stabilize them against proteolytic degradation by phago-cytes and affinities of selective organ deposition..

Renal dysfunction in AL amyloidosis is frequently caused by glomerular injury due to deposit of amyloid and observes high albuminuria and nephrotic syndrome. Its progression leads to kidney failure, and in many cases requires dialysis.

Transplant eligible patients

Transplant group(n=31✕)
Non-transplant group (n=49)
✕Transplants for 2 patients had been performed in other hospitals

Observation Days (Day)
P=0.00321

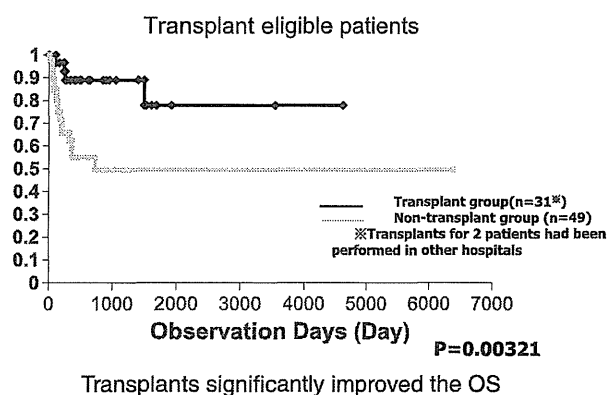Transplants significantly improved the OS

Fig. 12 Autologous stem cell transplantation (ASCT) for AL amyloidosis. ASCT in the early stage of AL amyloidosis is effective for the OS and good QOL. In our experiences, group of ASCT showed good OS compared with the others ($P = 0.00321$)

Therapy of AL amyloidosis

The target of chemotherapies is the amyloidogenic clonal plasma cells in the bone marrow. Complete remission is the normalized kappa/lambda ratio of serum FLC, the surrogate markers. Similar to MM, the recovery of function in the damaged organ requires the improvement of primary disease. However, the recovery from renal dysfunction with amyloid deposits requires a longer complete remission period. High-dose chemotherapy followed by autologous peripheral blood stem cells (ASCT) is effective in treating AL amyloidosis (Fig. 12).

The response criteria are roughly classified into hematological response comprised of elimination of M protein, etc. and organ response. In case of renal dysfunction, it is judged by decrease of albumin. The four-year survival rate in transplantation group and non-transplantation group is 71 and 41 %, respectively, showing higher survival rate in transplantation group [44], and in the patients who survive over 1 year and obtain complete remission after ASCT, over 10 years of prognosis can be expected [45]. In our faculty, we conducted high dose chemotherapy with ASCT during 2005–2010 in 15 patients with renal amyloidosis who were 65 years old or younger and had good PS, and every case showed good results (Fig. 13). Poor

Recovery of albumin levels of kidney-type AL amyloidosis by ASCT

ASCT (n=15)

