Transfusion and Apheresis Science ■■ (2016) ■■–■■

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Is it possible to cure myeloma without allogeneic transplantation?

Eirini Katodritou [a,b], Sofia Papadaki [a], Pavlina Konstantinidou [a], Evangelos Terpos [b,c,*]

[a] Department of Hematology, Theagenion Cancer Hospital, Thessaloniki, Greece
[b] Greek Myeloma Study Group, Athens, Greece
[c] Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

ARTICLE INFO

Keywords:
Multiple myeloma
Translantation
Allogeneic
Bortezomib
Immunomodulatory drugs

ABSTRACT

During the last decades, a better understanding of the biology of multiple myeloma (MM) has led to the application of novel treatment strategies for MM patients. The new anti-myeloma regimens produce higher incidence of durable and of better quality responses and they improve overall survival, challenging the dogma of incurable disease, outside the context of allogeneic transplantation. This review presents all these strategies that aim to cure MM, including continuous treatment i.e. induction, consolidation and maintenance, treatment of asymptomatic MM and monitoring minimal residual disease using modern techniques, such as multi-parameter flow cytometry, molecular assays and advanced imaging.

Contents

1. Introduction

Over the past decades, there were major advances in the treatment of multiple myeloma (MM). The introduction of novel agents and their combinations has led to impressively high quality and durable response rates both in patients with MM who are eligible and non eligible for transplant [1]. As a consequence, progression free survival and overall survival have been prolonged substantially and the quality of life of MM patients has been dramatically improved [1]. However, despite the remarkable progress in treatment, MM is still considered an incurable malignancy; most patients experience sequential relapses with shorter progression-free intervals following each relapse [2]. With autologous stem cell transplantation (ASCT) 3–10% of patients remain

* Corresponding author. Department of Clinical Therapeutics, School of Medicine, Alexandra General Hospital, National and Kapodistrian University of Athens, 80 Vas. Sofias Avenue, 11528 Athens, Greece. Tel.: +30 213 216 2846; fax: +30 213 216 2511.
E-mail address: eterpos@med.uoa.gr (E. Terpos).

http://dx.doi.org/10.1016/j.transci.2016.01.015
1473-0502/

in complete remission (CR) for more than 10 years and thus, they are considered "operationally cured" [3,4]. Allogeneic transplantation is still regarded as the single therapeutic method with a virtually curative potential; however, this treatment modality can be applied in a selected group of young and fit patients, due to excess morbidity and mortality [5].

During the last years, there is growing evidence supporting the theory of intraclonal heterogeneity in MM i.e. the co-existence of multiple diverging tumor subclones that demonstrate competition for survival and differences in drug sensitivity [6,7]. Intraclonal heterogeneity is evident from the stage of monoclonal gammopathy of undetermined significance (MGUS), increases gradually through asymptomatic to symptomatic MM [8], and it is likely, from the "Darwinian" point of view, to be the essential substrate for myeloma evolution, progression and relapse, representing, one of the major impediments to curing MM [6,7]. Consequently, we could speculate that treatment of early disease would probably control intraclonal heterogeneity and prevent the accumulation of secondary genetic events that may lead to disease refractoriness and drug resistance [9].

Under the light of the extensive knowledge that derive from evolutionary biology and the availability of novel therapeutic tools, the dogma of MM being an incurable disease has been challenged [7,10]. Modern strategies targeting to cure myeloma are currently based on three pillars: a) upfront sequential treatments for symptomatic MM i.e. induction, consolidation and maintenance, aiming to achieve deep and durable responses early in the course of the disease, reduce clonal heterogeneity, minimize outgrowth or generation of further mutated tumor subpopulations and modify residual disease biology; b) treatment of patients with smoldering MM (SMM) i.e. patients with less tumor burden, genomic instability and intraclonal heterogeneity compared to advanced disease and finally; and c) optimization of methods to monitor minimal residual disease (MRD) and re-evaluation of response criteria, in order to avoid over or under-treatment.

