Successful venetoclax salvage in the setting of refractory, dialysis-dependent multiple myeloma with t(11;14)

A 53 year-old man presented in October 2017 with back pain on a background of an 8-year history of monoclonal gammopathy of uncertain significance (MGUS). Subsequent imaging revealed lytic lesions at the level of L1 on whole spine Magnetic Resonance Imaging (MRI) and an X-ray skeletal survey showed lytic lesions in the skull. Laboratory investigations revealed mild anemia with hemoglobin of 12 g/dL, but normal renal and bone profiles. Serum protein electrophoresis showed an IgG kappa paraprotein of 62 g/L. A bone marrow aspirate and biopsy demonstrated the presence of over 90% kappa-restricted clonal plasma cells, consistent with multiple myeloma. Albumin was 33 g/L, beta-2-microglobulin 6.25mg/L, and lactate dehydrogenase was within normal limits. Cytogenetic testing revealed a IgH-CCND1/ t(11;14) translocation with hyperdiploidy (three copies of 5p15.2 and CEPI5). Gene expression profiling (GEP) using SKY92 identified a high risk expression profile. The patient was therefore Multiple Myeloma International Staging System (ISS) stage III (R-ISS stage II) at diagnosis, but with the presence of high risk GEP.

He was enrolled on a phase Ib trial evaluating the combination of weekly cyclophosphamide, bortezomib, dexamethasone (CyBorD) in combination with daratumumab (DARA) as the initial therapy for symptomatic myeloma in patients eligible for an autologous stem cell transplant (ASCT) (*NCT02955810*).[1] Following three cycles of induction his M-band had fallen from 62 g/L to 42 g/L. During cycle 4 in the setting of rising serum kappa light chains, he developed acute non-oliguric renal failure, with features consistent with light chain nephropathy on renal biopsy. He subsequently commenced thrice weekly dialysis. Treatment was changed to lenalidomide and dexamethasone, which was discontinued after one cycle due to lack of response/progression, and plasma exchange was performed, bringing the M-band down from 47 g/L to 16 g/L. The choice of lenalidomide and dexamethasone was made given the lack of an immunomodulatory agent in the first line regimen, in line with current guidelines, and reflecting the lack of availability of carfilzomib at the time in Ireland.[2]

He was switched to third-line treatment with pomalidomide, bortezomib and dexamethasone (PVD), which was commenced due to evidence of efficacy in patients with lenalidomide-refractory disease,[3,4] but this failed to achieve rapid control with his paraprotein rising back to 27 g/L. Given the presence of t(11;14) we felt there was a strong rationale to consider the addition of the BCL2-inhibitor venetoclax and the patient now met criteria for compassionate access (progression on both a proteasome inhibitor and an immunomodulatory drug). Venetoclax was provided by AbbVie on compassionate access and administered at 400 mg once daily for the first week, then escalated to 800 mg daily. Nausea prevented further dose-escalation. Within three cycles of adding venetoclax to PVD, the paraprotein had fallen to 5 g/L and a bone marrow examination revealed less than 5% clonal plas-

