

ADDING FLUDARABINE TO CYCLOPHOSPHAMIDE-DEXAMETHASON INDUCTION THERAPY IMPAIR STEM CELL HARVEST IN MM

Report from an interim analysis of the NMSG 13/03 randomized placebo controlled phase II trial.

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BACKGROUND AND OBJECTIVES Recent data have indicated that the myeloma cell hierarchy includes resistant circulating clonal memory B cells, which differ considerably from the classical end stage plasma cells infiltrating the bone marrow. The pathophysiological significance of these cells is unknown, but hypothetically they may serve as “sleeping” myeloma stem cells responsible for and “feeding” post-treatment relapse and disease progression. The impact of chemotherapy resistant B cells in MM needs to be evaluated by in vivo targeted therapy. A previous open phase II pilot study has indicated that addition of the DNA repair inhibitor Fludarabine to induction therapy (VAD) was clinical feasible with only minor toxicity. A beneficial outcome was suggested including a reduction of MRD following the addition of Fludarabine. Here we report the conclusions from the subsequent phase II randomized, placebo controlled trial with the main objective to generate data on toxicity, safety and efficacy by adding Fludarabine to the induction with Cyclophosphamid plus Dexamethason.

DESIGN AND METHODS This was a randomized, placebo controlled, single blinded, phase II study evaluating toxicity and safety of Fludarabine added to Cyclophosphamide and Dexamethasone (CyDex) as induction therapy in younger patients with untreated and treatment demanding newly diagnosed multiple myeloma. The treatment regimen CyDex as standard induction therapy was documented in NMSG trial #11/01.

Patients were randomized at diagnosis either to CyDex + Placebo (control Arm A) or CyDex + Fludarabine (experimental Arm B). See Figure 1.

Arm A (Conventional arm): CyDex + placebo, two (three) cycles of CyDex: Cyclophosphamide 1000 mg/m² IV day 1 and Dexamethasone 40 mg/day PO on day 1 to 4, and 9 to 12 + placebo PO; repeated once day 21.

Arm B (Experimental arm): CyDex plus Fludarabine, two (three) cycles of CyDex: Cyclophosphamide 1000 mg/m² day 1 IV and Dexamethasone 40 mg/d (or other steroids in equipotent dose) PO on days 1 to 4, and 9 to 12, combined with Fludarabine 40 mg/m² PO day 1-3 each cycle; repeated once day 21.

Dosage Adjustments: For patients with creatinine clearance below normal values the dosage of Fludarabine/Placebo was reduced by 50%. Patients with pre-therapeutic creatinine clearance below 30 ml/min were excluded.

TREATMENT CYCLES DURING INDUCTION All patients in the conventional arm received the scheduled cycles of therapy. However, in the experimental arm this was only the case for 11/17 patients as 6 patients were stopped before or following the first cycle (Table 1).

TOXICITY AND ADVERSE EVENTS Based on the CTC criteria no difference in severe toxicity was found. However, analysis of laboratory quantities following the second treatment showed a borderline reduction of blood lymphocytes from mean 1.12 (SD 0.4) to 0.73 (SD 0.6); p=0.055 and an increased plasma creatinine level from mean 57.8 (SD 14.2) to mean 124.2 (SD 28.8); p=0.035. All other variables registered were with no difference including performance score.

RESULTS AND CONCLUSION Fifteen of 17 patients and 12/17 were primed with Cyclophosphamide and rhG-CSF in arm A and B, respectively. Based on an interim toxicity and safety analysis, the trial was stopped following inclusion of 34 of planned 80 patients due to a reduced number of patients (4/17) actually harvested in the experimental arm compared to the control arm (11/17; p<0.05).

In conclusion, the scheduled Fludarabine dosage in 2 cycles combined with alkylating therapy impairs stem cell mobilization and standard therapy in young MM patients and should not be administrated up front.

Figure 1 Study Design

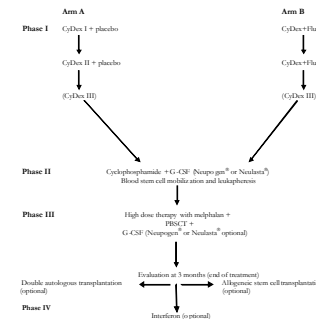


Table 1 Number of treatment cycles during induction therapy (phase I)

Variable	Placebo (n) %	Intervention (n) %	P value
no treatment	(0) 0.0	(3) 17.6	0.054 (Mann Whitney test)
1 treatment	(0) 0.0	(3) 17.6	
2 treatments	(15) 88.2	(9) 52.9	
3 treatments	(2) 11.8	(2) 11.8	

Table 2 Fraction of patients subjected to harvest of an autograft (phase II)

Variable	Placebo (n)	Intervention (n)	P value
Number of patients subjected to at least one harvest	(11) 64.7 %	(4) 23.5 %	0.037
Mean Total harvest of CD34+ cells +/- SD	(11) 736 +/-465	(4) 416 +/-248	0.12
Mean average number of CD34+ cells per harvest +/-SD	(11) 584 +/-501	4, 251.2 (152.6)	0.071
Number of apheresis to collect >5 x 10 ⁶ CD 34+ cells/kg	Placebo (n)	Intervention (n)	P value
no harvest session/mobilization failure	(6) 35.3 %	(13) 76.5 %	0.11
1 harvest session	(7) 41.2 %	(02) 11.8 %	
2 harvest sessions	(2) 11.8 %	(01) 05.9 %	
3 harvest sessions	(2) 11.8 %	(01) 05.9 %	