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652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 28, 2023

Gain1q in Myeloma Randomized Clinical Trials- How Is It Reported and How Does It Impact Outcomes: A Systematic Review

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Introduction:

Extra copies of chromosome 1q21 (+1q: gain=3 copies, amp=4 or more copies) have been associated with worse outcomes for patients with multiple myeloma (MM). We performed a systematic review to evaluate current reporting of +1q, efficacy of existing regimens for +1q, and prognostic implications of +1q in MM randomized controlled trials (RCTs).

Methods:

We searched three databases for MM RCTs. Our inclusion criteria were all published MM RCTs from 2012-2022. Each MM RCT was analyzed for reported data on +1q. The following features specific to +1q were collected: +1q reported or not as a high-risk cytogenetic alteration, definition of gain1q with respect to percentage of cells with abnormality detected, documentation of distinction between Gain1q and Amp1q in analysis, prevalence of +1q in enrolled population, outcomes of patients [Overall Survival (OS) and Progression Free Survival (PFS)] in patients with +1q in the experimental versus control arm and in patients with and without +1q.

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A total of 124 trials were included. Among these trials, 28 (23%) studies reported data on +1q, including 26 studies that reported data in the primary manuscript and two studies that reported in separate publication. These trials reported a total of 2692 patients with +1q which represented 25% of all the patients enrolled. Out of 28 trials, three trials (11%) specified the criteria for categorizing patients as +1q (example in IKEMA and IFM-99: the presence of at least three copies in at least 30% of analyzed plasma cells was required). Only four trials (14%) reported survival data on gain and amp separately and the remaining 24 (86%) studies reported for gain or did not specify gain vs amp. Amongst the trials that reported +1q, 22 (79%) considered this to be a high-risk cytogenetic abnormality.

Amongst trials that met primary endpoint showing improvement in PFS and clearly reported on +1q, the following drugs also improved PFS for those with +1q (when comparing hazard ratio (HR) for intervention versus control arm in the +1q subgroup): lenalidomide (len) maintenance in Myeloma XI, selinexor in BOSTON, and isatuximab in IKEMA and ICARIA.

Several trials met their endpoint and showed improvement in PFS in the +1q cohort in same direction as overall study results but had confidence intervals for +1q subgroup that crossed 1. These included addition of carfilzomib in Myeloma XI, addition of carfilzomib vs bortezomib to len and dex for +1q (but not in Amp1q) in ENDURANCE, addition of elotuzumab to pomalidomide and dex, and bortezomib-based treatment before and after autologous stem cell transplantation (auto-SCT) vs no bortezomib (Table 2).

Seven studies reported HR for patients with +1q in the trial (across both arms) compared to those without. In six studies (all studies other than SWOG1211), worse outcomes were seen with respect to OS and PFS for those with +1q versus without (Table 2).

Important interventions for which subgroup analysis of +1q was not presented in trial results, and hence conclusions about the efficacy of the drugs specifically for patients with +1q cannot be ascertained included pomalidomide and ixazomib. Although subgroup analysis of various daratumumab trials has shown improvement for high-risk MM, the effect on gain1q was not isolated. Two recent contemporary trials that isolated effect of auto-SCT (DETERMINATION and IFM-2009) did not report +1q. However, in FORTE Trial, adverse prognostic implications of +1q were not seen in the arm receiving carfilzomib, len, dex and auto-SCT, indicating a possible role of carfilzomib and auto-SCT in ameliorating the adverse prognostic implications of +1q. Although len maintenance improved PFS after auto-SCT as maintenance in Myeloma XI overall for those with +1q, it did not appear to improve PFS for patients with isolated +1q (with no other concurrent genetic abnormalities).

Conclusion:

This systematic review of MM RCTs finds considerable heterogeneity in the reporting of +1q

subgroup analysis of randomized myeloma trials. Most interventions that have shown to be successful in randomized trials and have clearly reported on the +1q subgroup have shown concordant direction of results and benefit of the applied intervention in the +1q subgroup. A more standardized approach to reporting of this abnormality is needed.

Disclosures

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Figure 1

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Table 1 Characteristics of multiple myeloma randomized clinical trials that reported +1q.

