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SPECIAL NOTE

Multiple myeloma in Korea: past, present, and future perspectives. Experience of the Korean Multiple Myeloma Working Party

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The incidence of multiple myeloma suggests an ethnic difference. Compared to Caucasians, who have an incidence rate of 3–5/100,000, Asians show much lower incidence rate compared to them, in the range of 0.5–3/100,000. In Korea, The very first case report of multiple myeloma was published in 1959 [1], and was followed by a few case reports until the 1970s. Since that time, the number of cases of multiple myeloma in Korea increased steadily, reaching 100 cases/year in 1990 [2] and 500 cases/year in 2000 [3], and it is still going up. Currently in Korea, 1,000 patients are estimated to be diagnosed with multiple myeloma, and 700 patients are assumed to die of this disease every year, and 4,000–5,000 patients are suffering from this disease [4]. The most updated, age-standardized, incidence rate of multiple myeloma in Korea is 1.4/100,000, and ranked as the third most common among the hematologic malignancies, only surpassed by non-Hodgkin's lymphoma and acute myeloid leukemia [5]. Besides, the mortality from multiple myeloma

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has remarkably increased compared with the mortalities from the other hematologic malignancies, such as leukemia and lymphoma. Indeed, the incidence and mortality of multiple myeloma in Korea have increased more than 30 times during past 30 years [5] (Fig. 1). This unprecedented phenomenon could be explained in two ways. The first one is an increased detection. Expanding medical insurance coverage increased routine checks, and increased awareness of this disease could partly explain in the increased detection, especially in early period of 1980s. The second explanation is a true increase in the incidence of multiple myeloma. Air pollution, and increased exposure to potential carcinogens and radiation are all associated with rapid industrialization, and are suspected as reasons for the increased incidence of multiple myeloma. Another possible reason for the increase is the aging of the Korean population. Koreans have experienced a 17-year median life span over the past 33 years. Since the year of 2,000, Koreans entered an aging society and are heading to an aged society in the year 2020. Moreover, the speed of aging in Korea is known to be fastest in the world. Thus, in the future, we expect more increasing aged population and the incidence of multiple myeloma, considering Japanese model [5]. The median age of the patients with multiple myeloma also increased from mid-fifties in 1980s to 66 years in 2007 [3].

There have been 3 important advances in the treatment of multiple myeloma. The first one was an emergence of effective chemotherapy using alkylating agents in the early 1960s. The second was an introduction of high-dose therapy (HDT) with stem cell supports in the 1980s, and the third was the advent of targeted agents in 2000s. In the era of conventional chemotherapy, Korean hematologists had to conduct small scale, both prospective and retrospective studies, single center studies that were written in Korean and published in domestic journals. Because multiple myeloma was a relatively rare disease in Korea at that time, it was not easy for a single institute to enroll enough patients into even small phase 2 trials. At times, it took a sometimes more than 5 years, to finish small phase 2 studies even in relatively large hospitals. These studies were simple repeats of Western studies testing the efficacy such of melphalan with prednisone (MP), multi-drug combinations such as M2 protocol [vincristine, carmustine, cyclophosphamide, melphalan, and prednisone (VBCMP)], vincristine with doxorubicin and dexamethasone(VAD) or merely reporting clinical features. The treatment results were almost the same or slightly inferior to Western studies because the patients tended to be diagnosed later in their course of disease [6–13]. There was no room for new drug trials or creative new combination using the existing drugs. Besides, it was before the emergence of official organization or motivated hematologist to conduct multicenter trials. It was only during the era of HDT with autologous stem cell transplantation (ASCT) we realized that multi-center trials are the only way to overcome the problems of a small number of the patients. The emergence of small study groups based on geographic distribution or personal acquaintance occurred spontaneously. These groups began to conduct small-scale multi-center studies of HDT with ASCT, initially as a retrospective study testing the feasibility of HDT with ASCT [14], followed by prospective trials [15]. Later, more sophisticated prospective trials based on cytogenetics including FISH and serum beta2-microglobulin [16], in which allogeneic transplantation is included for high-risk subgroup, were attempted. Multicenter trials for basic studies in myeloma physiology also began [17]. Small retrospective studies on the efficacy of novel agents such as bortezomib [18] or thalidomide [19] in patients with refractory or relapsed myeloma were also conducted. However, these trials were still not nationwide studies.

