TREATMENT AT RELAPSE: WHAT TO DO FIRST?

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Over the last years and because of the introduction of novel drugs, autologous stem cell transplant as well as maintenance as part of the first line of therapy, together with the better knowledge of the disease biology and new techniques to measure the residual disease, the duration of the response after the diagnosis is longer than in the past. However, most patients will finally progress and we have to consider some patients and disease-based factors in order to make the right choice: i) chronological age; ii) frailty; iii) organ function; iii) risk status; iv) life style and family support and vi) treatment history.

The first consideration at the moment of the relapse is if we should treat biochemical or clinical relapses and it is highly recommended to treat at the biochemical relapse with the only exception of indolent diseases at the diagnosis (ISS-1, anaemia as the only myeloma defining event…). The second consideration is to evaluate the treatment history and the refractoriness to the previous drugs. Today, most patients at the moment of first relapse, are exposed to proteasome inhibitors and immunomodulatory drugs and refractory to lenalidomide and over the last months, some patients are also exposed to the anti-CD38 monoclonal antibodies.

According to the most recent guidelines and phase 3 clinical trials, if the patient is eligible for anti-CD38 monoclonal antibodies because the patient is naive or sensitive, the optimal choices are carfilzomib-dexamethasone plus either daratumumab or isatuximab or pomalidomide-dexamethasone plus daratumumab. If the patient is not eligible for anti-CD38 monoclonal antibodies, the possibilities would be either pomalidomide-dexamethasone plus bortezomib or Selinexor-dexamethasone plus bortezomib. Of note, venetoclax-dexamethasone alone or in combination will be reserved for patients with t(11;14). These recommendations would be applicable to patients in first relapse. There are some other combination recommended for third line and beyond, and based on pomalidomide-dexamethasone, if the patient has not been previously exposed, in combination with either isatuximab or elotuzumab although it is also possible to combine with cyclophosphamide.

In summary, we have to follow the current guidelines for the management of MM at first relapse although the treatment landscape is rapidly evolving and phase 3 trials are ongoing with the objective of incorporating the BCMA-targeted therapy at first relapse.

AL AMYLOIDOSIS: MECHANISMS OF DISEASE AND BIOMARKERS

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Light chain (AL) amyloidosis is caused by usually small B cell, usually plasma cell, clones that produces a monoclonal light chain (LC) causing organ toxicity, aggregating and forming deposits in tissues. Biomarkers of clonal and organ involvement play a key role in the diagnosis, treatment stratification and in the therapeutic strategy, including response assessment. Serum and urine immunofixation (IFE) and free LC (FLC) measurements are used to detect the amyloid LC. Investigation of chromosomal abnormalities in plasma cells offers precious information for the choice of treatment. Patients with t(11;14) have poorer outcomes with bortezomib and dexamethasone (BDex) with/without cyclophosphamide. These patients can be treated with BDex plus melphalan, daratumumab-bortezomib combinations, and possibly in the future with venetoclax. On the other hand, gain1q21 is associated to a dismal outcome after first-line melphalan and dexamethasone or after lenalidomide or daratumumab-based regimens in relapsed/refractory disease. Patient survival is best predicted by cardiac biomarkers that are also used for stratification in clinical trials and to establish treatment decisions. Proteinuria and estimated glomerular filtration rate are used to assess the risk of dialysis. The replacement of 24h-proteinuria with urinary albumin/creatinine ratio for renal staging has been recently proposed. Hematologic response (HR) is assessed by IFE and FLC measurement and organ response (OR) by changes in NT-proBNP and proteinuria,

HOW TO TREAT HIGH RISK PATIENTS

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Whilst outcome has improved for multiple myeloma patients, the treatment of high-risk and ultra-high-risk disease remains challenging. Recent evidence regarding molecular diagnostics as well as retrospective and novel prospective data regarding improvements with innovative treatment approaches will be discussed in this presentation.

HOW TO TREAT UNFIT AND FRAIL PATIENTS

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Therapeutic options have greatly expanded over recent years defining new standards of care in multiple myeloma (MM). However, MM is a heterogeneous disease as are the patients it affects. As the median age of MM at presentation is 70 years, treating physicians are faced with the quandary of how to efficiently identify frail individuals that may have more difficulty tolerating and recovering from systemic therapy. The implantation of MRD should help in avoiding over and under treatment and may become a surrogate biomarker for accelerated drug development and operational cure.

BIOMARKERS

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months to minimize the risk of false-negative results. Mass spectrometry is also emerging as a potent technique to detect low levels of paraprotein as a surrogate for residual disease. In addition imaging techniques, particularly PET-CT, has an important role for MRD assessment outside of the BM. Currently MRD has been incorporated in numerous clinical trials with different aims: 1. to evaluate treatment efficacy; 2. to compare two treatment approaches; 3. adapted therapy intensity according to MRD follow-up; 4. to adapt maintenance duration; 5. to introduce Early Rescue Intervention (ERI) strategies. The implantation of MRD should help in avoiding over and under treatment and may become a surrogate biomarker for accelerated drug development and operational cure.