Study Characteristics	No. of studies reporting +1q (%)	No. of studies not reporting +1q (%)
Pharmaceutical company funded	11 (39)	44 (46)
Cooperative group/single-center (not pharmaceutical company)	17 (61)	52 (54)
Frontline or consolidation/maintenance	20 (71)	60 (63)
Relapsed/refractory	8 (29)	36 (37)
Multinational	12 (43)	53 (55)
Limited to a single country except the US	12 (43)	25 (26)
Limited to the US	4 (14)	18 (19)
Year 2012-2015	4 (14)	37 (39)
Year 2016-2019	11 (39)	49 (51)
Year 2020-2022	13 (47)	10 (10)

Table 2 Survival Outcomes in trials that reported separately on +1q.

Study name	Drug regimen	HR for OS (95% CI) p-value	HR for PFS (95% CI) p-value
Hazard Ratio of Intervention vs control in patients with +1q			
BOSTON	Sel, bort, and dex vs bort and dex	Amp: 0.85 (0.41-1.76) 0.33 Gain: 0.62 (0.40-0.96) nr	Amp: 0.63 (0.34-1.17) 0.07
Myeloma XI	Len maintenance	-	For all gain1q, 0.46 (0.33-0.62) 0.455 For isolated gain1q, 1.50, (0.9-2.7) 0.2
IKEMA	Isa plus car–dex vs car–dex	0.57 (0.33-0.98)	0.582 (0.368-0.932)
Myeloma XI+	cyc/thal, dex or cyc/len/dex vs cyc, car, len, dex	-	0.63 (0.38-1.06) 0.89
ENDURANCE	Addition of car vs bort to len and dex	Gain: 0.5 (0.28-0.90) 0.018 Amp: 1.56 (0.64-3.78) 0.32	Gain: 0.75 (0.49-1.14) 0.17 Amp:1.46 (0.73-2.92) 0.281
Myeloma XI	Addition of vorinostat to len maintenance	1.04 (0.52-2.04) 0.445	1.2 (0.68-2.11) 0.453
ELOQUENT-3	Addition of elotuzumab to pom and dex	-	0.56 (0.29-1.09)
HOVON-65/GMMG-HD4	Bort before and after ASCT vs no bort	0.58 (0.30-1.12) 0.1	0.76 (0.48-1.18) 0.22
ICARIA	Isa plus pom and low-dose dex vs pom and low-dose dex	0.72 (0.48-1.07) 0.25	0.41 (0.2-0.7) 0.137
Hazard Ratio of Patients with +1q (in all arms of trial) vs no +1q			
HOVON87/NMSG18	Mel, pred, and len/thal	1.63 (1.13-2.35) 0.01	1.42 (1.1-1.83) 0.007
ENDURANCE	Car/bort with len and dex	Gain: 1.4 (nr) 0.133 Amp: 1.78 (nr) 0.018	Gain: 1.46 (nr) 0.003 Amp: 1.8 (nr) 0.001
IFM-99	Thal maintenance	2.00 (1.56-2.58) 0.001	1.42 (1.15-1.75) 0.001
HOVON-65/GMMG-HD4	Bort before and ASCT vs standard treatment without bort	Combined gain/amp: 1.9 (1.2-2.9) 0.0052 Gain: 1.66 (nr) 0.0319 Amp: 3.95 (nr) 0.0009	Combined gain/amp: 1.7 (1.3-2.3) 0.0002 Gain: 1.65 (nr) 0.0010 Amp: 2.48 (nr) 0.0062
FORTE	Three arm trial respectively: first arm receiving car, len and dex with auto-SCT, second receiving car, cyc and dex with auto-SCT, and third receiving car-len-dex without auto-SCT. A second randomization then done for maintenance with car plus len or len alone	Gain: 1.88 (0.98-3.58) 0.056 Amp: 5.88 (3.1-11.17) <0.001	Gain :1.65 (1.14-2.37) 0.007 Amp: 3.04 (1.99-4.65) <0.001
Myeloma IX	Cyc, vincristine, dox and dex or cyc, thal and dex, followed by mel with ASCT vs either mel and pred or cyc, thal and dex	1.53 (1.20-1.94) 0.001	1.46 (1.21-1.76) <0.001
SWOG-1211	Bort, len, and dex with or without elotuzumab	0.776 (0.388, 1.552)	0.761 (0.459, 1.261)

Abbreviations: HR: hazard ratio, OS: overall survival, PFS: progression free survival, CI: confidence interval, sel: selinexor, bort: bortezomib, dex: dexamethasone, len: lenalidomide, car: carfilzomib, Isa: isatuximab, cyc: cyclophosphamide, vin: vincristine, dox: doxorubicin, thal: thalidomide, pom: pomalidomide, ASCT: autologous stem cell transplantation, pred: prednisone, mel: melphalan, nr: not reported

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