New hope for relapsed and refractory multiple myeloma

Myeloma remains an incurable neoplasm despite the development of novel classes of drugs that have greatly prolonged survival of patients over the past 10 years. Patients with advanced refractory or relapsed and refractory myeloma who do not benefit from these newly developed proteasome inhibitors or immunomodulatory drugs have a median overall survival of only 9 months; this period is an important historical reference to improve for future drug development for patients with refractory or relapsed and refractory myeloma. Thus, the need persists for the development of new antmyeloma drugs.

Current preclinical and drug development research focuses on either developing more next-generation proteasome inhibitors and immunomodulatory drugs—known for their potent activity in myeloma—or seeks to discover new classes of agents such as monoclonal antibodies. Progress in myeloma research has been rapid; however, the period from the discovery of a drug until it becomes available for use in patients can be many years. Myeloma is a disease of elderly people, and so the wellbeing of patients is a key consideration in balancing between safety profiles and ability to control the disease. Furthermore, prolonged survival with myeloma implies the need to repeatedly control tumour cells because each time an individual relapses neoplastic cells develop increased drug resistance. Consequently, novel drugs are needed both to overcome resistance to previous treatment in relapsed patients, and to maintain a class effect. Moreover, patients with either refractory, advanced, or end-stage myeloma are more fragile and at risk of developing severe complications compared with those at earlier relapse and thus new agents need improved tolerability.

Pomalidomide, an immunomodulatory thalidomide analogue, is a promising antmyeloma agent with encouraging responses in patients with refractory or relapsed and refractory myeloma. Pomalidomide has a potent antmyeloma activity in vitro and in vivo, acting both directly on myeloma cells and on the marrow microenvironment.4 In recent studies, pomalidomide has shown clinical efficacy in lenalidomide and bortezomib refractory or relapsed and refractory myeloma, but has yet to show superiority over existing standards of care in patients with end-stage or relapsed and refractory myeloma.

In The Lancet Oncology, Jesus San Miguel and colleagues have presented results from a multicentre, open-label, randomised phase 3 trial of the combination of pomalidomide plus low-dose dexamethasone compared with high-dose dexamethasone alone, one of the standards of care in refractory or relapsed and refractory myeloma at the time the study was initiated. The trial enrolled 455 patients with at least two previous treatments who had failed both prior bortezomib and lenalidomide. Patients in the pomalidomide plus low-dose dexamethasone group had significantly longer median overall survival times than did those treated with high-dose dexamethasone alone (12.7 months [95% CI 10.4–15.5] vs 8.1 months [6.9–10.8]; p=0.0285). Moreover, 95 (31%) of 302 patients in the pomalidomide plus low-dose dexamethasone group achieved a partial response or better. These data are similar to those of previous phase 1 and 2 studies. Importantly, pomalidomide plus low-dose dexamethasone significantly prolonged survival endpoints despite 50% of patients assigned to the control group also receiving pomalidomide after the recommended unmasking of pomalidomide on the quality of life will be described in a subsequent report, but it seems logical to assume that the combination was generally well-tolerated. The effect of pomalidomide on the quality of life will be described in a subsequent report, but it seems logical to assume that the oral availability of pomalidomide, rapid onset of response, increased depth of response and prolonged survival will improve the quality of life of patients with refractory or relapsed and refractory myeloma. Moreover, although the dose modification definition of pomalidomide according to the creatinine clearance is still ongoing, preliminary reports suggest it might not be necessary to modify the dose of pomalidomide in renal insufficiency. This is an important consideration because patients with advanced myeloma frequently have renal insufficiency that often requires a dose adaptation for many drugs.
Questions remain about how to build on these findings and improve further the benefit to patients who have refractory or relapsed and refractory myeloma. Several triplet pomalidomide-based studies are being done, and, although still preliminary, the results seem positive. Pomalidomide can be used in combination with almost all existing antimyeloma drugs because of its favourable safety profile. One might also consider moving pomalidomide earlier in the relapse setting, to first relapse, for example, after lenalidomide for first-line treatment or to consolidation or maintenance if lenalidomide failed as an induction regimen. The potent immunomodulatory activity of pomalidomide also makes it an ideal candidate to use in immunotherapeutic regimens.

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I have received honoraria for lectures and consultancy from Celgene, Janssen, LeoPharma, Sanofi, Amgen, Novartis, and Onyx.

Multigene assays for late recurrence of breast cancer

Worldwide, each year, oestrogen-receptor-positive breast cancer accounts for more than two-thirds of breast cancer cases. In women with this type of disease, more than half of recurrences occur more than 5 years after diagnosis (late recurrence).1 Tumour characteristics such as positive nodal status and increased tumour size have been associated with increased risk of late recurrence.2

In The Lancet Oncology, Dennis Sgroi and colleagues3 report the results of their study that compared three assays for their ability to predict early and late recurrences in 665 women with oestrogen-receptor-positive, node-negative breast cancer given either tamoxifen or anastrozole monotherapy in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial. Two of the assays were multigene assays—the breast-cancer index (BCI) and the 21-gene Oncotype DX recurrence score—and the third was IHC4, a score based on four protein markers detected by immunohistochemistry. After adjustment for tumour size, histological grade, age, and treatment (clinical treatment score), all three assays provided independent information for early recurrence, whereas only BCI, using a linear combination of its component variables, did so for late recurrence. Although the addition of BCI improved the performance of the clinical treatment score, the treatment score already provided most of the information for the risk of late recurrence. The proportion of patients who had a distant recurrence at 10 years in the low-risk groups identified by each assay were 4·8% for BCI, 6·5% for the 21-gene recurrence score, and 6·2% for IHC4, with around 60% of patients classified as low risk by all three signatures.

So, is the BCI test ready for prime time in treatment decision making for women who have undergone 5 years of hormonal therapy? The answer is yes. In analyses of archived samples from two prospective trials, the test was shown to refine prognosis beyond the clinicopathological characteristics for late recurrence (up to 10 years from initial breast cancer diagnosis) in postmenopausal patients with oestrogen-receptor-positive, node-negative breast cancer who had undergone 5 years of...