What are the available options for patients relapsing beyond the third line of therapy?

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Welcome to *Managing Myeloma*. My name is Dr. Paul Richardson, and it's my pleasure to discuss various options that are available for patients who constitute an area of true unmet medical need: they are relapsing beyond the third line of therapy. These patients are typically refractory to both immunomodulatory treatments and proteasome inhibitors in this setting. Typically, these patients will have already had lenalidomide-based therapy, they will have had bortezomib-based treatment, they will have had pomalidomide, and they will have also received carfilzomib or even ixazomib as well. In this context, they therefore constitute a challenging population for whom to consider treatment options.

There are certain key principles. They would be defined as what we would call quad-refractory patients and most importantly they might be ideal candidates for monoclonal antibody therapy. In the approved setting, this would incorporate the paradigm-changing CD38 targeting monoclonal antibody daratumumab which could be given in this setting and ideally in combination with other drugs, not least of which because these patients usually are highly resistant. Beyond the various combinations that could be considered, a guiding principle might be to visit classes of drug that have not been most proximally exposed to the patient immediately at the time of this third-line treatment failure and therefore have a better chance of restoring response.

In the context of daratumumab therapy, it's also worth mentioning very exciting recent data with elotuzumab combined with pomalidomide and dexamethasone, showing activity in a relapsed/refractory population with a very encouraging progression-free survival benefit; suggesting that this particular combination, partnered with an appropriate proteasome inhibitor, might be a very reasonable way forward.

In the context of proteasome inhibitors, we of course are blessed with various choices and they have overlapping or different effects which can make appropriate choices reasonable. For example, if the patient has had bortezomib and then gone on to carfilzomib, a very reasonable next choice might be ixazomib, or the other way around. Similarly, it's worth mentioning that the combination of bortezomib and panobinostat can be very active – particularly in highly resistant patients – with appropriate attention to supportive care and in particular dose and schedule. We can reasonably dose-reduce panobinostat from 20 to 15 to 10, and dose and schedule bortezomib accordingly to optimize outcome.

In this patient population, we have the exciting promise of a number of clinical trials. The good news for patients is that there are numerous options available. I just want to touch on a few to show guiding principles. In terms of immune therapy, there are some very important options available for patients in this setting. These include drugs such as antibody drug conjugates which are showing great promise, even the single agents combined simply with premedication.

Similarly there is earlier data now emerging for so-called bispecific antibodies that are T-cell engagers, or BiTEs. In that same context, of course, there's the tremendous excitement around CAR-T therapy or cellular therapy as it's more broadly considered. Obviously, CAR-T constitutes a very exciting paradigm. Within that context, referral to appropriate specialist centers for protocol-directed approaches is particularly exciting.

I do also want to mention, however, that there is some real progress being made in a number of other areas, especially in the context of small molecule inhibitors such as venetoclax. There are also very exciting new trials becoming available using next-generation immunomodulatory drugs (or so-called CELMoDs) with some very exciting early promise being shown. Furthermore, there are absolutely brand new classes of drugs under study including the so-called selective inhibitors of nuclear export proteins. The paradigm drug here of course is selinexor which, in combination with other drugs, is showing great promise in penta-refractory patients.

In that same spirit, there are a number of new drugs being studied. One interesting and very exciting example is of a so-called targeted alkylator, which actually doesn't necessarily do it complete justice because it's more of a highly targeted therapy than it might be initially appreciated. This is melflufen which is highly peptidase-active or activated and has preferentially taken up the bi-malignant myeloma cells in the context of its intravenous administration and is less absorbed by normal tissues, making it truly selective in its effects with some very exciting early results having been shown in several phase 2 studies.

There are other numerous examples, but the key takeaway is that these clinical trials are particularly important for patients at this stage in their illness. Furthermore, it's worth mentioning that supportive care really matters. The use of newly available bone or anti-bone resorptive agents such as denosumab can be very valuable, especially in patients with renal impairment.

Finally, I'd like to mention that of course if patients aren’t candidates for protocol-directed treatment, or if bridging strategies are needed, there are of course cytotoxics available that in combination with novel agents can be very valuable. Of course the workhorse cyclophosphamide, a great drug in the appropriate setting; bendamustine appropriately partnered with bortezomib or other such PIs may be helpful; and combination strategies which can be intensive but very helpful as a bridging treatment, such as DCEP with the appropriate cautions and precautions around both cytopenia and infection.

I hope these comments are helpful and help guide you in this particularly vulnerable population, and thank you again for viewing this activity.