Gentle yet effective combination therapy with novel agents in elderly multiple myeloma patients

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Multiple myeloma (MM) is a typical disease of the elderly and in the near future physicians will have to treat a constantly rising number of patients who are not eligible for high-dose chemotherapy and autologous stem-cell transplantation, which is the standard treatment in younger fit patients. Elderly patients have a heterogeneous capability to resist stressors, such as MM and its treatment; yet the presence of comorbidities and frailty, evaluated through the geriatric assessment, can identify a consistent portion of frail patients (about 30% in clinical trials and about 50% in "real-world" data) at higher risk of treatment-related toxicities and, as a consequence, at increased risk of disease progression and mortality (Palumbo *et al*, 2015). Thus, full-dose treatment in frail patients is often not feasible.

In Europe, two standards of care are approved in transplant-ineligible newly diagnosed MM (NDMM) patients. Four 6-week twice-weekly cycles, plus five 6-week once-weekly cycles of bortezomib in addition to melphalan-prednisone (VMP, VISTA trial) produced a median progression-free survival (PFS) of 21.7 months, a median overall survival (OS) of 56.4 months, with 15% discontinuation rate due to adverse events, particularly due to peripheral neuropathy (San Miguel *et al*, 2013). Continuous lenalidomide 25 mg on days 1-21 in 28-day cycles with dexamethasone (Rd, FIRST trial) induced a median PFS of 26 months, a median OS of 59.1 months, with 22.6% discontinuation rate (Facon *et al*, 2017). To further improve these results, the combination of bortezomib and lenalidomide has also been investigated. The SWOG-S0777 study compared intravenous bortezomib-lenalidomide-dexamethasone (VRd) vs standard Rd in NDMM patients, stratified according to the intent to transplant or not. Although VRd showed higher PFS (43 vs. 30 months, respectively; HR 0.712, 96% CI 0.56-0.906; p=0.0018) and also better OS (75 vs. 64 months, respectively, HR 0.709, 95% CI 0.524-0.959; p=0.025), no ultimate conclusions about the treatment of elderly MM patients can be drawn, since this study was not restricted to elderly patients (median age 63 years) (Durie *et al*, 2017). Furthermore, the twice weekly intravenous bortezomib administration caused a higher incidence of neurological toxic effects than in the Rd group (33% vs 11%; p<0·0001), which led to earlier treatment discontinuation (23% vs 10% during induction). Different trials showed that once-weekly bortezomib significantly reduced the incidence of severe adverse events and the rate of discontinuation due to toxicity compared with the twice-weekly schedule (Mateos *et al*, 2010; Bringhen *et al*, 2010). In addition, bortezomib administered subcutaneously showed to be as effective as the intravenous administration, combined with an improved safety profile, and very positive effect on patient quality of life (QoL) (Moreau *et al*, 2011). Similarly, lenalidomide plus low-dose dexamethasone was better tolerated than lenalidomide plus high-dose dexamethasone and proved to be even more effective (Rajkumar *et al*, 2010). In relapsed and/or refractory MM patients, reduced-dose lenalidomide (15 mg for 21 days, every 28 days) with low-dose dexamethasone was explored (Quach *et al*, 2017). Median PFS was 8.9 months and median OS was 30.5 months, not significantly different from a matched cohort of patients from the phase III MM009/MM010 trial, where standard dose lenalidomide and high-dose dexamethasone were used. On the other hand, grade 3–4 neutropenia (29% vs. 41%), infections (23% vs. 31%) and venous thromboembolism (3% vs. 13%) were reduced in the low-dose lenalidomide trial compared to the MM0009/MM010 trial.

The combination of lenalidomide and bortezomib and the feasibility of this approach in elderly MM patients is still an open question. Even with the limits of the low number of patients and the design of the trial (absence of a comparator arm and absence of a uniform maintenance treatment), the paper by O'Donnell may partly answer some questions about the safety profile and the efficacy of this combination. This modified RVD lite regimen, including lower doses of lenalidomide (15 mg

for 21 days/every 35 days) and weekly subcutaneous bortezomib, produced high response rate (86%), deep responses (very good partial response or better 66%), longer PFS (median 35.1 months) and promising OS data, with fewer toxic effects and treatment discontinuations (4%). Of note, dose modifications were needed in 78% of patients, and the authors conclude that this preventive strategy permits patients to stay longer on treatment. Such a conservative approach should be suggested, in particular, in frail patients: an initial gentler therapy may be used, and possible dose escalations may be considered in the subsequent cycles if the treatment is optimally tolerated, in the absence of significant toxicities, or in case of inadequate response. Unfortunately, in this trial, a frailty or comorbidity evaluation was not performed, therefore, the study does not completely reflects a real life population, precluding meaningful considerations for frail patients. Nevertheless, the results of this trial support the general notion that induction with a triplet is beneficial also in elderly NDMM patients and can inform decision making for frontline therapy, particularly for fit patients. VRd lite may potentially represent a new standard of care, if results will be confirmed in larger well-designed trials including appropriate age and frailty stratification. In the future, this triplet regimen will probably be further optimized with the introduction of second-generation new drugs. However, considering the high drug costs of novel agents, VRd regimen could represent a sensible/effective option for MM patients in the next years.

Conflicts of interest statement: Alessandra Larocca received honoraria from Amgen, BMS, Celgene and Janssen-Cilag. Mattia D'Agostino has no conflicts of interest. Mario Boccadoro has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, Abbvie, BMS, and research funding from Celgene, Janssen, Amgen, BMS, Mundipharma, Novartis, Sanofi.

