Experimental therapy except monoclonal antibodies

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In the last two decades, several new agents have been introduced in the treatment of multiple myeloma (MM) patients. Proteasome inhibitors (PIs) and immunomodulatory drugs (IMIDs) were the first drugs that proved to be able to significantly improve progression-free survival (PFS) and overall survival (OS). For many years, bortezomib-dexamethasone (Vd) and lenalidomide-dexamethasone (Rd), followed by pomalidomide-dexamethasone (Pd), have been the cornerstones of the treatment of relapsed/refractory MM. In recent times, second generation PIs (carfilzomib and ixazomib) have been combined with lenalidomide in the relapsed setting: Carfilzomib plus Rd (KRd) significantly improved PFS and OS vs Rd alone; ixazomib plus Rd (IRd) significantly improved PFS. Carfilzomib plus dexamethasone (Kd) significantly improved PFS and OS vs Vd. The combination of Pd plus bortezomib has been also evaluated in an early relapse setting, showing an improved PFS in comparison with Vd. Most of the treatment recommendations for relapsing MM patients suggest using these novel combos in the early phases of the disease (first and second relapse). The major challenge for clinicians will be how to choose the best option for each patient, in order to maximize the efficacy and minimize toxicities and costs, in the context of the several options available including monoclonal antibodies. Newer agents, with a different mechanism of actions, have shown their efficacy as single drugs in later lines of therapy, in patients heavily pretreated. These agents include novel alkylating agents (melflufen), bcl2 inhibitor (venetoclax), and selective inhibitor of nuclear export (selinexor). The efficacy and safety in heavily pretreated patients provide the rationale to combine these drugs with backbone treatments and to move these combinations in the early-line setting. In the treatment scenario with drugs that target a single mechanism of the tumor cell, the identification of biomarkers that can predict tumor response is extremely important. For instance venetoclax showed a marked activity as single agent in patients harboring t(11;14)and in patients with high-bcl2 levels in combination with bortezomib. Another field of development, besides monoclonal antibodies, are CAR-T cells, currently under evaluation in the heavily pretreated setting, with promising preliminary results.