Doted line showed two cases of HD after ASCT
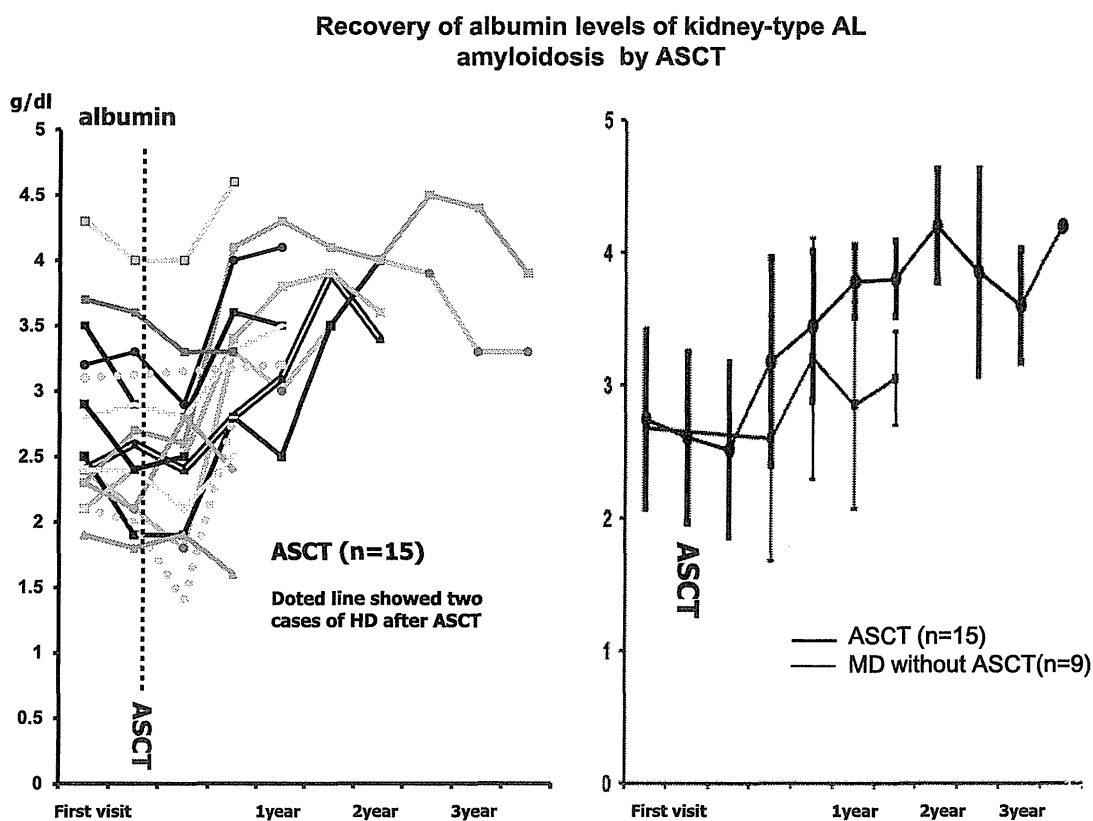
ASCT (n=15)
MD without ASCT(n=9)

Fig. 13 Effect of ASCT for renal type of AL amyloidosis. Early recoveries of the albumin concentration occurred by ASCT in the early stage

prognostic factors in high-dose chemotherapy are poor PS, symptomatic cardiac failure, organ failure in more than two organs (heart and kidney), and old age (over 65 years of age), and these cases are non-transplant candidates [46]. MD (melphalan and dexamethasone), thalidomide (Thal/Dex), cyclophosphamide-thalidomide (CTD), and the combinations of MM therapy are the first option for the transplant ineligible. In MD therapy, approximately 60–70 % of hematological improvement and approximately 50 % of improved organ were observed [47]. In overseas, clinical studies are conducted on novel agents (lenalidomide, thalidomide, and bortezomib) of myeloma in combination with melphalan, dexamethasone and cyclophosphamide against AL amyloidosis. Of these, bortezomib is considered most promising because improvement of organs can be expected in addition to its rapid hematological improvement with high rate. On the other hand, peripheral neuropathy and cardiotoxicity were reported as major adverse events of bortezomib, patients have to be carefully observed with these complications. Lenalidomide shows poor tolerability in AL amyloidosis patients at 25 mg/day which is a standard dose in multiple myeloma, and its MTD is 15 mg/day in AL amyloidosis. Around 50–70 % of hematological improvement and around 20–50 % of improvement in organs was reported in lenalidomide therapy of AL amyloidosis [48, 49]. Appropriate use of lenalidomide depending on the state of patients should be considered because it has a different profile of adverse events from bortezomib. Because thalidomide and lenalidomide were reported to worsen renal function in patients with renal amyloidosis, careful monitoring should be given when used in such patients. Transplantation of the involved organs is also an option in the overseas.

Conclusion

As mentioned above, the therapy and treatment strategy of MM and AL amyloidosis have largely changed in these recent years. At same time, it is becoming more important to control the disease in a long-term fashion, maintaining QoL of patient because it is still difficult to cure the disease. The increase in the number of treatment options means that personalized medicine which selects a treatment corresponding to the systemic condition of the patient, and the purpose of the treatment will be more important. It is important to treat MM as chronic disease by taking into full consideration efficacy and safety of novel drugs and by effectively combining them with existing drugs. Also we should consider how we could help patients through the treatment to live long actively in the society.

MM and AL amyloidosis are caused by functional abnormality of monoclonal plasma cells, and high-dose chemotherapy supported with autologous peripheral blood stem cells is effective to these diseases. However, they are still difficult to be cured and require long-term disease control. In recent years, introduction of novel agents has changed their treatment strategies.

