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ORAL ABSTRACTS

654.MULTIPLE MYELOMA: PHARMACOLOGIC THERAPIES

Final Analysis of the Randomised UK MRA Myeloma XI+ Trial Examining Krdc (carfilzomib, lenalidomide, dexamethasone and cyclophosphamide) As Induction Therapy for Newly Diagnosed Multiple Myeloma Patients

Charlotte Pawlyn, PhD[1,2], Faith E Davies, MD[3], Martin F Kaiser, MD[2,1], Ruth M de Tute, MSc,PhDFRCPath[4], Heather McIntyre[5], Jeanine Richards[5], Sharon Jackson[5], Elizabeth Hodson[5], Anna Hockaday[5], Catherine Olivier[5], John R Jones[6,7,8], Matthew W. Jenner[9], Gordon Cook, PhD DSc[10], Walter Martin Gregory, PhD[5], Mark Drayson[11], Roger G Owen, MD MRCP, FRCPath[4], Gareth Morgan, MD, PhD[3], David A. Cairns, PhD[10], Graham Jackson, MD[12]

[1] The Institute of Cancer Research, London, United Kingdom
[2] The Royal Marsden NHS Foundation Trust, London, United Kingdom
[3] Perlmutter Cancer Center, Multiple Myeloma Research Program, NYU Langone Health, New York, NY
[4] HMDS, Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom
[5] Leeds Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom
[6] Kings College Hospital, London, United Kingdom
[7] Brighton and Sussex Medical School, Brighton, United Kingdom
[8] East Sussex NHS Trust, Eastbourne, United Kingdom
[9] University Hospital Southampton, Southampton, United Kingdom
[10] Cancer Research UK Clinical Trials Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, United Kingdom
[11] University of Birmingham, Institute of Immunology and Immunotherapy, Birmingham, United Kingdom
[12] University of Newcastle, Department of Haematology, Newcastle, United Kingdom

Introduction

The UKMRA/NCRI Myeloma XI+ phase III randomized trial for NDMM patients compared intensified induction with a carfilzomib containing quadruplet (KRdc) vs a response-adapted approach of sequential triplet therapies. An interim analysis at a median of 35 months follow-up demonstrated a significant improvement in progression-free survival in the KRdc group (HR 0.63, 95% CI 0.51, 0.76, p <0.001). Here we present updated analysis after a median 102 months of follow up, including analysis of the co-primary endpoint overall survival.

Methods

Using an adaptive trial design the Myeloma XI trial, which initially randomized patients between CRd and CTd, was amended to randomly assign patients 2:1:1 between KRdc, CRd and CTd (Myeloma XI+). KRdc was given in 28 day cycles (carfilzomib (K) 36mg/m^2 IV d1-2, 8-9,15-16 (20mg/m^2 #1d1-2), lenalidomide (R) 25mg PO d1-21, dexamethasone (d) 40mg PO d1-4,8-9,15-16, cyclophosphamide (C) 500mg PO d1,8), CRd (28d, C 500mg PO d1,8, R 25mg PO d1-21, D 40mg PO d1-4, 12-15) and CTd (21d, C 500mg PO d1,8,15 thalidomide 100-200mg PO daily, D 40mg PO d1-4,12-15). Induction regimens were continued for a minimum of 4 cycles and to maximum response. Suboptimal responders (MR/PR) to CTd/CRd were randomized between pre-transplant intensification with a proteasome inhibitor (bortezomib, CVD) containing triplet or no further therapy prior to ASCT, patients with refractory disease (SD/PD) all received CVD. For all patients a maintenance randomization post ASCT compared lenalidomide to observation. Centrally analysed cytogenetic data was available for a representative subset of patients. High-risk (HiR) was defined as presence of t(4;14), t(14;16), t(14;20), del(17p) or gain(1q) and ultra-high risk (UHiR) the presence of more than one lesion. MRD assessment was performed using next generation flow with a median sensitivity of 2x10^{-5}.

Results

1056 patients underwent induction randomization, allocated to KRdc n=526, CTd n=265 and CRd n=265. The groups were well matched for baseline variables with median age 61 (range 33-75). No change in the toxicity profile emerged with long-term follow up.