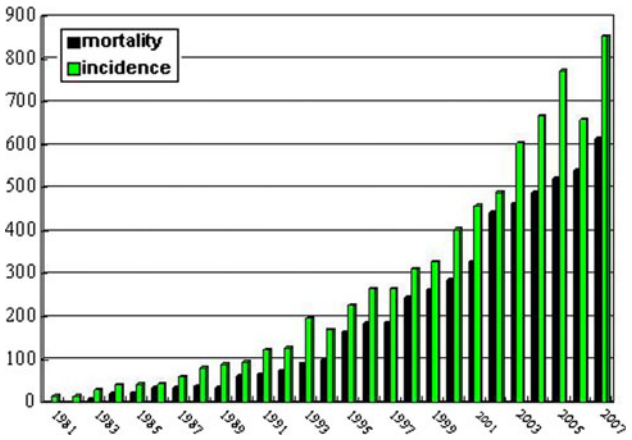

Fig. 1 Changes of incidence and mortality of multiple myeloma over 30 years in Korea

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The Korean Society of Hematology (KSH) which celebrated its 50th anniversary in 2008 decided to launch official study groups in 2005; these study groups were working parties for major hematologic diseases. The Korean Multiple Myeloma Working Party (KMMWP) which began in November 2005 was one of the 11 working parties launched under the auspices of the KSH. KMMWP immediately began a retrospective study on the toxicities of bortezomib in Korean population; this study had never before been published in Asians [20]. Bortezomib toxicities, whose profiles were similar to Western data, were reported. The most commonly observed toxicities were thrombocytopenia (47%) and sensory neuropathy (42%), while the gastrointestinal toxicities were reported lower than Western data. The comparison of various myeloma staging systems in predicting the efficacy of HDT was also published [21]. The Southwest Oncology Group (SWOG) staging system and International Staging System (ISS) at diagnosis were able to predict progression-free survival (PFS) as well as overall survival (OS) after HDT with ASCT, but the Durie–Salmon system (DSS) was not. We collected bone marrow samples of Korean myeloma patients, and performed cytogenetic study in the central laboratory. We published cytogenetic characteristics of Korean patients with multiple myeloma using FISH technique [22]. We found that 13 q deletion (45.6%), IgH translocation (41%), and 1q gain (38.8%) were the most common cytogenetic aberrations in Korean patients with multiple myeloma.

The KMMWP immediately began prospective multicenter trials testing the efficacy of targeted agents such as bortezomib or thalidomide in relapsed myeloma [23, 24] as well as in newly diagnosed myeloma either in transplantation candidates [25, 26] or in non-transplant candidates [27]. Approximately 20 institutes have participated in each study. These protocols were registered to the National Institute Of Health (NIH) of USA (http://ClinTrials.gov), and were posted to the website of the Multiple Myeloma Research Foundation (MMRF). These were conducted for the first time under strict monitoring in Korean hematology study history. All of these studies showed very high response rates with acceptable toxicities, confirming the high efficacy of novel agents in the treatment of multiple myeloma.

