outlook

The screening imperative

There is enough evidence to begin testing, and treating, people at high risk of multiple myeloma much earlier, says S. Vincent Rajkumar.

Despite multiple therapeutic advances, almost all people with multiple myeloma eventually become resistant to treatment and die of the disease. The lack of a potentially curative treatment means that myeloma has a tremendous personal and societal burden owing to shortened life expectancy, reduced quality of life and the cost of care. But multiple myeloma is always preceded by a premalignant condition, called monoclonal gammopathy of undetermined significance (MGUS), characterized by the presence of an abnormal monoclonal immunoglobulin protein in the blood, and sometimes by a precursor condition called smouldering multiple myeloma, that can be present for many years prior to diagnosis. Researchers now think that multiple myeloma is difficult to treat because physicians have conventionally delayed therapy until end-organ damage, which in myeloma consists of bone destruction, anaemia and renal failure, is detected. It is time to start systematically screening for, and treating, early-stage multiple myeloma in the groups of people at the highest risk, so that we can provide them with the best chance of long-term remission.

Smouldering myeloma is a clinically defined entity that falls between MGUS and multiple myeloma in the disease spectrum. It is associated with a higher tumour burden compared with MGUS, and, unlike MGUS, in which the risk of progression is too low (1% per year) to justify most interventions, the risk of progression in smouldering myeloma is high (typically 10% per year). Using simple biomarkers, researchers can now identify a subset of people with smouldering myeloma who have a 25% risk per year of progression, and in whom early therapy can be particularly beneficial. In fact, scientists now have data that show that early intervention can delay organ damage and prolong the life of people in this group. In a randomized trial conducted in Spain, early therapy for high-risk smouldering myeloma with lenalidomide and the steroid dexamethasone was found to improve progression-free and overall survival[1]. And a randomized trial in the United States found that early therapy with lenalidomide alone can delay time to organ damage in people with high-risk smouldering myeloma[2].

Although data show that early therapy is beneficial in smouldering myeloma, and might be an important prerequisite for finding an effective treatment, currently smouldering myeloma is diagnosed only when a monoclonal protein is incidentally discovered during tests for unrelated symptoms. Without widespread screening, only a small proportion of people with myeloma will be diagnosed at the smouldering stage. This presents a difficult dilemma. The promise of early intervention can be realized only by the systematic identification of people at high risk through screening, but just a subset of people will actually benefit from early treatment. So who should be screened?

Screening for MGUS is not advocated because the risk of progression is too low, and therapy has not been shown to be effective. A randomized trial in Iceland is investigating whether population-based screening for MGUS is beneficial, but results will take many years to arrive. Screening to detect multiple myeloma at its smouldering stage, however, is justifiable now, because early therapy has been shown to provide clinical benefit – but only in populations in which the prevalence of multiple myeloma is particularly high. There are two such populations: Black people and immediate relatives of people with multiple myeloma.

Multiple myeloma is twice as common in Black people as in white people, with an even greater disparity in younger age groups. In two large studies[3,4], we have determined that the higher risk of multiple myeloma in Black people is because of a two- to threefold higher risk of MGUS, rather than an increase in the risk of progression of MGUS to multiple myeloma. We also have compelling preliminary data that suggest MGUS starts at a much earlier age in Black people than in white people. Similarly, multiple myeloma and its premalignant precursor stages are also more common in immediate relatives of someone with the disease. These are the populations in which screening for multiple myeloma would be most helpful.

Until now, the benefits of early intervention were unclear, and physicians were satisfied with the serendipitous identification of smouldering myeloma. But this is no longer the case. A passive approach can not be justified when data are available on the benefits of early therapy in people with high-risk smouldering myeloma. The main risks of screening for early-stage multiple myeloma are the psychological impact of the diagnosis on quality of life, the cost of follow-up and the risk and inconvenience of bone-marrow tests. An efficient strategy is to initiate screening for early-stage multiple myeloma in just two specific high-risk populations: Black people over the age of 50 with one or more relatives with the disease, and people of other ethnicities over the age of 50 who have two or more relatives with the disease. In these populations, evidence suggests that up to 25% could have MGUS, and the potential risks of screening are probably outweighed by the benefits of early detection of high-risk smouldering myeloma and the availability of interventions that have been shown to delay organ damage and improve overall survival. This risk-adapted strategy protects people at high risk while we wait for evidence of the benefit of screening from randomized controlled trials for everyone else.

"A passive approach can not be justified when data are available on the benefits of early therapy."

S. Vincent Rajkumar is a multiple-myeloma specialist at the Mayo Clinic in Rochester, Minnesota.
e-mail: rajkumar.vincent@mayo.edu

1. Mateos, M.-V. *et al. N. Engl. J. Med.* **369**, 438–447 (2013).
2. Lonial, S. *et al. J. Clin. Oncol.* **38**, 1126–1137 (2020).
3. Landgren, O. *et al. Blood Cancer J.* **7**, e618 (2017).
4. Landgren, O. *et al. Leukemia* **28**, 1537–1542 (2014).