clone essentially rules out inherited conditions, as this is a marker of acquired disease.[15] Accordingly, in patients found to have a PNH clone by flow cytometry, none had a germline mutation. Thus, it remains unclear as to whether gene panels will be useful, especially in patients beyond their second decade of life, and particularly if they have a PNH clone.

Another potential benefit of targeted gene panels may relate to HSCT donor selection. As the use of alternative donor sources (matched unrelated donors, haploidentical donors, and cord blood) increases, we need assurances that we are not transplanting defective stem cells. One could argue to always use unrelated donors. However, there is ample evidence that time to treatment matters in severe pancytopenia. Thus, the use of a related donor without increased susceptibility to marrow failure would decrease the time to HSCT without having to search for an unrelated donor.

In conclusion, the study by Keel and colleagues is an important first step in helping to define the incidence and clinical importance of germline mutations in young patients with severe bone marrow failure. Future prospective studies and improved technology are needed before a more widespread application of targeted gene panels and/or genome sequencing can be recommended in routine clinical practice.

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Autotransplants in older multiple myeloma patients: hype or hope in the era of novel agents?

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doi:10.3324/haematol.2016.154807

Multiple myeloma (MM) is a malignant disease characterized by the proliferation of clonal plasma cells (PCs) in the bone marrow (BM), and typically accompanied by the secretion of monoclonal immunoglobulins that are detectable in the serum and/or urine. Increased understanding of the genetic alterations, the interactions between malignant PCs and the BM niche and their role in disease progression and the acquisition of therapy resistance, has helped in the development of novel agents, used in combination with cytostatic therapy, including autologous stem cell transplantation (ASCT). The most common indication for ASCT in Europe and the United States is MM, nevertheless elderly patients are often excluded from ASCTs, due to the patients' and/or physicians' choices, subjectivity towards its effectiveness in older cohorts, large prospective studies mostly lacking in elderly cohorts, the effectiveness and broad availability of novel agents and the fear of transplant-related toxicity.[1,2]

The median age of MM patients at diagnosis is approximately 70 years, with 60% aged 65 or older and ~30% being older than 75 years. The transplant age cutoff has been proposed to be <70 years. In clinical trials for ASCT, the age cutoff is even lower, and commonly 65 years, even if the feasibility of ASCT is established as being up to the

age of 70-75 years in fit patients.[3–5] This age cutoff is unfortunate, since many elderly patients are excluded from ASCT, albeit this population is largely increasing: the percentage of Europeans aged >65 years is projected to amplify from 85 million in 2008 to 151 million in 2060, urging us to designate therapy protocols for elderly cohorts.[5]

ASCT in younger patients, ≤65 years of age, has shown superiority compared to novel agent-based standard treatment: in 2014, the GIMEMA study group reported improved time to next treatment, progression-free survival (PFS) and overall survival (OS) of tandem melphalan 200mg/m^2 (MEL200) with ASCT *vs*. 6 cycles of melphalan-prednisone (MP) with lenalidomide (MPR). PFS was improved by 20 months (median PFS 43 *vs.* 22.4 months, HR 0.44, 95% CI 0.32-0.61, *P*<0.001) and the 4-year OS rate was 82% *vs.* 65% (HR 0.55, 95% CI 0.32-0.93, *P*=0.02), respectively.[6] A similar randomized, multicenter, phase 3 trial with ASCT *vs*. cyclophosphamide-dexamethasone-lenalidomide chemotherapy alone confirmed the benefit of ASCT.[7] Both studies tested immunomodulatory drugs (IMiDs), rather than bortezomib-based induction. As a result, preliminary results of the IFM/DFCI 2009 trial were of particular interest as they verified higher complete responses (58% *vs.* 46%, *P*<0.01), lower minimal residual disease persistence and a higher 3-year PFS rate (61% *vs*. 48%, HR 1.5, 95% CI 12-1.9, *P*<0.0002) with bortezomib, lenalidomide, dexamethasone (VRD) plus ASCT *vs.* VRD alone.[8]

Since novel agent treatment is available today, and has impressively demonstrated its superiority to MP alone, leading to FDA and EMA approval of MP-thalidomide (MPT), bortezomib-MP (VMP), MPR and lenalidomide-dexamethasone (Rd) in non-transplant eligible MM patients, the question of standard *vs.* novel agent treatment has been answered in favor of the latter in elderly patients.[1,9] Whether ASCT adds to induction in 60-70 year old patients has been marginally addressed, despite the fact that various groups have verified that ASCT is feasible and that due to novel agents (and possibly also transplants), the prognosis has improved: the Mayo Clinic grouped 1038 patients into two 5-year periods by diagnosis; the median OS for patients in the 2001-2005 cohort *vs.* the 2006-2010 cohort was 4.6 *vs*. 6.1 years, respectively (*P*=0.002). The improvement was primarily seen among patients >65 years, where the 6-year OS strikingly improved from 31% to 56% (*P*<0.001). Only 10% of patients died during the first year compared with 16% in the earlier cohort (*P*<0.01). This improved outcome was closely linked to the use of novel agents.[10]

To thoroughly test novel agent combinations compared to standard treatment and ASCT in elderly patients, the IFM 99-06 study randomized standard MP *vs.* MPT *vs*. ASCT, whereby MEL100 conditioning was applied. This trial demonstrated that both MPT and ASCT with 'low-dose conditioning' were superior to MP alone. However, this study was hampered by the fact that the chosen dose of MEL100 made the protocol more applicable, but also reduced its efficacy.[11] Randomized trials using higher MEL140 or MEL200 conditioning have rarely been performed in elderly patients, although a pragmatic age limit of 70 has been suggested, above which a full dose of MEL200 may generally be inappropriate.[3]