In salvage setting, 6 cycles of bortezomib with doxorubicin and dexamethasone (PAD) followed by 12 cycles of thalidomide with dexamethasone (TD) consolidation resulted in a very high response rate (RR) of 83.6% including 51.4% complete response (CR), 13.4% near complete response (nCR), 5.4% very good partial response (VGPR), and 13.4% partial response (PR) [23] by modified EBMT criteria with additional categories of nCR and VGPR. With the median follow-up of 27 months (range 13–39 months), the median PFS was 18 months (95% CI 9.7–26.2 months), with a 1-year PFS rate 56.9% and 3-year PFS rate 25.7%. Median OS was 35.1 months (95% CI 18.5–51.7 months), 1-year survival rate 75% and 3-year survival rate 27.3%. We also studied the efficacy and safety of a four-drug combination of bortezomib, cyclophosphamide, thalidomide, and dexamethasone (Vel-CTD) for patients with relapsed or refractory multiple myeloma [24]. The overall best response rate was 87.2%, with 45.7% CR 8.6% VGPR, and 32.9% PR. After a median follow-up of 12.6 months, the median PFS was 14.6 months and the 3-year PFS was 14.5%. The median OS was 31.6 months and the 3-year OS was 47.2%. These 2 trials showed very high response rates in salvage setting. The reason for this high response is not easily explainable. This could be explained as selection bias. However, these high responses were not durable and were not translated into improved survival.

In the front-line treatment setting for transplant candidates, 2 cycles of bortezomib (Velcade) with thalidomide and dexamethasone (VTD) followed by 2 cycles of the classic vincristine with doxorubicin and dexamethasone (VAD) regimen resulted in 96% response rate including 28% CR + nCR before HDT [25]. In another study, 4 cycles of cyclophosphamide with thalidomide and dexamethasone (CTD) also resulted in 86.5% RR including 38% CR [25]. For the transplant-ineligible patients, 6 cycles of bortezomib with thalidomide and dexamethasone (VTD) induction therapy followed by 8 cycles of melphalan with thalidomide and prednisone (MPT) consolidation resulted in 95% RR, including 74% CR, 5% nCR, 11% VGPR, 5% PR, and 5% progressive disease (PD) [27].

These were the first studies reporting the efficacy of targeted agents as front-line therapies in an Asian area. These trials used the analysis of the cytogenetics using both conventional cytogenetics and FISH in the central laboratory. We built bone marrow sample delivery system for these trials. We realized the importance of sharing clinical samples as well as ideas for basic studies on myeloma. Serial multicenter basic studies have been done on the incidence of genetic polymorphisms of NQO1 gene [28] and CYPA1 gene [29] that can, at least partly, explain the relatively lower genetic susceptibility of myeloma in the Asian population, antagonistic interaction of polyphenols on bortezomib treatment [30], incidence of interleukin-6 receptor gene (*IL6R*) amplification [31], and its implication in the prognosis of MM, and methylation profiles of *p14*, *p15*, and *p15* gene and its prognostic implications in MM [32].

Next, we constructed the Korean Myeloma Registry (KMR), a web-based patient registry system. Currently, more than 4,000 patients who were diagnosed after the year of 2,000 are registered from 41 institutes. We have documented the basic feature of this population [33].

The median age was 64 years, and there is a slight male predominance. The ISS I/II/III score were 17, 31, and 39%, respectively. The median survival time was 50 months, and was well delineated by the ISS. Based on registry data, we already completed some retrospective multi-center studies. We analyzed the importance of attaining CR before HDT [34]. Patients who achieved CR before HDT (continued CR) had significantly higher survival rate than patients who achieved CR only after HDT (induced CR) ($P = 0.018$) We compared the results of reduced intensity stem cell transplantation (RIST) following autotransplant versus tandem autotransplant [35]. There was no significant difference in the event-free survival (EFS) ($P = 0.26$), OS ($P = 0.13$), treatment-related mortality (TRM, $P = 0.35$), and disease-related mortality (DRM, $P = 0.33$) between ASCT/RIST group ($n = 30$) and tandem ASCT group ($n = 126$). We also analyzed the survival difference between the tandem ASCT group versus the single ASCT retrospectively [36]. We found that tandem transplant is an independent prognostic factor for PFS ($P = 0.002$) and OS ($P = 0.044$) in our patient population.

