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Dynamic changes in serum complements during chemotherapy in patients with Multiple Myeloma and their correlations to disease markers

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INTRODUCTION

Multiple myeloma is associated with severe perturbations in immunity predisposing to infections. Reductions in normal immunoglobulins,abnormal T cell functions, abnormalities of complement system have also been reported (Cheson *et al*, 1980; Kraut & Sagone, 1981; Lugassy *et al*, 1999; Zurlo *et al*, 1989).

It is not known whether the clinical improvements seen with new anti-myeloma therapy is reflected in corresponding improvements in the immunological abnormalities involving complement system.

AIM

We undertook a study to investigate the quantitative abnormalities of complement proteins (C3 and C4) during chemotherapy. In addition, the functional status of the complement system was studied by CH50 assay.

Institutional approval was obtained from the Trust Research & Development Committee.

Recent introduction of a number of highly effective anti-myeloma drugs have resulted in significantly improved survival in patients with newly diagnosed and relapsed patients with this condition. It is, however, not known whether the clinical improvements (remission rate, depth of remission, remission duration, long term survival etc.) seen with new anti-myeloma therapy is reflected in any improvements in the immunological abnormalities involving the complement system

METHOD

- This was a **prospective non-randomised laboratory based study** using surplus diagnostic material (serum). Serum samples for CH50 assay were collected and frozen at -80C within an hour of collection
- Patients with established multiple myeloma requiring chemotherapy and those with relapsed disease were identified.
- Serum concentrations of complement proteins C3 and C4 were studied by immunoturbidometry using Roche Cobas analyser. CH50 assay used liposome encapsulated G6PD to mimic invading microorganism. Antibody added along with complement from patient serum lyses the lysosome, releasing the G6PD which was measured (Optilite®CH50 Reagent from The Binding Site Group Ltd).
- The CH50 assay was performed in batches following the manufacturer's instructions. Correlations were made between the disease markers and the complement levels

RESULTS

51 complement assays were carried out on 31 patients between January and December 2019. Batched CH50 testing was performed on 24 cases. The median CH50 was 87.75 U/ml (41.68 - 95.06).

Low C3 Levels (<0.75g/L) with a median of 0.65g/l was seen in 3 (6%) patients prior to starting chemotherapy.

Low C4 levels (<0.14g/L) with a median of 0.05 g/l was seen in 17 (38%) patients of which 10 (58%) were pre-chemotherapy and 7(41%) were during chemotherapy

There were no discernible changes in complement levels during chemotherapy

Only one (4%) patient had a low CH50 (38.44 U/ml). It is noteworthy that this patient had a normal C3 and C4 levels (1.13g/L and 0.43 g/L respectively).

Disease parameters of patients with reduced serum C4 levels

Paraprotein	Stage of Disease	Chemotherapy	Albumen	C3 g/L (0.75-1.65)	C4 g/L (0.14-0.54)	CH50
IgGλ 47	Pre-treatment	Post VCD	42	1.32	0.03	46.95
κ Light chain 8451	Pre-treatment	New diagnosis	40	1.64	0.03	
IgAκ 56	Pre-treatment	New Diagnosis	37	1.78	0.03	
IgGλ 43	Pre-treatment	New Diagnosis	36	1.82	0.03	44.66
IgGλ 42	Pre-treatment	New Diagnosis	36	0.63	0.05	
IgGκ 45	Pre-treatment	New Diagnosis	42	0.85	0.05	
IgGκ 10	During treatment	Daratumumab	22	1.1	0.05	
IgAλ 18	During treatment	CTD	38	1.59	0.05	
IgGκ 25	Relapse	Post VCD	40	1.70	0.05	50.23
IgGκ 67	Pre-treatment	New Diagnosis	38	1.32	0.06	
IgA κ 1	During treatment	VTD	45	1.29	0.06	91.61
IgAλ 25	Pre-treatment	New Diagnosis	41	1.32	0.06	
IgG λ 42	During treatment	VCD	37	1.33	0.06	
IgGλL 40	During treatment	VCD	36	1.47	0.06	
IgA λ 48	Relapse	Post VCD	34	0.95	0.11	66.12
IgGλ 27	Pre-treatment	New Diagnosis	40	1.17	0.13	
IgGκ 67	Pre-treatment	New Diagnosis	28	1.35	0.13	

CONCLUSIONS

This study demonstrated that reductions in serum C3 level is uncommon in multiple myeloma. However**, significantly reduced C4 levels are seen in more than a third of patients with active disease. But there were no correlations between the disease parameters and the C4 levels.** In addition, there were no dynamic changes in serum complement levels during chemotherapy.

Significantly, the residual complement activity, as measured by CH50, remained within normal range even in patients with reduced C4 levels.

The results of this study raises questions regarding the performance and suitability of the CH50 assay technique employed to study functional complement activity in patients with myeloma.

Incorporating additional tests to investigate the activities of alternate and lectin pathways may provide valuable insight into the functional state of complement system in multiple myeloma.

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