Better understanding of the biology of the amyloidogenic plasma cell clone and the molecular mechanisms underlying the light chain misfolding, tissue targeting and toxicity will define disease-related prognostic criteria. Risk-adapted therapeutic strategies may be required.

However, it is important to take these diseases as chronic diseases. For this purpose, early diagnosis and timing of initiation of treatments is important. Moreover, understanding of characteristics of novel agents and using them in combination with existing drugs appropriately for individual patient is critical. In addition, collaboration with renal medicine is essential to avoid introduction of dialysis. Also we should consider how we could help patients by treatment to live long actively in the society.

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Current Therapeutic Strategy for Multiple Myeloma

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This is a review regarding the current therapeutic strategies in the management of multiple myeloma. Due to the introduction of several new effective therapeutic agents, multiple myeloma is one of the most active and changing fields in clinical oncology. Multiple myeloma is caused by the expansion of monoclonal plasma cells and secretion of M-protein (immunoglobulins, Bence Jones protein and free light chain). High-dose chemotherapy supported with autologous peripheral blood stem cells is an effective treatment for the disease. However, multiple myelomas are still difficult to cure and require long-term disease control. In recent years, the introduction of novel drugs (bortezomib, lenalidomide and thalidomide) has improved treatment.

Key words: multiple myeloma – ASCT – SPM – renal insufficiency

INTRODUCTION

Multiple myeloma (MM) is an incurable disease with a high incidence rate in the elderly. Responsiveness to treatments varies largely among patients due to the high heterogeneity of MM. The decision of which treatment is best has been a difficult issue in MM. However, changes in treatment strategies can be seen due to the introduction of novel drugs (bortezomib, lenalidomide and thalidomide) that have been able to achieve good quality responses. The treatment of MM has advanced remarkably in recent years; this article reviews the latest trends and future outlook for the treatment of MM.

HISTORY OF MYELOMA TREATMENTS

In 1962, Bergsagel et al. (1) reported that L-phenylalanine mustard (melphalan) could induce remission in approximately one-third of patients with MM. In 1967, Salmon et al. reported that high doses of glucocorticoids could induce remission in patients with refractory or relapsing MM (2). Combination therapy with melphalan and prednisolone in 1969 by Alexanian et al. had a better remission than melphalan alone (3). However, the response rate with alkylators and corticosteroids was only ~50%, and complete response (CR)

was rare. A cure was never the goal of therapy, as it was assumed to be unattainable. Instead, the goal was to control the disease as much as possible, providing the best quality of life to patients for the longest duration by judicious, intermittent use of the two available classes of active chemotherapeutic agents. In 1986, clinical studies evaluating high-dose therapy with autologous stem-cell transplantation (HDT-ASCT) with single ASCT (McElwain) and double ASCT (Barlogie) were conducted. In 1996, the first randomized study showed the benefits of HDT-ASCT vs. standard chemotherapy. Berenson et al. described the efficacy of bisphosphonate pamidronate in reducing the skeletal events in patients with advanced MM. In 1999, both the thalidomide and the first non-myeloablative mini-allogeneic transplants were introduced with several novel agents that target the biological pathway of the disease, as well as long-acting Adriamycin® analogues. In the past decade, thalidomide, bortezomib and lenalidomide have emerged as effective agents for the treatment of myeloma, producing spectacular results in combination with other known agents in terms of response rate, CR rate, progression-free survival (PFS) and more recently, overall survival (OS) (Fig. 1).

In 2001, a new classification system introduced the CRAB (hyperCalcemia, Renal impairment, Anemia, Bone disease)
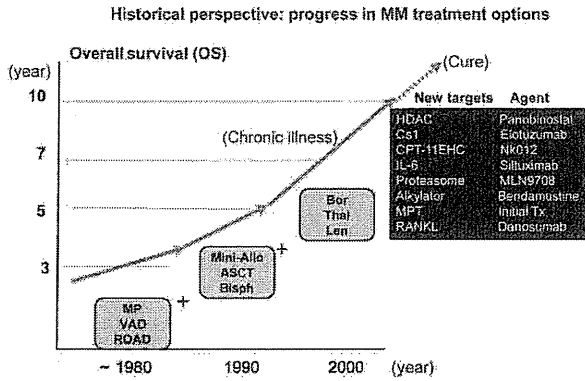
Historical perspective: progress in MM treatment options

