gammopathy and lytic bone lesions on X-ray. The disease is incurable, mainly due to the low complete remission (CR) rate (used to be in the region of 5%). Therefore, the main goal of treatment used to be symptomatic relief. This has been achieved with combination chemotherapy with melphalan and prednisolone. (Figure 1)

Pathogenesis involves immortalisation of a post-germinal centre B-lymphocyte, which homes to the bone marrow. Upon interaction with the marrow stroma, a paracrine cytokine loop involving IL-6 and IGF1 is triggered, which confers survival and proliferative advantage to the neoplastic plasma cell. At this stage, clinically the disease manifests as monoclonal gammopathy of unknown significance (MGUS), which transforms into clinically myeloma at the rate of 1% per year. At the early stage, myeloma plasma cells rely on the marrow micro-environment for its survival. However, upon acquisition of secondary genetic alterations or mutations including FGFR3 mutation, secondary translocations involving MYC, etc, the myeloma plasma cells will be able to survive in extramedullary sites and manifest as extramedullary plasmacytoma or plasma cell leukaemia. (Figure 2)

Major advances in the recent decade include the advent of autologous bone marrow transplantation and targeted therapy, which result in a much higher complete remission (CR) rate. Autologous haematopoietic stem cell transplantation (auto-HSCT) is performed after...
adequate initial control of myeloma by the use of chemotherapy that results in substantial eradication of tumour cells. This is followed by mobilisation and collection of stem cells from the patients, after which, the patients will undergo high-dose chemotherapy, and then infusion of stem cells collected earlier on, which is the essence of auto-HSCT). Targeted therapy (including bortezomib, thalidomide or lenalidomide) enables effective killing of myeloma tumour cells, and hence results in a high CR rate in particular those with bortezomib-containing regimens. Moreover, unlike chemotherapy, targeted therapy is not toxic to the marrow, and hence can be used in both young and old patients alike. Finally, initial control of myeloma can be substantially increased by the combination of targeted therapy together with chemotherapy. Therefore, targeted therapy alone may result in a CR rate of about 20%. The use of auto-BMT results in an additional CR rate of 20%-%. Therefore, the CR rate will be increased to up to 50% if myeloma patients are treated with targeted therapy initially, followed by auto-HSCT.

In Hong Kong, we have shown in an earlier study that use of targeted therapy for initial disease control, followed by auto-HSCT, results in a CR rate of 48% (compared with 5% in the past). Moreover, 75% of patients survive at 4 years from diagnosis, compared with 40% for myeloma patients not receiving targeted therapy or auto-BMT. One important finding from this study was that this CR rate (48%) and overall survival (75% at 4 years) were comparable to large studies in the US and UK while only 52% patients required the use of the expensive targeted therapy, bortezomib. Therefore, it is a strategy potentially able to maintain a high CR rate and favourable survival with a much lower cost.

Finally, there is substantial evidence that targeted therapy may overcome the adverse impact of high-risk cytogenetic alterations including deletions of chromosome 13, i.e. del(13), or the short arm of chromosome 17, i.e. del(17p), and reciprocal translocations between chromosomes 4 and 14, t(4;14) or translocations between chromosomes 14 and 16, t(14;16). (Figure 3) Patients carrying these chromosomal alterations have a low CR rate and a poor survival because of more drug resistant cases and more frequent relapse of disease. Therefore, targeted therapy will be an important component of therapy for myeloma patients carrying high-risk cytogenetic features. For instance, in a French randomised controlled trial in which newly diagnosed myeloma patients were randomised to receive the conventional combinational chemotherapy regimen, VAD (vincristine, Adriamycin and dexamethasone), or targeted therapy, bortezomib and dexamethasone (velcade/dexamethasone), it was shown that bortezomib/dexamethasone treated patients had similar CR rates and survivals in patients with or without del(13) or t(4;14)/t(14;16). On the other hand, in patients randomised to receive velcade/dexamethasone only, the CR rate and survival of patients carrying these high-risk chromosomal alterations were much inferior to those without. These finding testify that the incorporation of targeted therapy had overcome the adverse impact of these high risk chromosomal alterations in myeloma, and hence is particularly important as a frontline therapy in myeloma patients with high-risk chromosomal aberrations.

In Hong Kong, as bortezomib is an expensive drug, in order to make judicious use of it and maximise its clinical benefit, one possible way is to risk-stratify the patients. Therefore, bortezomib should be used as a frontline therapy in myeloma patients carrying these high-risk chromosomal aberrations including del(13), t(4;14) or (14;16). However, to execute this cost-effective treatment approach, there are several hurdles to further improve myeloma treatment in Hong Kong at present. First, the high-risk cytogenetic alterations can only be detected by a special technique called Fluorescent In-situ Hybridisation (FISH), which is an expensive test currently unavailable for myeloma patients in HA hospitals. Secondly, frontline use of targeted therapy, especially bortezomib, which is approved y the FDA for frontline treatment of myeloma, is not possible in the HA setting yet. Therefore, it will be important to make the FISH test available for myeloma patients. As targeted therapy has been shown to overcome the adverse prognostic impact of the high-risk cytogenetic alterations, it is important to treat these patients with frontline bortezomib-containing regimens, followed by auto-HSCT in those transplant-eligible patients. With the current financial constraints, judicious frontline use of targeted therapy with bortezomib-based regimens in high-risk myeloma patients does not only benefit the patients (as it increases the CR rate, and also reduces risk of relapse, and hence improves the quality-of-life of patients) but will also be cost-effective from the healthcare financing perspective as these “high-risk” myeloma patients are the ones who will progress/relapse quickly and require frequent hospital admissions for further disease and symptomatic control. Frontline use of bortezomib-based regimens in myeloma patients with high-risk cytogenetic features will translate into reduced hospital admissions and hence less hospital expenditure. Therefore, despite that myeloma is an incurable disease, significant advances have been made. Moreover, judicious frontline application of bortezomib-based therapy will be a cost-effective approach, and hence, the FISH test should be made freely available to all myeloma patients in the HA setting.

In addition, advances are being developed or actively sought in diagnostic techniques and imaging. To address developments in these different sectors, the Hong Kong Society of Myeloma has been established in March, 2010 to arouse public awareness of the disease,
educate oncologists about latest advances in myeloma, and improve patient care in the whole of Hong Kong. In summary, to make judicious use of expensive targeted drugs in myeloma, it is important to make FISH test available to all myeloma patients, and bortezomib-based therapy should be used upfront in those carrying high-risk chromosomal aberrations such as del(13), t(4;14) and t(14;20).

References