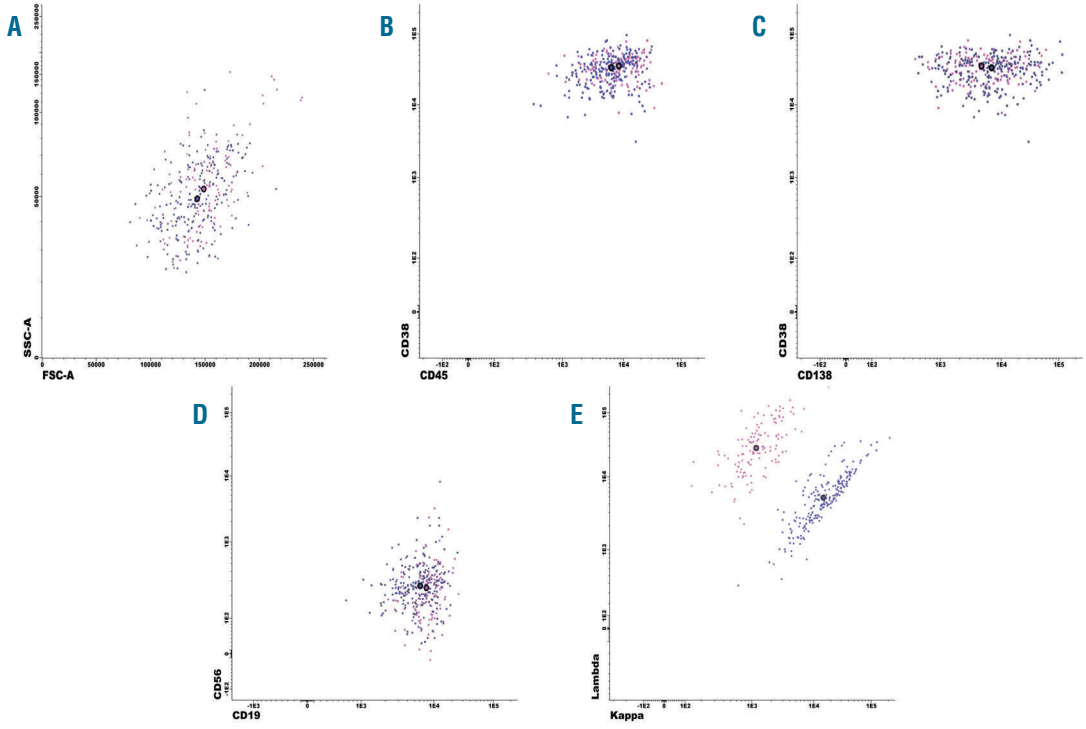

Figure 1. Next generation flow demonstrating non-clonal plasma cells only, taken nine months after autologous stem cell transplant (ASTC). Minimal residual disease (MRD) was assessed using the Euroflow validated antibody panel and guidelines at a sensitivity of 10-5. Data were analyzed using the Infinicyt™ software. Plasma cells accounted for 0.021% of the sample and had a normal phenotype ($CD38^{++}CD138^{++}CD81^{-}CD117^{-}CD27^{lo}CD19^{++}CD56\text{-}CD45^{hi}$). (A) forward scatter *versus* side scatter; (B) cells are strongly positive for CD45 and CD38; (C) cells are strongly positive for CD38 and CD138; (D) cells are strongly CD19 positive and CD56 negative; and (E) kappa *versus* lambda staining showing two non-clonal populations. Full report available in the *Online Supplementary Figure S1*.

ma cells. In view of this response a decision was made to proceed to a peripheral blood stem cell (PBSC) harvest with a view to a subsequent ASCT. Venetoclax was held for one week to facilitate PBSC mobilization and harvest, then stopped seven days prior to melphalan conditioning. PBSC harvest was unaffected by the use of venetoclax, yielding $9.26x10^6$/kg CD34 positive stem cells in total, of which $4.81x10^6$/kg were reinfused. In view of his renal failure a reduced dose of melphalan (140 mg/m^2) was administered over two days. The ASCT was tolerated well with grade 1 mucositis and an episode of sepsis (*K. varicolii* and *P. aeruginosa*) during the neutropenic phase, managed at ward level with antimicrobials and supportive care. Other adverse events during treatment have been grade 1 peripheral neuropathy and nausea.

Venetoclax was reintroduced at 800 mg daily 30 days post stem cell reinfusion. No dose reduction was implemented at this time as venetoclax was now being used as a single agent rather than in combination with a proteosome inhibitor (PI) and an immunomodulatory drug (IMiD), and the patient has not exhibited significant or dose-limiting toxicities. Response assessment by serum and urine protein electrophoresis, free light chain assay and bone marrow examination 100 days post ASCT confirmed a stringent complete response (sCR), with a bone marrow negative nine months later for minimal residual disease (MRD) by next generation flow (NGF) at a sensitivity of > 10-5 (Lower limit of detection: 0.00037%, lower limit of quantification: 0.00093%) (see Figure 1). Within six months of ASCT he became dialysis independent with stable renal function since. He is currently maintained on single agent venetoclax, and remains in sCR at the latest response assessment in July 2019 (no monoclonal band detected, free light chain ratio 1.97 [upper limit of normal in chronic kidney disease 3.1]). The changes in M-protein over time are shown in Figure 2.

Approximately 50% of cases of myeloma have a translocation which pairs the IgH promoter on chromosome 14 with one of five partner genes. The most common of these is CCND1 on chromosome 11, occurring in 15-20% and 40% of myeloma and plasma cell leukemia respectively. t(11;14) has previously been considered as a standard risk feature, however its impact on outcomes is controversial. There is evidence that t(11;14) patients undergoing ASCT in the era of PI and IMiD have significantly reduced overall survival (OS) when compared to the whole cohort, irrespective of the Multiple Myeloma International Staging System (ISS) stage.[5] Conversely, an International Myeloma Working Group (IMWG) multicenter cohort study, presented at ASCO 2019, has found that t(11;14) patients receiving a combination of PI and IMiD followed by ASCT have good outcomes, with a median OS of nearly 10 years.[6]

GEP using SKY92 can identify patients at high risk of progression and independently of the ISS is associated with worse outcomes in both newly diagnosed and relapsed patients.[7] The addition of ISS to SKY92 may further improve risk stratification.[8] The Prospective Multiple Myeloma Impact Study (PROMMIS) (*NCT02911571*) will assess changes to treatments made based on SKY92 results, progression free survival (PFS) and OS.