We studied the incidence of herpes zoster reactivation after treatment with bortezomib [37]. In our study, 22% out of 267 patients suffered from Varicella zoster reactivation. We also performed retrospective studies showing the incidence of thromboembolic complications with thalidomide use in Korean patients [38]. In that study, only 3.9% out of 360 Korean patients developed arterial or venous thrombosis. This rate was apparently lower compared to Western study of a Caucasian population, implying an ethnic difference of susceptibility to thromboembolism. We also compared the various induction regimens before autotransplant [39]. Bortezomib seemed to induce high rate of CRs compared to the other induction regimens. We published the cytogenetic characteristics of Korean myeloma patients as previously described [22]. A similar study was performed in Waldenstrom macroglobulinemia (WM) this year [40]. We found the difference in cytogenetic characteristics between MM and WM. We also discovered subtle difference between our data and Western data.

In the field of immunotherapy, antigen-presenting cells with increased potency, such as dendritic cells (DCs) or CD40-activated B cells [41, 42], were investigated by members of KMMWP. They reported the possibility of immunotherapy for MM with the use of myeloma-specific cytotoxic T lymphocytes (CTLs) that were stimulated in vitro by DCs pulsed with purified and optimized myeloma lysates [41]. The defective function of DCs in patients with MM was significantly affected by loading tumor antigens, and neutralization of VEGF could overcome this DC dysfunction through the elimination of abnormal signal transduction [43]. In addition, autologous DCs loaded with allogeneic myeloma cells can generate potent myeloma-specific CTL responses against autologous myeloma cells [44]. On the basis of these bench works, they are going to perform a clinical trial using potent DCs in patients with MM.

At last year's American Society of Hematology (ASH) meetings, we presented several retrospective studies such as clinical presentation of IgD myeloma [45], malignant pleural effusions of multiple myeloma [46], osteonecrosis of jaw [47], the FISH characteristics and survival [48], and the effect of bortezomib on bone metabolism [49].

In the past, due to the low incidence of multiple myeloma and other obstacles, we were not able to conduct high-quality studies. However, the changes described above made us able to present dozens of abstracts at international meetings such as International Myeloma Workshop (IMW), ASH, and European Hematology Association (EHA), etc. Most of the studies presented as abstracts were already published in peer-reviewed journals.

In 2009, we participated in 2 important global project of international myeloma working group, a FISH study and historical control project [50, 51]. KMMWP supplied substantial number of cases from Asia to these global trials. We also began to participate in the review articles of International Myeloma Working Group (IMWG) such as treatment guideline from 2009 [52].

In 2010, a few important sponsor initiated global clinical trials (SIT) of novel agents (velcade, revlimid, vorinostat, panobinostat, tanespimycin, masitinib: Vantage, First, Panorama-1 Study, etc.) were launched in Korea as well as investigator-initiated trials (IITs) such as Revlimid monotherapy for standard risk MM, shared with the Moffitt Cancer Center, USA. Moreover, a dozen of prospective studies (KMM93, KMM94, and KMM97) and retrospective studies (KMM95, KMM96, KMM101-107) of our own are ongoing. With these studies, we would like to provide new drug use opportunities to our patients as well as to contribute to the society of multiple myeloma research.

The KMMWP has been holding patient- and family-supporting seminars annually since it held the first seminar at 2006 joined by International Myeloma Foundation (IMF). Besides, more than a dozen of myeloma experts from all around the world visited Korea by its invitation. Also KMMWP is seeking for regional collaborations with Asian countries such as joint conference with Japanese Myeloma Study Group (JMSG).

Hopefully, the research activities on multiple myeloma in Asian countries will soon intensify, move toward the main stage of the world, and compete with US or European groups. There are ongoing activities for the establishing of national myeloma study groups in Asian countries. Some of the groups may experience the same thing we faced few years ago. We would like to share our experience with them for the proliferation of Asia myeloma study.

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