COST AND EFFICACY CONSIDERATIONS IN MULTIPLE MYELOMA (MM) PATIENTS (PTS)

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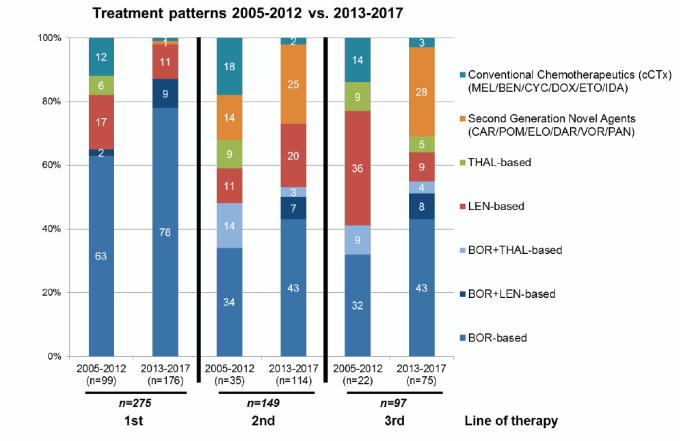
Introduction: Over the last decade MM diagnosis and therapy have greatly improved; notably due to an increasing number of "novel agents" (NA). Anti-MM-therapy has gained complexity, therefore their continuous evaluation is relevant. Analyses of chemotherapy (CTx) management, including efficacy and costs, have grown due to the numerous anti-MM treatment choices. In order to determine MM therapy sequence -therein allowing efficacy and costs- we performed data assessment of clinical practice patterns. Substance use was analyzed in view of treatment lines, changes in 2 treatment periods (2005-2012 vs. 2013-2017), "MM-pathway conformity" and costs. *Methods:* Data on therapy composition were collected for the years 2005 to 2017, separating 2 treatment periods for 1st, 2nd and 3rd-line therapy (Figure 1); the time cut-off being chosen to discriminate between NA- and non-NA-based regimens, and first generation PI- (bortezomib [BOR]), IMiD- (thalidomide [THAL], lenalidomide [LEN]) and second generation NA-use. *Results:* Pt characteristics were representative for tertiary centers; the median age was 63 years (27-89), 54% were 60-79 and 14% ≥80 years old. The ISS was predominantly advanced (II/III:62%). Pts showed substantial comorbidities and were classified as fit vs. intermediate-fit or frail according to the R-MCI in 33% and 67%, respectively. Of interest, 33% of pts could be enrolled in clinical trials (CTs) and 88% received 1st-line treatment at our center. Expectedly, numbers of pts decreased with subsequent lines of treatment, albeit the median time to 2nd-line therapy due to progression amounted to 2 years: 100% (275 pts) received 1st-line, 54% 2nd-line and 35% 3rd-line treatment (Figure 1). As depicted in Figure 1, 1st-line conventional CTx (cCTx) alone was rare and substantially declined over time from 12% 2005-2012 to 1% in 2013-2017. 73% were treated with BOR in 1st-line, 63 of 106 reinduced pts received BOR in 2nd- or 3rd-line. IMiD 2nd- and 3rd-line treatment was also common within different regimens and the combination of 2 NA increased over time. The use of second generation NA in 2nd- and 3rd-line treatment notably amplified in 2013 to 2017 in line with their approval. Our analysis also determined that 44% of second generation NA protocols were administered outside CTs, mainly due to tight CT inclusion criteria. Maintenance was performed in 57% of pts, predominantly with LEN and within DSMM CT protocols. *Conclusion:* NA combinations were used predominantly: while expectedly, BOR plays an important role in induction, LEN was subsequently used for maintenance and in outpt-regimens. A significant percentage of second generation NA was given outside CTs, displaying the fast implementation of MM-guideline care into clinical practice. Costs and efficacy results will be shown at the meeting, including via detailed review of the literature.

Conflicts of Interest (ME+RW): Educational Grants Amgen GmbH + Celgene GmbH.



PIs: BOR: Bortezomib; CAR: Carfilzomib
IMiDs: LEN: Lenalidomide; THAL: Thalidomide; POM: Pomalidomide
mAbs: ELO: Elotuzumab; DAR: Daratumumab
HDAC-inhibitors: VOR: Vorinostat; PAN: Panobinostat
cCTx: MEL: Melphalan; BEN: Bendamustine; CYC: Cyclophosphamide; DOX: Doxorubicin; ETO: Etoposide; IDA: Idarubicin

Figure 1. Clinical practice 2005-2012 vs. 2013-2017.