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Bibliography

Bringhen, S., Larocca, A., Rossi, D., Cavalli, M., Genuardi, M., Ria, R., Gentili, S., Patriarca, F., Nozzoli, C., Levi, A., Guglielmelli, T., Benevolo, G., Callea, V., Rizzo, V., Cangialosi, C., Musto, P., De Rosa, L., Liberati, A.M., Grasso, M., Falcone, A.P., Evangelista, A., Cavo, M., Gaidano, G., Boccadoro, M., Palumbo, A. (2010) Efficacy and safety of once-weekly bortezomib in multiple myeloma patients. *Blood*, **116,** 4745–53.

Durie, B.G.M., Hoering, A., Abidi, M.H., Rajkumar, S.V., Epstein, J., Kahanic, S.P., Thakuri, M., Reu, F., Reynolds, C.M., Sexton, R., Orlowski, R.Z., Barlogie, B. & Dispenzieri, A. (2017) Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *The Lancet*, **389,** 519–527.

Facon, T., Dimopoulos, M.A., Dispenzieri, A., Catalano, J. V, Belch, A., Cavo, M., Pinto, A., Weisel, K., Ludwig, H., Bahlis, N.J., Banos, A., Tiab, M., Delforge, M., Cavenagh, J.D., Geraldes, C., Lee, J.-J., Chen, C., Oriol, A., De La Rubia, J., White, D., Binder, D., Lu, J., Anderson, K.C., Moreau, P., Attal, M., Perrot, A., Arnulf, B., Qiu, L., Roussel, M., Boyle, E., Manier, S., Mohty, M., Avet-Loiseau, H., Leleu, X., Ervin-Haynes, A., Chen, G., Houck, V., Benboubker, L., Hulin, C. (2018) Final analysis of survival outcomes in the randomized phase 3 FIRST trial. *Blood***, 131,** 301-310.

Mateos, M.-V., Oriol, A., Martínez-López, J., Gutiérrez, N., Teruel, A.-I., de Paz, R., García-Laraña, J., Bengoechea, E., Martín, A., Mediavilla, J.D., Palomera, L., de Arriba, F., González, Y., Hernández, J.-M., Sureda, A., Bello, J.-L., Bargay, J., Peñalver, F.-J., Ribera, J.-M., Martín-Mateos, M.-L., García-Sanz, R., Cibeira, M.T., Ramos, M.L., Vidriales, M.B., Paiva, B., Montalbán, M.A., Lahuerta, J.J., Bladé, J., Miguel, J.F. (2010) Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *The Lancet Oncology*, **11,** 934–941.

Moreau, P., Pylypenko, H., Grosicki, S., Karamanesht, I., Leleu, X., Grishunina, M., Rekhtman, G., Masliak, Z., Robak, T., Shubina, A., Arnulf, B., Kropff, M., Cavet, J., Esseltine, D.-L., Feng, H., Girgis, S., van de Velde, H., Deraedt, W. & Harousseau, J.-L. (2011) Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *The Lancet Oncology*, **12,** 431–440.

Palumbo, A., Bringhen, S., Mateos, M.-V., Larocca, A., Facon, T., Kumar, S.K., Offidani, M., McCarthy, P., Evangelista, A., Lonial, S., Zweegman, S., Musto, P., Terpos, E., Belch, A., Hajek, R., Ludwig, H., Stewart, A.K., Moreau, P., Anderson, K., Einsele, H., Durie, B.G., Dimopoulos, M.A., Landgren, O., San Miguel, J.F., Richardson, P., Sonneveld, P., Rajkumar, S.V. (2015) Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood*, **125,** 2068–2074.

Quach, H., Fernyhough, L., Henderson, R., Corbett, G., Baker, B., Browett, P., Blacklock, H., Forsyth, C., Underhill, C., Cannell, P., Trotman, J., Neylon, A., Harrison, S., Link, E., Swern, A., Cowan, L., Dimopoulos, M.A. & Miles Prince, H. (2017) Upfront lower dose lenalidomide is less toxic and does not compromise efficacy for vulnerable patients with relapsed refractory multiple myeloma: final analysis of the phase II RevLite study. *British Journal of Haematology*, **177,** 441–448.

Rajkumar, S.V., Jacobus, S., Callander, N.S., Fonseca, R., Vesole, D.H., Williams, M.E., Abonour, R., Siegel, D.S., Katz, M., Greipp, P.R. & Eastern Cooperative Oncology Group (2010) Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *The Lancet Oncology*, **11,** 29–37.

San Miguel, J.F., Schlag, R., Khuageva, N.K., Dimopoulos, M.A., Shpilberg, O., Kropff, M., Spicka, I., Petrucci, M.T., Palumbo, A., Samoilova, O.S., Dmoszynska, A., Abdulkadyrov, K.M., Delforge, M., Jiang, B., Mateos, M.-V., Anderson, K.C., Esseltine, D.-L., Liu, K., Deraedt, W., Cakana, A., van de Velde, H., Richardson, P.G. (2013) Persistent Overall Survival Benefit and No Increased Risk of Second Malignancies With Bortezomib-Melphalan-Prednisone Versus Melphalan-Prednisone in Patients With Previously Untreated Multiple Myeloma. *Journal of Clinical Oncology*, **31,** 448–455.