The randomized multicenter study by the German Multiple Myeloma Study Group (DSMM II) in 434 patients aged 60-70 years is therefore a long awaited trial endeavor, that, before the era of novel agents, tested non-induction with short-term dexamethasone alone *vs*. 4 cycles of conventional anthracycline dexamethasone induction (mostly VAD) with tandem MEL140 conditioning.[12] The treatment duration was short with a median of 7.7 months with induction and 4.6 months without it. The median PFS on the intention-to-treat basis with induction *vs*. without was 21.4 months *vs.* 20 months (HR 1.04; 95% CI 0.84-1.28; *P*=0.36), respectively. Importantly, for patients ≥65 years of age, the outcome was not inferior to those <65 years of age. As expected, patients with low-risk cytogenetics (defined as the absence of del17p13, t(4;14) and 1q21 gains) showed a favorable OS compared to those with high-risk cytogenetics. Of note, MEL140 was associated with a tolerable safety profile and treatment-related deaths were low (1%). Remarkable features of the study were that it represented the largest prospective multicenter tandem ASCT trial in elderly patients, that MEL140 could promptly be repeated 2 months after the first ASCT, that tandem ASCT was well tolerated, with deaths occurring early with induction[10] rather than with ASCT itself (6% *vs*. 1%, respectively), and that even without novel, and at that time unavailable induction and maintenance treatment, long-term survival was achieved. An interesting subgroup of 27 patients (6.4%) were survivors in first remission at 5 years; these were characterized by the presence of low-risk cytogenetics (100%), double transplant (85%) and ISS stage I/II (70%).[12]

Despite the fact that cross-comparison of other trials and representative historical data sets is problematic, median OS in the IFM 99-06 study with MP, MPT and MEL100 was 33.2, 51.6 and 38.3 months, respectively,[11] and in the Medical Research Council (MRC) study with MP, cyclophosphamide-thalidomide-dexamethasone (CTD) *vs*. ASCT in patients >64 years 30.6, 33.2 and 53 months, respectively,[13] thus the median OS in the DSMM II trial (median follow-up: 5.2 years) of 53.4 months with induction and 55.9 months without induction is encouraging, the more so since no modern induction or maintenance treatment were available and therefore not used in this trial.[12] The paper by Straka *et al.*[12] encounters today's challenge, however, due to its enrollment from 2001 to 2006, the long follow-up until its publication and the unprecedented MM success, that non-induction or VAD induction is no longer employed, rather, highly effective induction, consolidation and maintenance approaches are employed as pre- and post-transplant strategies.[1,6,7,14,15] Thus, the MEL140 tandem ASCT back-bone of the DSMM II trial seems the most relevant today. This well-tolerated treatment element has indeed been transferred to the follow-up DSMM study testing Rd with or without tandem MEL140, followed by lenalidomide maintenance in newly diagnosed 60-75 year old symptomatic MM patients.[16]

Additional questions that the DSMM II trial could not answer were: which patients with what assessment tools are best assigned to ASCT, whether MEL140 *vs.* 200 should be used, and which induction and maintenance strategy is best in elderly patients? A much smaller French multicenter trial in ≥65 year old patients used bortezomib-

based induction, MEL140 in 18 (36%) and MEL200 in 32 (64%) patients and consolidation with either Rd or bortezomib-based treatment, confirming the safety and efficacy of ASCT as first-line treatment in elderly MM patients.[17] Although this study was not sufficiently powered to pick up differences between the two melphalan schedules, and the median follow-up, at 21 months, was shorter, the estimated PFS and OS rates at 2 years were encouraging with 76% and 88%, respectively, suggesting that MEL200 may induce superior PFS and OS rates in elderly patients. Nevertheless, since this was a non-randomized study and patients were selected (e.g., those with MEL200 were fitter and not comparable to all newly diagnosed elderly MM patients), objective, prospective and proficiently performed fitness tools might be of benefit before intensive treatment is induced, the more so, since patients and physicians fitness ratings are not as objective as defined tests and scores.[1,18,19] However, geriatric tests have been criticized as being time-consuming, and few data as yet show a correlation between geriatric assessment and clinical outcome.[5] We and others have, however, shown that one can get a straightforward score and homepage help to swiftly assess MM patients within 1-2 minutes,[18–20] which can be used before intensive therapeutic interventions, such as ASCT. This seems important, since the population of elderly patients is heterogeneous and older patients are likely to have frailties complicating their management.

For the elderly with MM, novel drugs, ASCT and advances in supportive care have increased response rates and OS in the past several years.[1,5,9,10] Present clinical research focuses on the balance between treatment efficacy and quality of life, the optimum sequencing of treatment, and how to induce long-term remission. Given the results of the DSMM II trial, ASCTs should be considered in elderly patients, if these are appropriately assessed and deemed fit for the procedure. Modern, well tolerated induction and maintenance approaches, e.g., with IMiDs and/or proteasome inhibitors, have been shown to improve PFS and OS in MM,[6,7,14,15,21] and therefore are currently used. Moreover, immunotherapy to stimulate antitumor immunity after ASCT is of particular interest, since T cell exhaustion has been identified as a distinguishing feature of relapse after ASCT.[5] The pipeline of promising new treatments raise hopes for continuous improvements, the Straka[12] and Garderet[17] trials demonstrating another essential treatment element, how this can be achieved in elderly patients.

Funding

This work is supported by the Deutsche Krebshilfe [grants 1095969 and 111424 to ME and RW]

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