WHAT KIND OF TRIALS DO WE NEED IN THE FUTURE TO ADDRESS OPEN ISSUES IN NDMM? BETTER RESEARCH, BETTER IMPACT

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Therapeutic options have greatly expanded & designing clinical trials that will impact on the delivery of a new standard of care has arrived at an interesting cross road. MM is a heterogeneous disease as are the patients it affects. It is time to consider a new clinical trial research strategy that answers these questions, as this is the fundamental principles of *Better Research, Better impact*. Designing clinical studies that utilise biomarkers is the key to stratified research studies in the future. These biomarkers include determinants of host response biology (HRB), tumour molecular landscaping & response biomarkers (minimal residual disease; MRD). HRB determinants can include end-organ damage parameters, clinical scoring systems of fitness, immune system quantitation and serial markers of age-related inflammation. Less fit patients represent a substantial proportion of newly diagnosed patients requiring treatment. Whilst age does not necessarily equate to fitness to tolerate therapy nonetheless age-related inflammation is perhaps the most important physiologic correlate of the age-related frailty syndrome. Recent clinical scoring systems which are able to delineate patients into fit, unfit & frail groupings, with respective differences in PFS and OS in clinical trials have been highlighted. The clinical relevance of genomic heterogeneity in MM (copy number variances, translocations & mutational aberrations) is reflected in the fact that a significant proportion of MM patients relapse early & show short survival with current therapies. Defining these high & ultra-high risk patients at diagnosis to stratify treatment & offer the prospect of improving outcomes remains a laudable goal. Two validated molecular approaches for risk prediction widely used include genetic risk profiling [e.g. del(17p), t(4;14)] & gene expression risk profiling, [e.g. EMC92]. However, what is the most relevant clinical intervention for such higher risk patients remains to be defined. In addition, in patients without such risk factors, could they be more appropriately treated using stop/start designations such as time limited maintenance? The presence of MRD is a reproducible and independent predictor of both progression-free (PFS) and overall (OS) survival outcomes in MM. MRD is considered as a potential surrogate / intermediate end point for regulatory purposes. However, should MRD negativity not be utilized to direct treatment? Can MRD be used as a "stop/go" marker e.g. can maintenance strategies be safely withdrawn? If patients persist as MRD positive should we look to escalating on-gong therapy? Lastly, when real world databases are interrogated, it is clear that clinical studies, especially regulatory phase III studies, do not represent the patients we treat day-by-day in our clinic, equating to 40-50% of the true myeloma population. This represents a significant issue when translating the efficacy and tolerability of treatment regimens into practice as we see it. Therefore, in designing studies going forward, we need to be mindful of a number of disease and patient related determinants, realising the mantra that "one size doesn't fit all" which will inevitably allow us to deliver *Better Research, Better Impact*.

HOW TO MAKE SENSE OF THE MANY TREATMENT OPTIONS AVAILABLE AT RELAPSE ? COST/EFFICACY CONSIDERATIONS

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In the recent years, six new agents have been approved by FDA and EMA (Pomalidomide, Carfilzomib, Panobinostat, Elotuzumab, Ixazomib and Daratumumab). In relapsed Multiple Myeloma (MM), randomized studies comparing standard doublets(bortezomib-dexamethasone or lenalidomide-dexamethasone) versus triplets with the addition of one of these six agents, have all shown a significant improvement of PFS and sometimes of OS. Therefore these triplets are becoming new standards for the treatment of relapsed MM. However, all these agents are very expensive, and the cost of one month of treatment with triplets may reach 150 000 USD. In many countries, these costs are not affordable when they are not covered by public or private insurances. This situation raises the question of equal access to treatment for all patients. Even in rich countries, government policies for reducing health-care costs may induce limited prescriptions or reimbursement/ pricing delays . This question of affordability/availability is a challenge for cancer treatment in general. In MM it is becoming critical because the number of patients treated and the duration of treatments are increasing dramatically thanks to the recent therapeutic advances. There are many stakeholders who may play a role in trying