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Safety and efficacy of a combination therapy with Revlimid, Adriamycin and dexamethasone (RAD) in relapsed/refractory multiple myeloma (MM): a single-centre experience

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Abstract: Despite therapeutic milestones achieved, the optimal therapy of relapsed/refractory MM remains controversial. Treatment options have increased over the last few years, especially with the availability of novel agents for routine care and within clinical trials. Lenalidomide is an oral immunomodulatory drug with significant activity in this setting and has been approved by EMEA in association with Dexamethasone for the treatment of patients with at least one prior therapy. To improve response rate and long term outcome of relapsed/refractory MM patients, new Lenalidomide combinations are investigated with promising results. Knopp et al recently reported that RAD association induces substantial and durable remission rate with an acceptable toxicity profile in pretreated MM patients.

However, in their schedule Adriamycin was given as continuous infusion over 96 hours, necessitating of patients hospitalization and sometimes a CVC insertion. A modification of Knopp RAD regimen, including Adriamycin as a bolus single dose, days 1,4, was proposed to facilitate the administration in the out patient setting.

Response to Reviewers: According to your suggestion, I have corrected the name of the first author of original RAD paper.

Thank you.

Safety and efficacy of a combination therapy with Revlimid, Adriamycin and Dexamethasone (RAD) in Relapsed/Refractory Multiple Myeloma (MM): a single centre experience

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Dear Editor,

Despite therapeutic milestones achieved, the optimal therapy of relapsed/refractory MM remains controversial [1]. Treatment options have increased over the last few years, especially with the availability of novel agents for routine care and within clinical trials [2]. Lenalidomide is an oral immune-modulatory drug with significant activity in this setting and has been approved by EMEA in association with Dexamethasone for the treatment of patients with at least one prior therapy [3]. To improve response rate and long term outcome of relapsed/refractory MM patients, new Lenalidomide combinations are investigated with promising results [4-6]. Knop et al recently reported that RAD association induces substantial and durable remission rate with an acceptable toxicity profile in pretreated MM patients [7].

However, in their schedule Adriamycin was given as continuous infusion over 96 hours, necessitating of patients hospitalization and sometimes a CVC insertion. A modification of Knopp RAD regimen, including Adriamycin as a bolus single dose, days 1,4, was proposed to facilitate the administration in the out patient setting.

Between May and December 2008, 10 patients (4 M/6 F) with relapsed/refractory MM were planned to receive six 28 days cycles RAD.

Main pre-treatment characteristics were the following: median age 69 years (range 50-78); WHO performance status 0-3; median Hb 8.95 gr/dl (range 8.3-12.1); median B2M 4.4 mg/L (range 2.5-9.1); median bone marrow plasma cell infiltration 40% (range 5-80); median time from MM diagnosis to treatment 33 months (range 11-130). All patients had received more than two chemotherapy regimens (range 1-6). Five patients were previously treated with autologous stem cell transplantation.

RAD schedule included: Revlimid 25 mg days 1-21, Adriamycin 40 mg/m² i.v. days 1,4, Dexamethasone 40 mg p.o. days 1-4. Peg-filgrastim was administrated on day 6. Aspirin 100 mg/die was given as prophylaxis for thrombosis. The International Myeloma Working Group criteria were used for definition of response [8]; toxicity was graded according to NCI-CTC criteria. Of the 10 pts, 2 were not evaluable for response because of early withdrawal due to progression of the disease. At the end of treatment, a clinical response was observed in 7 patients (4 VGPR and 3 CR) and disease progression in 1. The best response was observed after a median of 8 weeks of treatment (range 4-12) (Table 1).

Myelotoxicity was the primarily and major side effect. Leukopenia and thrombocytopenia of grade 2 were observed in 5/8 patients while of grade 4 in 1 patient, leading to dose reduction. One patient died for infectious complication (pneumonia). Other non haematological side effects were fever (1 case), fatigue (3 cases), diarrhoea (2 cases). No relevant neurological symptoms were found. After a median follow up of 54 weeks (range 8-80) all six patients have experienced a progression of disease, requiring a new salvage therapy. Median time to progression was 16 weeks (range 12-24). In conclusion, although weakened by the small number of cases and short lived duration, these data showed that this modified RAD is feasible, well tolerated and effective in refractory/relapsed MM allowing the patients management in an out patient basis.

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Table 1. Results

pts	Age (years)	previous treatment lines	nr RAD	response	Time to best response weeks	TTP* (weeks)	FUP° (weeks)
LP	61	1	2	VGPR	4	Died in remission	8
AMM	69	2	3	PG	8	12	32
VF	74	4	6	RC	12	16	80
LC	66	3	6	VGPR	8	12	52
GS	70	3	6	RC	8	24	60
AC	78	3	6	VGPR	8	16	56
CA	76	1	5	RC	12	18	68
RM	78	7	1	VGPR	12	14	40
LT	40	1	1	PG	-	-	-
AL	54	5	1	PG	-	-	-

* time to progression

° follow up

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