Development of a Sequencing Model Using Patient-level Data to Optimize Patient Outcomes in Multiple Myeloma

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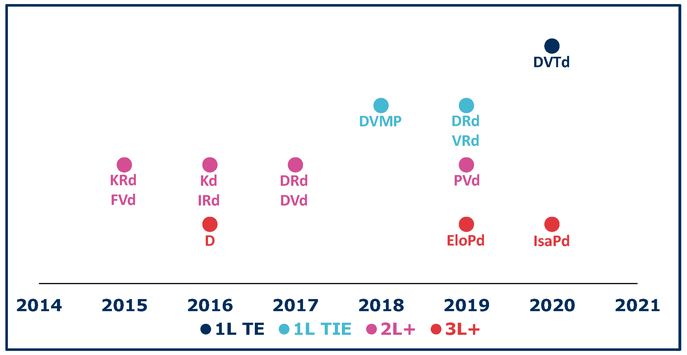
Background

Multiple myeloma (MM) is characterized by the proliferation of malignant plasma cells within the bone marrow.[1] In 2016, more than 130,000 patients worldwide were diagnosed with MM (an incidence of more than 2 per 100,000).[2] MM occurs most commonly in people over the age of 60 and incidence is increasing; between 1990 and 2016, the number of incident cases increased by 126% globally.[2, 3]

The goal of treatment is to delay progression, thus maintaining patient quality of life, and prolonging survival. Several new combination therapies have recently been licensed for MM across treatment lines (**Figure 1**). It is therefore vital to select the most effective sequence of treatments, to ensure optimal patient outcomes.

Objective: Our aim was to develop a decision analytic model to compare alternative treatment sequences in patients with MM, and to explore strategies to optimize patient outcomes.

Figure 1: New treatment combinations available in MM per setting



Methods

Patient population

The model considers two distinct patient subgroups: first-line transplant eligible (1L TE) and first-line transplant-ineligible (1L TIE). Patients are tracked over the course of their disease as they move from one treatment line to the next.

Treatment regimens

Treatment regimens differ across the 1L TE, 1L TIE and relapsed or refractory (RR) settings. Regimens included in the model were those licensed by the European Medicines Agency or recommended in local guidelines at the time of model conceptualization (**Figure 2**).

Model structure

Ideally, empirical data would inform the efficacy of all treatment sequences and allow for direct comparison. However, given the wide range of available treatment options and the fact that patients receive multiple lines of therapy over the course of their disease, these data do not exist. In lieu of these data, we developed a state-transition model using treatment-line-specific patient-level data.

Figure 2: Available treatment options

1L TE
- DARA + BORT + THAL + DEX (DVTd)
- BORT + THAL + DEX (VTd)
- BORT + LEN + DEX (VRd)
- BORT + CYCLO + DEX (VCd)
- BORT + DEX (Vd)

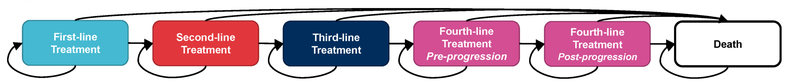
1L TIE
- DARA + LEN + DEX (DRd)
- DARA + BORT + MEL + PRED (DVMP)
- LEN + DEX (Rd)
- LEN + BORT + DEX (VRd)
- LEN + MEL + PRED (MPR)
- BORT + MEL + PRED (VMP)
- THAL + MEL + PRED (MPT)

2L+
- DARA + LEN + DEX (DRd)
- DARA + BORT + DEX (DVd)
- LEN + DEX (Rd)
- BORT + DEX (Vd)
- CAR + LEN + DEX (KRd)
- CAR + DEX (Kd)
- IXA + LEN + DEX (IRd)
- POM + BORT + DEX (PVd)
- ELO + LEN + DEX (EloRd)
- BORT + CYCLO + DEX (VCd)
- PAN + BORT + DEX (FVd)
- THAL + DEX (Td)