2. Upfront sequential treatment for MM

Modern therapeutic approaches for the treatment of MM are based on the concept of applying sequential drug combinations given as induction, consolidation and maintenance [7,11]. This strategy aims to minimize tumor burden as much as possible (induction), to reduce aggressive subclones and impede the development of secondary mutations early in the course of the disease (consolidation) and finally, to modify MM biology, i.e. to drive the disease through clonal competition toward the dominance of more benign clones (maintenance) [6,7]. This sequential approach or continuous treatment could theoretically, lead to disease eradication and probably to "operational cure": i.e. sustained complete response (CR) beyond 10 years, for at least some MM patients [7,10].

2.1. Induction therapy: the role of depth of response

Induction treatment aims to reduce as much as possible the tumor burden [11]. This is reflected by the achievement of high quality response rates, i.e. at least very good partial response (vgPR) or CR, according to conventional definitions [12]. The category stringent CR (sCR) defined by negative immunofixation, normal free light chain ratio (FLCR) and absence of myeloma cells in the bone marrow by immonohistochemistry/immunofluorescence, expresses further deepening of the magnitude of response and has been incorporated in the uniform response criteria [12].

In transplant eligible patients the use of doublet or triplet combinations of novel agents with or without chemotherapeutic drugs induce overall response rates (ORR) of 60–100%, at least vgPR of 20–70% and CR of 7–35%, before ASCT; post-ASCT, CR rates reach 40–50% in most of the studies [13]. Triplets incorporating both proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) induce deeper response compared to doublets, suggesting that using compounds with a distinct mechanism of action may result to a more effective killing of different subclones that are differentially sensitive to treatment [7,11]. Several studies have demonstrated that the achievement of deep response rates and sustained remission is the first important step of MM cure [14]. Achievement of at least vgPR and CR has proven a strong prognostic factor for PFS and prolonged OS after ASCT following induction with or even without novel agents [3,15]. In addition, Barlogie et al. have demonstrated that OS was significantly longer in patients with CR sustained for more than 3 years compared to those with CR of less than 3 years or patients who never achieved CR [16]. With regard to the importance of sCR, Kapoor et al. have recently shown that achievement of sCR leads to a 5-year OS of 80% of patients compared to 53% of patients achieving CR, suggesting that there is a need for more thorough evaluation of the residual disease after induction treatment and ASCT [17]. With regard to patients non-eligible for transplant, many studies and a pooled analysis of three phase 3 trials including 1175 patients treated with melphalan-prednisone (MP) vs. MP plus thalidomide (MPT), demonstrated that CR is significantly correlated with prolonged OS [14,18]. Despite the well recognized prognostic value of CR, there are studies suggesting that this is probably limited in high-risk patients identified by gene expression profiling (GEP) rather in patients with standard prognostic profile [19]. Moreover, it was recently shown that newly diagnosed patients with MGUS-like GEP or multiparameter flowcytometric (MFC)-defined MGUS-like immunophenotype, enjoy a prolonged OS, even more than 10 years, despite displaying similar or even lower incidence of CR [20,21]. Interestingly, some patients who achieve partial remission (PR) may be considered as "operationally cured", as they remain alive for more than 10 years, in an MGUS-state, without signs or symptoms of symptomatic MM [20–22]. Of note, Pineda-Roman et al. supported that CR is an independent predictor for OS only in MM patients with unknown prior history and not in those with "evolved" MM, i.e. patients with preceding MGUS or smoldering MM [23]. Taken together, there is a definite need to identify patients who will have a real survival advantage with intensive therapeutic strategies aiming at a cure. In patients with a more "benign" disease, the main goal of treatment should be "control" rather than "cure", as they can achieve prolonged survival without aggressive therapies that carry excess toxicity [24].

Please cite this article in press as: Eirini Katodritou, Sofia Papadaki, Pavlina Konstantinidou, Evangelos Terpos, Is it possible to cure myeloma without allogeneic transplantation?, Transfusion and Apheresis Science (2016), doi: 10.1016/j.transci.2016.01.015