Myeloma Treatments by Drug Class

Current Myeloma Therapies			
Immunomodulators (iMiDs) It is not clear why this drug class is effective, but iMiDs are known to inhibit the growth of cancer cells. Their effects are also connected to a protein called cereblon. Patients with low cereblon levels don't respond well to iMiDs. They are also known to be an immune system stimulator and are frequently used in maintenance therapy and in combination with other drugs.	Revlimid (lenalidomide) Used since 2005	Pomalyst (pomalidomide) FDA approved 2013	Thalomid (thalidomide) Used since 1990s for myeloma. Drug has been around since 1950s.
Proteasome Inhibitors (PIs) Proteins on top of cells have vital functions, but need to be processed once they complete their function. The proteasome is like a trash compactor that chews up the extra proteins and recycles it or discards it. Proteasome inhibitors work by stopping enzyme complexes (proteasomes) in cells from breaking down proteins important for keeping cell division under control. New PIs are now in development.	Velcade (bortezomib) Infusion. Used since early 1990s.	Kyprolis (carfilzomib) Infusion. FDA approved 2015.	Ninlaro (ixazomib) Oral pill. FDA approved 2015. Oral option is great for convenience.
Steroids Steroids cause programmed cell death of myeloma cells, also called apoptosis. We hate this class of drug but it works and can reduce myeloma cells by 50% as a single agent. Drat.	Dexamethasone. The drug we love to hate.	Prednisone. Another steroid that makes other people immediately stupid. Used mostly in Europe.	
Stem Cell Transplant Stem cell transplant is a very effective treatment for multiple myeloma due to the effectiveness of melphalan, the chemo used during transplant. Stem cell transplant using a patient's own cells is the most common type of transplant performed in myeloma.	Single Autologous (your own cells)	Tandem Autologous Transplants (two back-to-back transplants within 3 months of each)	Allogeneic (donor cells)

IMMUNOTHERAPIES

Monoclonal Antibodies

These antibodies are effective to recruit and activate the immune system to kill myeloma cells. They are carriers of killing mechanisms to hit the surface of a specific protein that is commonly found on the surface of myeloma cells. For example, most myeloma cells have the CD38 protein on their surface, which makes it a popular target. Current monoclonal antibodies include:

Darzalex (daratumumab), targets CD38. FDA approved 11/2015
Empliciti (elotuzumab), targets SLAMF-7. FDA approved 11/2015
Isatuximab, targets CD38. FDA approval pending.

CAR T Cells

Chimeric antigen receptors (CAR) T Cells take a patient's own T cells (immune system fighter cells) and engineer them to hit targets present on myeloma cells. After they are engineered, they are given back to the patient. CAR T Cell treatments have had dramatic, positive results for some patients. Researchers are looking for appropriate targets that are on the surface of myeloma cells but are not on the surface of normal cells, some targets are BCMA, CD229, and CD19. The perfect target is not yet known. CAR T treatments have been proven effective in some leukemias and are now entering myeloma clinical trials. Open BCMA CAR T cell trials are at UPenn and the NIH but have limited openings. Memorial Sloan Kettering and MD Anderson plan to create CAR T cell research programs in 2017. The Myeloma Crowd Research Initiative is funding CAR T cell research. You can learn more here: http://www.myelomacrowd.org/mcri1.

Vaccines

Cancer vaccines are designed to stimulate an immune response against tumor-specific or tumor-associated antigens, encouraging the immune system to attack cancer cells bearing these antigens. Vaccines in myeloma are best used when there is low tumor burden. Vaccine approaches are now being used as a preventiive approach in smoldering myeloma and as an approach to extend the effectiveness of myeloma treatments, now in clinical trials post-transplant.

T Cell Immunotherapies

Researchers are working on ways to take a patient's own T cells, grow them up and expand them outside of the body and then give them back. The Myeloma Crowd Research Initiative is supporting such an approach by Dr. Ivan Borrello at Johns Hopkins who takes T cells from the bone marrow that are most indicative of the patient's myeloma prior to transplant, grows them up in the presence of the tumor and returns them to the patient post-transplant. This doubles down on the immune system regrowth post-transplant while personalizing the treatment for all tumor clones inside of each patient. Learn more about Dr. Borello's work here: http://www.myelomacrowd.org/mcri1.

