Computational and Structural Biotechnology Journal 10 (2014) 38–40

COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL

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

Mini Review

Advances in multiple myeloma therapy during two past decades

Ivan Spicka

Charles University in Prague, First Faculty of Medicine, 1st Medical Department — Clinical Department of Haematology of the First Faculty of Medicine and General Teaching Hospital, Czech Republic

ARTICLE INFO

Available online 11 June 2014

Keywords:
Multiple myeloma
Bortezomib
Lenalidomide
ASCT

ABSTRACT

Multiple myeloma (MM) is a clonal B-cell malignancy characterized by aberrant expansion of plasma cells within bone marrow and extramedullary sites. It is one of the most common haematological malignancies; it accounts for 1.4% of all tumours and is responsible for 2% of cancer-related mortality. Over the last decades, the paradigm of MM therapy has changed dramatically - from the conventional combination of oral melphatan + prednisone, high-dose chemotherapy with stem cell (ASCT) support for younger patients to the present paradigm with the use of one (or more) of 3 major new targeted agents - the first-in class proteasome inhibitor bortezomib, the immunomodulatory drug thalidomide, and its more potent derivative lenalidomide. Their use as a part of initial therapy is associated with high overall response rates as well as high rates of complete response (CR), both for elderly patients unable to undergo ASCT and for younger patients treated prior to ASCT. Altogether, the advent of novel agents has resulted in a 50% improvement in median survival. Moreover, the development of new drug classes based on preclinical rationale and the introduction of next-generation agents are likely to further expand treatment options and improve outcomes for especially relapsed MM. This review highlights important historic landmarks as well as more recent events that have played an important role in the evolution of myeloma targeted therapy.

Contents

Multiple myeloma (MM) is a clonal B-cell malignancy characterized by aberrant expansion of plasma cells within bone marrow and, less frequently, within extramedullary sites. It is one of the most common hematological malignancies; it accounts for 1.4% of all tumors and is responsible for 2% of cancer-related mortality. According to the results of an extensive analysis based on data from across Europe, the USA and Japan, the median survival of patients treated from 1981 to 2000 with high-dose therapy with autologous stem-cell transplantation (ASCT) ranged from 5 to 7 years while, in contrast, it ranged from 3 to 5 years in elderly patients treated with conventional therapy [1].

Over the last three decades, the paradigm of MM therapy has changed dramatically – from the conventional combination of oral melphalan + prednisone and then high-dose chemotherapy with stem cell (ASCT) support for younger patients to the present paradigm with the use of one (or more) of 3 major new targeted agents – the first-in class proteasome inhibitor bortezomib, the immunomodulatory drug thalidomide, and its more potent derivative lenalidomide. Their use as a part of initial therapy is associated with high overall response rates as well as high rates of complete response (CR), both for elderly patients unable to undergo ASCT and for younger patients treated prior to ASCT. Altogether, the advent of novel agents has resulted in a 50% improvement in median survival [2]. Moreover, the development of new drug classes based on preclinical rationale and the introduction of next-generation agents are likely to further expand treatment options and improve outcomes for relapsed MM.

In terms of bortezomib, initial phase I/II and confirmatory phase III clinical trials were soon followed by its approval for the therapy of refractory/relapsed multiple myeloma [3,4]. The potential use of combinations was suggested by numerous preclinical studies; for example, sensitization of myeloma cells derived from both melphalan-sensitive and melphalan-resistant myeloma lines was observed when bortezomib was added to melphalan [5,6]. In combined phase I and II studies, bortezomib administered in combination with melphalan demonstrated encouraging activity and manageable toxicity in patients with refractory/

E-mail address: spicka@cesnet.cz.

http://dx.doi.org/10.1016/j.csbj.2014.05.005
2001-0370/

relapsed MM [7]. This resulted in the initiation of a phase I/II study focusing on the effect of the combination MP + bortezomib (MPV) in newly diagnosed patients older than 65 years, resulting in 32% CR, a median time to progression (TTP) of 27 months, and estimated overall survival (OS) of 85% at 38 months [8]. These exciting results lead to the initiation of the VISTA trial — a multicenter trial designed to compare the efficacy of MPV versus MP [9]. A randomized, open-label, phase 3 study, was carried out in 151 centers across 22 countries. A total of 682 patients either older than 65 years or younger not eligible for ASCT were enrolled. The percentages of partial responses (PR) or better were 71% vs. 35%, respectively ($P < 0.001$), and CR rates were 30% vs. 4%, respectively ($P < 0.001$). Median time to progression (the primary study endpoint) was 24 months in the bortezomib-treated group, compared with 16.6 months in the control ($P < 0.001$). Median duration of response in both groups was 19.9 vs. 13.1 months. This effect was especially pronounced in patients who attained CR, with the median remission duration in the bortezomib group of 24 months, compared to 12.8 months for the control. Clinical benefit was independent of age, sex, region, initial beta-2 microglobulin, albumin, clinical stage according to International Staging System (ISS) and creatinine clearance [10]. Results obtained in patients with unfavorable cytogenetics (which is one of the main negative prognostic factors in MM patients for all therapies used so far, including ASCT) – t(4,14), t(4;16) translocations, 17p deletion, or 13q deletion – were comparable with those in the group without these, both in terms of CR rates and in terms of similar TTP and OS. According to a recent follow-up analysis after 3 years, MP + bortezomib has a highly significant impact on improved OS (HR, 0.653; $P < .001$), with an associated 35% reduction in risk of death. Median OS has still not been reached at the time of publication in the bortezomib group, versus 43.1 months for the control arm, with 109 (32%) and 148 (44%) patients having died, despite significant crossover. This confirmed survival advantage represents an important finding, because the OS benefit with VMP versus MP was seen both overall and in an analysis restricted to patients who had received subsequent therapy, despite 50% of patients treated with MP being rescued with bortezomib-based therapy in the relapsed setting [11].

