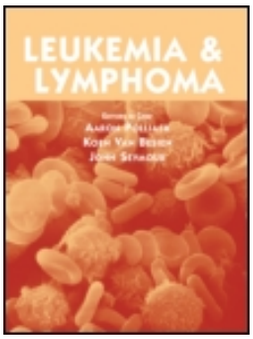

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COMMENTARY

Risk adapted therapy for multiple myeloma: back to basics

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The last decade has been witness to a miraculous transformation in the treatment paradigm for multiple myeloma (MM), fueled by rapid evolution in our understanding of the disease biology, as well as the introduction of several effective therapeutic agents [1]. The immunomodulatory drugs (IMiDs; thalidomide, lenalidomide and pomalidomide) and the proteasome inhibitors (bortezomib and carfilzomib) have become the backbone of current treatment regimens for newly diagnosed and relapsed MM, and have been combined among themselves as well as with older drugs such as alkylating agents (melphalan, cyclophosphamide, bendamustine), anthracyclines and corticosteroids. Increasing insight into the biological underpinnings of the disease has allowed a better understanding of the disease heterogeneity, especially with respect to the genetic abnormalities. This together with the increasing treatment options has expectedly led to the development of risk adapted treatment strategies in MM such as mSMART (Mayo Stratification of Myeloma and Risk-Adapted Therapy; www.msmart.org), which uses a combination of fluorescence *in situ* hybridization (FISH) based study of chromosomal abnormalities, plasma cell proliferation and gene expression profiling data, when available, to estimate risk, and combines this with a treatment algorithm based on the best available data and consensus opinion [2]. While the new drugs and the modern methods of risk assessment have benefited patients, with overall survival of this disease having nearly tripled over this time period, we should not lose sight of other key aspects of the disease [3]. The article by Zhou *et al*. in this issue of the journal highlights two such key issues, the frequent presence of comorbidities in this patient population and the continued importance of some of the older drugs such as the alkylating agents [4].

MM is a disease of the elderly, with the median age at diagnosis of nearly 70 years in the Western hemisphere and a slightly younger population in Asian countries [5]. It is not surprising that many of these patients present with a wide spectrum of comorbidities. Some, like renal abnormalities and bone disease, are clearly related to MM, but others such as heart disease are either unrelated to MM or may be exacerbated by the MM and its therapy. Ischemic cardiomyopathy and valvular heart disease are not uncommon in this older population, the former more prevalent in the Western population and the latter more common in the developing countries. In addition, coexisting amyloidosis can be present in as many as 10% of these patients and may also develop later in the course of the disease, and should not be ruled out of the differential even if not present at the time of initial diagnosis [6]. These comorbidities should be taken into account when deciding on the therapy to be administered, and represent another aspect, albeit an important one, of risk-adapted therapy. The adaptation may take the form of avoidance of particular drugs or attenuating the doses used. Among the older drugs, anthracyclines have been most commonly associated with cardiac toxicities, with high-dose melphalan contributing to a smaller proportion of patients with drug-induced cardiomyopathy. Among the newer drugs, both bortezomib and carfilzomib have been linked to cardiac toxicity, and this may represent a class effect [7,8]. Dose reduction based on the presence of comorbidities and performance status has been another widely accepted approach, as suggested by the Italian investigators [9]. This system classifies patients based on a frailty index, and recommends specific dose reductions for the commonly used drugs.

The current study also highlights the continued utility of the older drugs in patients with relapsed disease. Patients who have relapsed after being exposed to the IMiDs and proteasome inhibitors have relatively poor survival. Use of the older drugs such as the alkylators can provide sustained and meaningful disease control in many of these patients, and should be considered and discussed with patients before moving on to comfort care measures. The regimen of cyclophosphamide and prednisone in particular merits mention. In a study from Princess Margaret Hospital, patients with relapsed MM were treated with oral cyclophosphamide at 500 mg once weekly and oral prednisone at 100 mg on alternate days [10]. Among the 66 patients, 36 (61%) responded to treatment, 24 (41%) of whom had a partial response. The median progression-free and overall survival was 18.6 months and 28.6 months, respectively. The current study utilizes a daily approach compared to the weekly approach taken by the Canadian investigators, with patients receiving 50 mg daily of cyclophosphamide

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and 15 mg daily of prednisone. The authors have previously reported the efficacy of this approach in a smaller group of patients [11]. Other studies have also utilized a similar continuous low-dose approach in patients with relapsed disease with good efficacy [12]. The current study highlights the safety and efficacy of using such a well-tolerated regimen, with a very low risk of cardiac toxicity in a group of patients with pre-existing heart disease, making a strong case for patient adapted therapy, albeit different from the popular concept of risk adapted therapy.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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