Figure 1. Historical perspective: progress in MM treatment options. 1970, MP; 1986, HDT with ASCT; 1999–2000, new drugs (bortezomib, lenalidomide and thalidomide) were epoch making. The CS-1 antibody (Elotuzumab) and IL-6 antibody (Siltuximab) may be effective with some combinations. Bendamustine, a bifunctional agent, shares properties of alkylating agents and purine analogs. New combination trials of new agents, as shown in the right side may be promising.

features of organ damage (4). In 2004, the International Staging System was introduced. The results obtained from new combinations have indeed been remarkable and have created a relatively new philosophy of treating myeloma with the goal of a potential cure rather than the disease control.

During the past two decades, HDT-ASCT has become the standard treatment option for patients with untreated MM who are <65 years of age; however, HDT-SCT is not usually recommended for older patients and patients with clinically significant co-morbidities.

A recent study has shown that long-term survival improved significantly in younger patients, while only limited improvement was achieved in elderly patients. Improved treatment for such older patients ineligible for HDT-SCT was much awaited. Should we treat patients with myeloma with multidrug, multitransplant combinations to pursue the goal of potentially curing a subset of patients, recognizing that the increase in adverse events (AEs) and decrease in the quality of life (QoL) will be substantial? Or, should we consider myeloma as a chronic incurable disease with a goal of disease control, using the least toxic regimens, emphasizing a balance between efficacy and the quality of life, and reserving more aggressive therapy for after relapse or the refractory phase.

INDUCTION THERAPY FOR PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

The effect of novel agents on outcome in patients with newly diagnosed multiple myeloma (NDMM) was dramatically improved over previous therapies (5). Treatment of newly diagnosed MM and maintenance therapies are shown in the National Comprehensive Cancer network (NCCN) guidelines, version 1.2013.

BORTEZOMIB

BORTEZOMIB AND DEXAMETHASONE (DOUBLET)

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. It is cytotoxic to a variety of cancer cell types *in vitro* and causes suppression of tumor growth *in vivo* in non-clinical tumor models, including MM. Specifically, bortezomib is effective in MM via its inhibition of nuclear factor-κB activation, its attenuation of interleukin-6-mediated cell growth (direct apoptotic effect), and possibly antiangiogenic and other effects (6). Bortezomib was approved in the USA in 2005 for the treatment of MM patients with a history of at least one prior therapy, based on the results from the Phase 3 Assessment of Proteasome inhibition for EXtending remission study, which showed superiority of bortezomib over high-dose dexamethasone in patients with relapsed MM (7). An Intergroupe Francophone du Myélome (IFM) Phase 2 study investigated BD as the induction therapy before transplantation in 48 patients with previously untreated MM (8). The response rate was 67%, including 21% CR or near complete remission (nCR) and 31% achieved at least a very good partial response (VGPR). Therefore, 55% of posttransplantation patients achieved VGPR or better. Toxicities were generally mild to moderate and proved manageable; there was no treatment-related mortality. In a report of 48 patients with untreated symptomatic myeloma, Jagannath et al. administered bortezomib 1.3 mg/m^2 twice weekly plus dexamethasone 40 mg on the day of and the day after bortezomib. The CR/nCR rate was 19%, and the partial response (PR) rate was 71%, giving a 90% overall response rate (ORR) (9).

BD AND A CYTOTOXIC DRUG (DOXORUBICIN OR CYCLOPHOSPHAMIDE) (TRIPLET)

In a Phase 3 study, the PAD regimen (bortezomib, dexamethasone and doxorubicin) was compared with VAD (vincristine, dexamethasone and doxorubicin) as induction therapy before ASCT (10). Superior CR/nCR rates were seen with PAD compared with VAD after both induction (11 vs. 5%, respectively) and ASCT (30 vs. 15%). PAD induction followed by ASCT and subsequent bortezomib maintenance was associated with significantly longer PFS and OS compared with VAD induction and post-ASCT thalidomide maintenance therapy. The (preliminary) overall CR rate including maintenance was 27% (PAD arm) and 5% (VAD arm), $P = 0.001$. Two additional Phase 2 studies confirmed the activity of a PAD-like induction regimen incorporating pegylated liposomal doxorubicin (11).