KRdc was associated with a significantly longer median PFS than triplet therapy, KRdc 56 vs CTd/CRd 37 months (HR 0.69, 95%CI 0.60, 0.80, p<0.001). Improved PFS was seen in all cytogenetic risk groups: SR median KRdc 64 vs CTd/CRd 42m (HR

0.71, 95%CI 0.51, 1.00), HiR 45 vs 36m (HR 0.70, 95%CI 0.47, 1.03), UHiR 34 vs 20m (HR 0.49, 95%CI 0.21, 1.12). MRD negativity was achieved in 26.9% of those tested at the end of induction (KRdc 38.5% vs CRd 16.3% vs CTd 10.8%) and in 47.7% after ASCT (KRdc 57.0%, CRd 36.7%, CTd 37.7%). MRD negative status was associated with improved PFS with all regimens and KRdc was associated with improved outcomes compared to CRd/CTd even in those achieving MRD negativity. Early achievement of MRD negativity with KRdc (after induction) was associated with improved PFS compared to those who achieved MRD- after ASCT.

Analysis of OS for contemporaneously randomised patients was numerically longer with KRdc vs CTd/CRd (OS at 60 months 76% vs 71%, HR 0.87, 95%CI 0.72, 1.06, p=0.168). As the trial closed prior to the planned event-driven analysis (419/466 of required contemporary deaths) due to funding constraints, resulting in some loss of power for the OS analysis, an additional OS analysis was performed incorporating all patients randomised across the study (KRdc n=526, CTd n=1021, CRd n=1021) with appropriate adjustment for temporal changes in the control group. These data suggested KRdc significantly prolonged OS compared to CTd/CRd (OS at 60 months 76% vs 68%; HR 0.80, 95%CI 0.67, 0.95, p=0.011). The greatest OS benefit was seen in patient with ISS stage 3 and HiR/UHiR disease. PFS and OS results were consistent when an optimal control group (i.e. excluding those randomised to no CVD if PR/MR) was used.

Conclusions

The addition of carfilzomib to an immunomodulatory agent, dexamethasone and cyclophosphamide triplet was associated with deeper responses and a significantly longer PFS. OS was significantly improved when including non-contemporaneous controls, adjusted for temporal trends. This suggests a clinically significant improvement in overall survival and emphasises the importance of early combination of PI and IMID therapy rather than a response adapted approach, with particular benefit in patients with aggressive disease defined as HiR or UHiR.

Disclosures Pawlyn: *Abbvie:* Honoraria; *GSK:* Honoraria; *Janssen:* Honoraria; *Pfizer:* Honoraria; *BMS/Celgene:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *iTEOS Therapeutics:* Honoraria; *Menarini Stemline:* Honoraria; *Sanofi:* Honoraria. **Davies:** *Takeda:* Other; *Janssen:* Other; *Regeneron:* Other; *GSK:* Other; *Sanofi:* Other; *AbbVie:* Other; *Bristol Myers Squibb:* Other. **Kaiser:** *GSK:* Consultancy; *Pfizer:* Consultancy, Honoraria; *J&J/Janssen:* Consultancy, Honoraria, Research Funding; *Roche:* Consultancy; *Pfizer:* Consultancy, Honoraria; *BMS/Celgene:* Consultancy, Honoraria, Research Funding; *Sanofi:* Consultancy; *Regeneron:* Consultancy; *Poolbeg:* Consultancy, Honoraria. **Cook:** *Celgene:* Research Funding; *Janssen:* Consultancy, Research Funding; *Amgen:* Consultancy, Speakers Bureau; *Bristol Myers Squibb:* Consultancy, Honoraria; *Janssen-Cilag:* Honoraria, Speakers Bureau; *Takeda:* Consultancy, Honoraria, Research Funding, Speakers Bureau. **Drayson:** *Abingdon:* Current equity holder in publicly-traded company. **Morgan:** *Janssen:* Speakers Bureau.

Off Label Disclosure: Carfilzomib for newly diagnosed myeloma patients

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