Apoptosis is controlled by a fine balance between proapoptotic proteins (eg. BIM, BAX, BIM) and antiapoptotic proteins (*e.g.* BCL-2, BCL-XL, and MCL-2).[9] Translocation (11;14) is associated with elevated levels of BCL-2 relative to MCL-1 and BCL-XL. This disruption to normal regulation of apoptosis confers a pro-survival advantage. It also renders the malignant cells susceptible to treatment with the BCL-2 inhibitor venetoclax, resistance to which is usually mediated by MCL-1.[10] Pre-clinical data has shown that the BCL2/MCL-1 mRNA ratio was the most powerful biomarker predicting *in vitro* sensitivity to venetoclax.[11]

A phase I study of single agent venetoclax (+/- dexamethasone) reported an overall response rate of 40% in

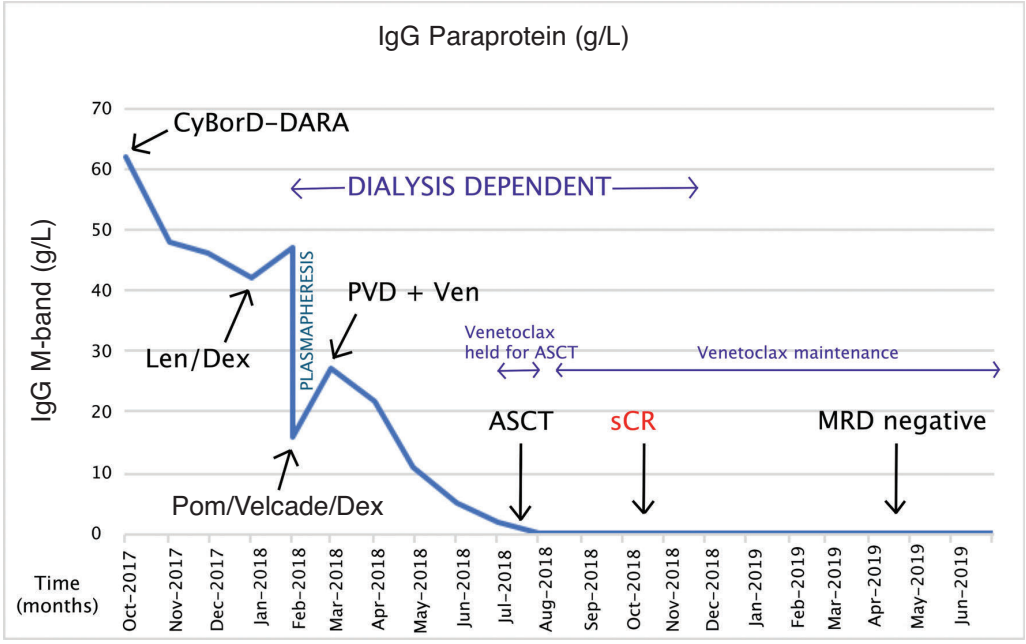

Figure 2. Changes in IgG M-protein over time according to line of therapy. DARA: daratumumab; CyBorD: cyclophosphamide, bortezomib, dexamethasone; Len/Dex: lenalidomide/ dexamethasone; Pom/Velcade/Dex: pomalidomide, bortezomib and dexamethasone; PVD+Ven: pomalidomide, bortezomib and dexamethasone + venetoclax; ASCT: autologous stem cell transplant; sCR: stringent complete response; MRD: minimal residual disease.

relapsed refractory multiple myeloma (RRMM) patients with t(11;14) with very good partial remissions (VGPR) or better achieved in 27%. However, although the median number of prior therapies was 5, none of the cohort had been exposed to daratumumab.[12] Bortezomib induces the BH3-only protein, Noxa, which antagonises MCL-1, thereby sensitising MM cells further to venetoclax.[10,13] A phase Ib trial of venetoclax with bortezomib in RRMM produced promising results,[14] but the subsequent phase III trial (*BELLINI, NCT02755597, M14-031*) was suspended after interim analysis showed increased mortality, primarily due to infection, in the investigational arm. Initial results, presented at the European Haematology Association Annual Meeting 2019 reported that the excess of deaths in the venetoclax arm of the trial were predominantly in patients with progressive disease. Overall, PFS was prolonged in the venetoclax arm at 22.4 *versus* 11.5 months, and subset analysis of t(11;14) patients showed particular benefit in this group, although data is immature.[15] Preliminary results from the NCI phase I/II study using a combination of daratumumab, bortezomib and dexamethasone with or without venetoclax in RRMM with assessment for t(11;14) were presented at ASCO 2019 (*NCT03701321*), and several other studies are currently on hold. Importantly, no literature exists regarding the use of venetoclax in patients with severe renal failure or dialysis-dependent renal failure, as most of the trials have excluded patients with a creatinine clearance of <30 mL/min or requiring dialysis. Given that renal excretion has been shown to play little role in venetoclax elimination, which is primarily dependent upon hepatic enzymatic activity,[16] the use in end-stage renal failure (ESRF) patients should theoretically be safe. Our case supports this hypothesis as the treatment has been tolerated with a minimal adverse event (AE) reported.

We believe this case illustrates several key points, the most important of which is the ability to salvage high risk, multi-refractory t(11;14) patients with venetoclax. The depth of the response achieved indicates the importance of BCL-2 in mediating resistance in some patients with t(11;14) and suggests that at least in this patient population any risk of increased infection is likely justified by the potential benefit. Finally, our ability to administer this drug in the setting of ESRF argues for further studies evaluating the safety of venetoclax in patients with reduced renal function.

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