Checkpoint Inhibitors

The immune system is like a car that has a gas pedal and a brake and can speed up and slow down when it sees foreign cells. Because a myeloma patient's immune system is not killing these cells, the myeloma has convinced the immune system to put on the brakes. Checkpoint inhibitors take that brake off. These drugs are typically not used alone. Research is still ongoing to find the best combination for us in multiple myeloma. They have been successfully used in solid tumors.

Yervoy (ipilumumab)
Opdivo (nivolumab)
Keytruda (pembrolizumab)

Risk and Multiple Myeloma

Did you know that there are different types of myeloma? A single patient can even have several different kinds of myeloma or "clones." Clones can be either less or more aggressive. As patients receive treatment and experience relapse, their myeloma changes and clones that weren't problematic before can become more of a challenge. Listed below are some risk factors that make myeloma low- or high-risk. Knowing the genetic features can help patients know if they should have more or less aggressive approaches in their treatment.

MYELOMA GENETIC FEATURES

As research has progressed, the detail of the abnormal genes and chromosomes has led to the identification of at least seven disease sub-types. Approximately 60% of myeloma patients will fall into one of these classifications. In addition to cells having more or fewer chromosomes than a healthy cell, **FISH testing** and **gene array testing** can show chromosomal abnormalities, like a deletion of a chromosome or chromosomes that have moved from their proper position (called a **translocation**). For example, t(14;16) means that chromosome 14 and 16 have exchanged (translocated) chromosomal material. If a gene or chromosome has been deleted, it will be described as, for example, del(17p13), which is the deletion of the tumor-suppressor gene and is associated with myeloma that responds poorly to treatment.

MYELOMA CELL GENETIC FEATURES	LOW RISK TRANSLOCATIONS	HIGH-RISK TRANSLOCATIONS
	CCND1 t(11:14)(q13;a32), 16% of patients MUM1 t(6;14)(p21;32), 2% of patients t(12;14)(p13;q32), 1% of patients	FGFR3/MMSET t(4;14)(P15;q32), 15% of patients. Less common in MGUS and more frequent in smoldering myeloma CCDN2 t(14;16)(q32;q32), 5% of patients. Also called the C-MAF translocation. CCND2 T(14;20)(q32;q11), 2% of patients. Also called the MAFB translocation.
	LOW RISK GENE ADDITIONS OR DELETIONS	**HIGH-RISK GENE ADDITIONS OR DELETIONS**
	Del 13 found in FISH test, 50% of patients	Del 13 found by metaphase (conventional) cytogenetics, 17% of patients Del(17p13), <5% of newly diagnosed patients but in more than 15% of patients with multiple relapses. Many patients acquire this deletion over time with relapse as their clones change.

OTHER TESTS / LAB RESULTS		
DIPLOID STATUS Cells have two pairs of chomosomes, hence the term "diploid".	**Hyperdiploid** myeloma cells have **more** chromosomes than normal. This occurs in about 45% of myeloma patients and is **less aggressive**.	**Hypodiploid** myeloma cells have **fewer** chromosomes than normal. This occurs in about 40% of myeloma patients and is **more aggressive**.
LIGHT CHAIN STATUS	Most myeloma patients know that they have a certain type of myeloma like IgG kappa or IgA lambda. The kappa or lambda portion is the **light chain**. When myeloma progresses, the myeloma cells start to produce more light chains than heavy chains. This can be measured by the Free Light Chain Assay test on a blood specimen. In general, **the higher the free light chains, the more aggressive the disease is. Therefore, the serum free light chain test is a better predictor of outcome than the amount of M-protein in the serum**. So this means that if you have IgG Kappa, you want to watch the kappa number more than your M-spike number. The kappa number alone is also more important to watch than the kappa/lambda ratio number which can be easily thrown off by a drop in the opposite light chain.	
LDH LEVELS (SERUM LACTATE DEHYDROGENASE)	LDH levels are elevated in aggressive myeloma and is associated with poor prognosis if no explanation for its increase is available other than myeloma. May be an inicator of immune system function.	
BETA2 MICROGLOBULIN	Tests for severity of myeloma. Decrease shows good treatment response. Can also identify kidney damage.	
ALBUMIN	A protein found in the blood. Albumin proteins keep the blood from leaking out of blood vessels and are important for tissue growth/healing. Low values can indicate malnutrition, kidney or liver disease, inflammation, protein-losing problems or a sign of more advanced myeloma.	
CREATINE CLEARANCE	Creatinine clearance is the gold standard measurement for kidney function. This measures urine excretion of creatinine against serum creatinine. If serum creatinine is elevated, creatinine clearance is low.	