Can multiple myeloma become a curable disease?

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For decades, multiple myeloma (MM) has been considered a disease of the elderly, with few therapeutic options apart from alkylators and corticosteroids. The treatment goal was disease control, with response rates of 50%, with occasional complete responses (CRs) and median survival of 2-3 years.[1] In fact, a cure was considered unattainable. It is possible that this state of affairs, which has lasted for more than 30 years, is the reason why the myeloma community has developed a rather conservative outlook.

The introduction of high-dose therapy followed by autologous stem cell support (HDT/ASCT) produced three important changes in the myeloma landscape: i) CR in 15-30% of patients; ii) the possibility of long treatment-free periods with excellent quality of life (QoL); and iii) prolongation of survival by one year.[2] Nevertheless, the greatest change has occurred in the last decade with the discovery of novel agents such as immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib). These have contributed to doubling survival in myeloma patients as compared to the 1990s when only chemotherapy was used.[3,4]

Despite the fact that, until recently, MM was considered incurable, the introduction of HDT and novel drugs has sparked a new debate concerning myeloma treatment. What should our ultimate therapeutic goal be: "cure" or "disease control"? Is it a real debate or merely an intellectual exercise? To settle this, let us consider what we understand by "disease control". Many patients and non-myeloma specialists will take this to mean a treatment that enables the patient to survive for more than 20 years with a good QoL. In other words, we can convert the disease into a chronic condition. I am afraid this aim is far from being a reality in MM, at least at present, since even in the era of novel agents the median survival of elderly patients is 4-6 years and is not more than 8-10 years for young patients. Moreover, with this conservative approach, patients suffer the emotional burden of several relapses until the disease becomes refractory. In fact, in the era of chemotherapy, patients between 50-60 years of age lost 18 years of life.[5] Even if we accept that in the current era survival has improved to 8-10 years, would we be satisfied with this survival horizon for a 53 year-old man? The answer would almost certainly be *"No"*.

Therefore, the next question is whether a cure is a dream worth trying to make a reality.

The first reports of a myeloma cure concerned patients who underwent allogeneic transplant.[6] However, its high transplant-related mortality, the advanced age of patients, and donor limitations restrict this treatment to a small number of patients, and remains an investigative approach.[2,6,7] With HDT/ASCT, 3-10% of MM patients will remain in complete remission for more than ten years and can be considered "operationally cured".[2,8-10] Unfortunately, this is still a very small fraction of patients and it would need to be increased to 40-50% to be able to talk about MM as a potentially curable disease.

To achieve this goal we propose three actions.

i) *To eradicate the tumor clone, including the cancer stem cells*. This applies to all malignancies, and as a prerequisite implies achieving and maintaining the best response early in the disease course.

Today, achieving serological responses should be considered insufficient. Would a doctor treating a patient with chronic myeloid leukemia (CML) be satisfied with just a hematologic or cytogenetic response or would she or he continue treatment until a molecular response was obtained? In MM, it is becoming clear that the deeper the response the longer the survival.[11-14]

Nevertheless, it is important to consider that although eradication of cancer stem cells may be necessary to cure most malignancies, in some others, some residual tumor cells may persist under the control of the immune system. This may apply to tumors with a pre-malignant antecedent, such as MM and low-grade lymphomas, which are usually preceded by a monoclonal gammopathy of undetermined significance (MGUS) or a clonal benign lymphocytosis phase, respectively.[15,16] Thus, although achieving enduring complete remission would be a prerequisite for cure in most MM patients, there are some long-term survivors who do not achieve complete remission but revert to an MGUS-like profile. Whether these residual cells represent cancer stem cells or are merely clonal plasma cells without the capacity to develop a malignant disease remains to be determined. Nevertheless, it is important to distinguish these cases from those in which a suboptimal response is the result of a suboptimal treatment.