3L+
- DARA (D)
- POM + DEX (Pd)
- ELO + POM + DEX (EloPd)
- ISA + POM + DEX (IsaPd)
- PAN + BORT + DEX (FVd)

The model (**Figure 3**) considers four lines of treatment as studies show that only a small proportion of patients (1%) receive a fifth-line therapy.[4] Newly diagnosed patients (1L TE or 1L TIE) enter the model and receive 1L treatment. Following first relapse, patients progress to 2L treatment, 3L treatment and 4L treatment. In line with clinical practice, it is not assumed that all patients who progress will move directly to the next treatment line – from any treatment line, patients can transition to death, which is an absorbing state.

Figure 3: Model Structure



Clinical data

We based the model on trial data from CASSIOPEIA[5], MAIA[6] and ALCYONE[7] in the 1L setting; CASTOR[8] and POLLUX[9] in the RR 2L+ setting and SIRIUS[10] and GEN501[11] in the RR 3L+ setting. To inform transitions between treatment lines, we used estimates of progression-free survival (PFS) due to their availability and maturity, as a proxy for time-to-next-treatment data. We used overall survival (OS) curves to model mortality in the 4L, post-progression. In the previously treated settings, we performed patient-level data analysis to derive line-specific estimates of survival. Similarly, line-specific estimates of comparative efficacy were taken from published network meta-analyses or match-adjusted indirect comparisons. No combined network was available to model OS in 4L patients, and naïve comparison did not lead to plausible results. Therefore, we used a single OS curve for all patients.

As the previous number of treatment lines and the types of prior treatments may affect efficacy in the current line, we performed statistical analyses to assess the impact of these characteristics. However, adjustment was not applied in the base case as all regimens were assumed to be impacted in a similar way. Finally, we used separate distributions based on trial data to determine the proportions of patients who transition to the next treatment line or to the 'death' state.

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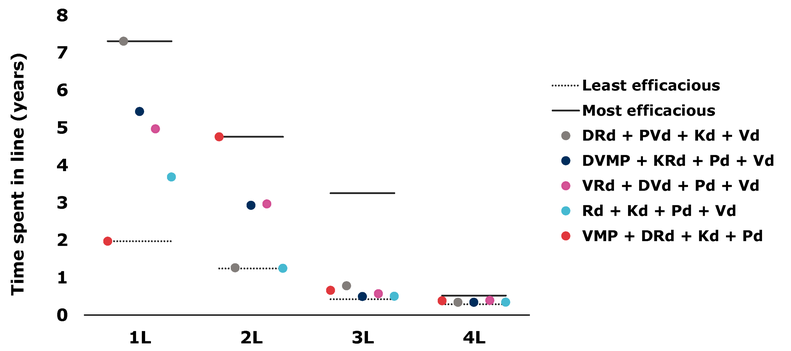
Results

We programmed the model to output a range of results including average time spent in each health state and the proportion of patients alive over time. Results were then displayed graphically to facilitate comparison between sequences. For illustrative purposes, results in terms of time spent in each line are displayed for the 1L TIE population in **Figure 4**.

Figure 4: Time spent in each line of treatment



Our next step was to analyse the information to determine how to optimize patient outcomes. We observed that PFS is highest in 1L and decreases with each subsequent line of treatment. Therefore, selecting the most effective treatments in 1L and 2L is important as these will have the most impact on long-term clinical outcomes.

Using the most effective treatment sequence strategy contributes to delayed progression and a lower number of deaths, resulting in more time spent progression-free and increased survival of patients with MM.

Conclusions

In the absence of data from sequencing trials, we developed a robust, evidence-based model to provide valuable insights into optimal treatment decisions.

Results indicate that efficacy and time on treatment in early lines are the strongest drivers for better long-term outcomes in patients with MM. Our analysis demonstrates the importance of selecting the most-effective treatments for use upfront, to ensure optimal patient outcomes.

References

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