In younger patients eligible for high-dose therapy the availability of new drugs such as thalidomide, lenalidomide and bortezomib has provided a key step in improving the results of ASCT. The combination of bortezomib plus dexamethasone (as evaluated in the IFM 2005-01 study) showed significantly better response rate when applied to conventional induction therapy prior ASCT [12]. Bortezomib may be considered for 2 years after autologous HSCT based on the HOVON-65/GMMG-HD4 trial. In this study eight hundred and twenty-seven newly diagnosed myeloma patients were randomized to receive 3 cycles of vincristine, adriamycin, dexamethasone (VAD) or bortezomib, adriamycin, dexamethasone (PAD) followed by autologous stem cell transplantation and maintenance with thalidomide 50 mg daily (VAD-arm) or bortezomib 1.3 mg/m(2) every 2 weeks (PAD-arm). Complete response (CR), including near CR, was superior after PAD induction (15% v 31%; $P < .001$) and bortezomib maintenance (34% v 49%; $P < .001$). After a median follow-up of 41 months, PFS was superior in the PAD arm (median of 28 months v 35 months; $P = .002$) [13]. Moreover, bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma according to subgroup analysis [14].

Various combination therapies of bortezomib with new classes of antimyeloma agents have shown promising results in preclinical studies and are currently being tested with the goal of improving response. Lenalidomide plus bortezomib and dexamethasone was investigated by Richardson et al. and has been found to result in high response rates: the ORR was 98%, with 71% of patients achieving a ≥VGPR and 36% of patients achieving a CR/nCR [15]. In general, VD, VTD, PAD or others are currently recommended as initial therapy for 3 or 4 cycles followed by stem cell harvest and ASCT. Four-drug combinations, as tested in the EVOLUTION trial with bortezomib (V), dexamethasone (D), lenalidomide (R) or cyclophosphamide (C) as VDC, VDR and VDCR, have yielded similar PFS and OS, but four-drug combinations induced more side effects, so that VDR and VCD were the preferred regimens for clinical practice [16].

Together with pomalidomide, lenalidomide is a synthetic derivative of thalidomide originally developed in the 1990s to achieve improved potency in the absence of significant side effects. In refractory/relapsed myeloma the time to progression was significantly longer in the patients who received lenalidomide plus dexamethasone than in those who received placebo plus dexamethasone (median, 11.3 months vs. 4.7 months; $P < 0.001$). Overall survival was significantly improved in the lenalidomide group (hazard ratio for death, 0.66; $P = 0.03$) [17]. Lenalidomide plus dexamethasone was superior to placebo plus dexamethasone also in similar study published by Weber [18]. Low-dose dexamethasone is associated with better short-term overall survival and with lower toxicity than high-dose dexamethasone in combination with lenalidomide [19]. As first-line treatment for patients with newly diagnosed MM, Palumbo et al. reported that MPR-R was associated with significantly increased progression-free survival (31 months) compared with MPR (14 months; HR: 0.49; $P < 0.001$) or melphalan — prednisone (13 months; HR: 0.40; $P < 0.001$) [20].

Patients invariably relapse after initial treatment strategies, so the concept of maintenance to prolong response is important. Maintenance therapy with alkylating agents, as well as interferon and steroids, does not impact on OS in MM patients. Although thalidomide consolidation/maintenance results in longer EFS/PFS times, particularly among patients failing to achieve high-quality responses after ASCT, the effect on OS is ambiguous, and many open questions remain. The shorter OS duration observed in several studies appears to be a result of a shorter survival time after relapse, which may be caused by different factors. Among others the possible selection of more resistant clones should be particularly mentioned [21,22]. The use of lenalidomide has now provided considerate enthusiasm for this approach based upon unprecedented improvement in PFD post-ASCT, as well as in patients ineligible for myeloablative therapy [20,23,24], although this benefit is not currently associated with an improved overall survival in one study [25]. Higher incidence of second primary malignancies (SPM) with prolonged use of lenalidomide was observed in initial randomized studies and risk of this complication is studied intensively. Studies on the role of bortezomib maintenance therapy post-ASCT and in elderly patients are ongoing, some are currently available. Mateos and colleagues investigated the role of maintenance therapy with bortezomib plus prednisone (VP) vs VT in elderly patients respectively assigned to induction with VMP and VTP. After a median of 13 month maintenance, there was a trend towards a lower TTP with VP compared with VT (1-year TTP: 71% vs 84%; $P = 0.05$), though no significant difference was found in terms of OS (89% vs 92%, respectively with VP and VT) [26].

Despite recent treatment advances, multiple myeloma (MM) remains an incurable disease in the majority of patients. Second-generation proteasome inhibitors (carfilzomib) and immunomodulatory agents (pomalidomide) have recently been approved. Active clinical research based on the knowledge of novel targets is ongoing. Some of these novel agents seem promising, such as monoclonal antibodies (anti-CD38 — daratumumab or anti-CS1 — elotuzumab) or the histone deacetylase (HDAC) inhibitors [27]. Other agents under investigation are kinase inhibitors, signaling pathway inhibitors or kinesin protein inhibitor Arry-520 [28]. With so many novel agents under investigation, future therapy in MM will probably involve the combined use of the already approved drugs with some of those newly discovered.

Acknowledgment

Supported by PRVOUK-P27/1LF and NT 12215-4/2011.

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