Another group of patients in whom complete CR may be misleading are those cases with rapid response but early relapse, as was found for Burkitt's lymphoma; they may benefit from short sequential therapies to avoid tumor cell escape and regrowth.[17] With these two exceptions, a pre requisite to obtain a cure would be to achieve and maintain the best response.

ii) *To use appropriate tools to evaluate treatment efficacy.* As already mentioned, the definition of CR is far from optimal, and sensitive techniques will contribute to the evaluation of minimal residual disease both at bone marrow (BM) level (by using molecular techniques, quantitative PCR, and immunophenotyping techniques such as flow cytometry)[13,18,19] and outside the BM (using imaging techniques such as MRI and PET-CT).[20-22] If myeloma continues to be evaluated by the M-component and morphology it will remain the Cinderella of hematologic malignancies in terms of the resources invested in monitoring treatment efficacy. Moreover, sensitive techniques will avoid both under- and over-treatment, particularly when evaluating

consolidation or maintenance therapies, with all the consequent frustration, cost and toxicity. In addition, it is necessary to perform comprehensive genetic studies at diagnosis to identify those cases that will be resistant to specific agents in order to avoid repetitive errors and cumulative toxicity, and to explore new experimental strategies in these cohorts.

iii) *To search for an appropriate balance between efficacy and toxicity with three different but complementary aims: QoL, survival prolongation and, eventually, the dream of a cure*. These goals should be present in the design of clinical trials, and adapted according to age and co-morbidities.

a) In fit, elderly (>65-70 years) and young patients with co-morbidities, the treatment goal should be to prolong survival and ensure QoL.

b) In very elderly patients (>85 years), the aim should be to ensure QoL and to avoid expensive treatments in a world of economical constraints.

c) In young patients (<65 years), the treatment goal of cooperative groups should be to investigate schemes for which a cure is on the horizon.

If we focus on young patients, it would be relevant to learn from previously incurable and now curable diseases such as Hodgkin's disease and acute lymphoblastic leukemia, in which the primary goal was to achieve a cure and only then to focus on reducing toxicity. In MM, for example, when considering whether ASCT is still needed upfront, one of the arguments against it is that other treatments offer similar efficacy with lower toxicity. Our position is that the philosophy for a cure should be based on the knowledge of those treatments that have demonstrated efficacy, and the investigation of optimal combinations, sequences, and of novel agents, instead of looking for soft replacements of equivalent efficacy that do not improve survival. Examples of this strategy are the results reported by Cavo *et al.*,[23] and the total therapy programs developed by the Arkansas group[17,24] that integrate all treatment tolls through induction, consolidation and maintenance. This approach has resulted in a 4-year CR duration estimated at 89% in patients defined as low-risk by GEP, equivalent to an estimated cure rate of 50%.[17] If the long-term follow up confirms this figure, for the first time we would be in the position to say that MM has become a potentially curable disease. Nevertheless, it should be noted that, as occurs in ALL, effective treatment is not always a matter of dose intensity but of dose density; in other words, the successful combination of sequential treatments.

Regarding risk-adapted treatment, to offer intensive therapies to high-risk patients while using softer approaches for those at low risk could be a mistaken philosophical approach. Thus, the benefit of treatment intensification in low-risk patients was recently demonstrated in a cohort who, although they were already in more than VGPR after ASCT, received intensification with VTD, and none of those who achieved a molecular remission has so far relapsed.[13] Accordingly, the risk of undertreating low-risk patients by concluding that they are already in conventional CR could be a serious error if cure is the goal. Clinical investigation based on large phase III randomized trials that integrate comprehensive genetic studies upfront and sensitive tools for monitoring treatment efficacy will be the best way to find appropriate answers to these questions.

In summary, although we have made great progress in both the understanding of MM biology and the discovery of novel drugs, we are still not in a position to be able to offer a cure for a substantial proportion of patients in the immediate future. In order to achieve this aim, we probably first need to accept that MM should no longer be considered as a single entity, and hence adapt our strategies as appropriate to the MM subtype, as occurs in other hematologic malignancies.

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