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POSTER ABSTRACTS

652.MULTIPLE MYELOMA: CLINICAL AND EPIDEMIOLOGICAL

The Impact of Epstein-Barr Virus Infection on Second Cancer Development in Newly Diagnosed Myeloma Patients Treated with Lenalidomide in the UK NCRI Myeloma XI Trial

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Background

Several factors have been linked to second primary malignancy (SPM) development in myeloma patients, including advanced age, immunocompromise and therapy, such as melphalan and lenalidomide (len). The impact of infection, including EBV is yet to be elucidated. Here we address this in the context of the UK NCRI Myeloma XI Trial for newly diagnosed transplant eligible (TE) and transplant non-eligible (TNE) patients.

Methods

Myeloma XI was a phase III, randomised, multi-centre, parallel group design, open-label trial comparing cyclophosphamide, thalidomide, len, carfilzomib and bortezomib induction combinations and len maintenance treatment in TE and TNE patients. TE patients received high dose melphalan supported by autologous stem cell transplantation (ASCT). Patients in both pathways were randomised to maintenance with len or observation. In total, 4358 patients entered. Planned SPM analysis was conducted in May 2019, with 318 patients developing an SPM prior to that point. Median follow-up from trial entry was 60 months (IQ range 47-76).

A nested cohort analysis was performed to determine EBV infection and immunity status in 170 SPM patients for which serum samples were available. Forty-two trial patients who did not develop an SPM were used as a control group. EBV assessment time-points included pre-induction, post induction, 4 months post ASCT (TE only) and 1 year post induction.

Peripheral blood serum samples were tested for EBV EBNA IgG Antibody/index (LIAISON®), EBV VCA IgM Antibody/Index (LIAISON®) and EBV positivity was determined using the artus® EBV RG PCR Kit from Qiagen. Active or recent EBV infection was evidenced by a positive EBV IgM antibody and/or EBV PCR.

Results

Of the 170 patients, 208 SPM were noted with 147 patients developing 1 SPM and 23 patients developing ≥2. One hundred and five patients developed an SPM following maintenance randomisation, with 76 receiving len and 29 being observed. The remaining 65 patients developed an SPM prior to maintenance. Eighty-four SPMs were diagnosed in 68 TE patients and 124 SPMs in 102 TNE patients.

Of the 170 SPM patients, 8 had evidence of recent or active infection at the time of testing, evidenced by either IgM EBV antibodies (n=5), positive EBV PCR (n=2) or both (n=1). The median EBV DNA copies/ml was 353 (range 337-428). The median IgM antibody titre was 71.5U/ml (26 - >160). No patients in the control group had evidence of recent EBV infection (p=0.36). Of the 8 patients with evidence of EBV infection, 6 developed >1 SPM, Table 1. Five had been treated in the TE pathway, with all developing post maintenance randomisation, and 4 of the 5 receiving len maintenance. None of the 3 TNE patients received len maintenance, with 2 developing an SPM prior to maintenance randomisation. The median time from EBV testing to SPM diagnosis was 17·9 months (0.5-51.7).

Two of the EBV positive patients developed a haematological SPM: myelodysplastic syndrome and Hodgkin lymphoma. Four patients developed a solid malignancy: lung, breast, ovary, and colon. The remaining cases were non-melanoma skin cancers, Table 1.

Immune status (EBV IgG) was also determined. In TE patients, the median EBV IgG titre was 65.3U/ml at diagnosis (<3 - 600, n=48), falling to 28.1U/ml following induction (<3 - 326, n=41) and recovering to 44.2U/ml one year post ASCT (<3 - 600, n=22). In TNE patients, the median IgG titre at diagnosis was 39.1U/ml (<3 to 517, n=72), falling to 31.2U/ml 4 months post induction (<3 - 287, n=42) and recovering to 51.3U/ml after 1 year (<3 - 554, n=41). In the SPM patients the IgG EBV titres were noted to be <20U/ml in 5 of the 8 patients. Three of the eight patients had no detectable EBV IgG level (<3U/ml)

Conclusions

These data suggest that EBV infection is unlikely to be a risk factor for SPM development in myeloma patients. This is supported by the finding that EBV IgG titres were consistent with immunity in most patients (>20U/ml) and even in the patients with possible EBV infection, EBV DNA was only identified in 3 patients, and at a low level. In addition, the SPM developed are not classically associated with EBV infection or reactivation. It is noted that EBV infection status was not always determined at the time of SPM development. Despite this, the data does show that EBV immunity recovers following therapy, even in the post ASCT setting. EBV monitoring is therefore not supported by this work, although in patients who develop ≥2 SPM, further clarification is required.

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Table 1. Treatment received and type of SPM developed in EBV positive patients.

SPM cases developed after maintenance randomisation			
TNE maintenance			
Patient number	**SPM description**	**Induction**	**Maintenance**
1	BCC	CRD(a)	No maintenance
	Ovarian	CRD(a)	No maintenance
TE maintenance			
Patient number	**SPM description**	**Induction**	**Maintenance**
2	BCC	CTD	Lenalidomide
	Lung	CTD	Lenalidomide
3	SCC	CRD	Lenalidomide
4	BCC	CTD	No maintenance
	Breast	CTD	No maintenance
5	Nodular sclerosing Hodgkin	CRD	Lenalidomide and vorinostat
6	MDS	CTD	Lenalidomide
SPM cases developed before maintenance randomisation			
TNE pre-maintenance			
Patient number	**SPM description**	**Induction**	**Maintenance**
7	Melanoma	CRD(a)	n/a
	Colon	CRD(a)	n/a
8	BCC	CRD(a)	n/a

Abbreviations: BCC, Basal Cell Carcinoma; SCC, Squamous Cell Carcinoma; MDS, Myelodysplastic Syndrome; CRD, cyclophosphamide, lenalidomide and dexamethasone; CTD, cyclophosphamide, thalidomide and dexamethasone, a, attenuated.

Figure 1

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