In addition, cyclophosphamide has also demonstrated substantial activity when combined with VD (CyBorD or VCD) in preparation for ASCT (12,13). In this trial, an additional 370 patients up to 60 years of age with untreated MM were enrolled to receive three 3-week cycles of induction treatment with V (1.3 mg/m^2 IV), Dex (40 mg/d oral) and

C (900 mg/m^2 IV) before scheduled high-dose melphalan and ASCT. All 370 patients (88.3% completed three cycles) were included in the intent-to-treat analysis. The ORR (ORR = CR + PR) was 84%, with 10% CR and 74% PR, 5.7% minor response (MR), 7.3% no change and 2.3% progressive disease.

BORTEZOMIB, MELPHALAN AND PREDNISOLONE THERAPY

Regarding the treatment of patients who are not eligible for transplantation, thalidomide, melphalan and prednisolone (MPT) and bortezomib, melphalan and prednisolone (MPB) have shown a significantly better OS benefit than that of MP and are the recommended treatments.

Five-year OS data from an MPB follow-up study have recently been published (14,15). After a follow-up period of 60.1 months, OS for those treated with MPB was significantly superior to those treated with MP; OS was 56.4 and 43.1 months, respectively. These data are remarkable because of the magnitude of improvement in OS (13.3 months). In comparison, MPT only showed an improvement in OS of 6.6 months in a meta-analysis (16). As a result of this VISTA study, MPB became the standard treatment for transplant-ineligible patients with NDMM.

To evaluate the safety, pharmacokinetics and efficacy of MPB therapy, we conducted a Phase 1/2 study for untreated Japanese MM patients who were ineligible for ASCT (17).

The continuity of treatment cycles and the incidence of interstitial lung disease were assessed. This Phase 1/2 study in Japan suggests that the recommended dose of bortezomib in MPB therapy is 1.3 mg/m^2 and that MPB therapy in newly diagnosed Japanese MM patients ineligible for ASCT is as effective as that shown in the VISTA trial.

In the past, achievement of a CR in MM was rare. New treatments can increase the rate of CR to the same level with high-dose therapy followed by ASCT (Fig. 2) (18–20). Also, the CR rate in Phase 3 trials in non-transplant patients
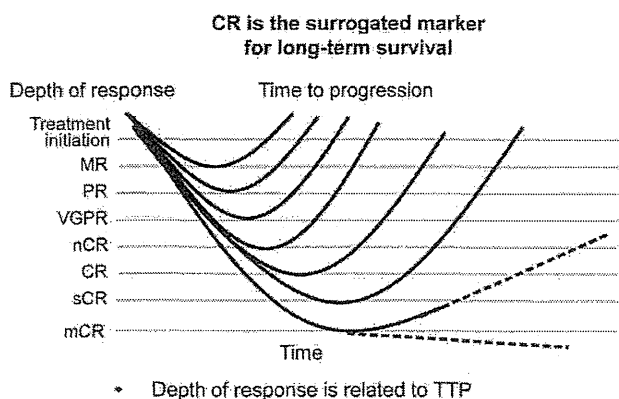

Figure 2. CR is the surrogated marker for the long survival. CR correlates with the long-term PFS and OS. Achieving CR and sustaining CR within a 3-year landmark from the treatment initiation was associated with highly superior survival. Adapted from refs Niesvizky et al. (18); Harousseau et al. (19); Chanan-Khan et al. (20).

was MPB, 30%; MPT, 16%; lenalidomide in combination with MP (MPR), 3.3% and lenalidomide in combination with MP followed by lenalidomide monotherapy (MPR-R), 9.9%.

SURVIVAL ANALYSIS OF BORTEZOMIB ADMINISTERED SUBCUTANEOUSLY VS. IV IN PATIENTS WITH RELAPSED MM

The Phase 3 MMY-3021 study compared the safety and efficacy of subcutaneously (SC) vs. IV administration of bortezomib in patients with relapsed myeloma (21). The Phase 1 study demonstrated non-inferior efficacy with SC vs. IV administration for the primary endpoint (ORR) after four cycles of single-agent bortezomib (22).

After a median follow-up of 11.8 months in the SC group and 12.0 months in the IV group, there were no significant differences in time to progression (median 10.4 vs. 9.4 months) or 1-year OS (72.6 vs. 76.7%) with SC vs. IV bortezomib, respectively. Peripheral neuropathy of any grade [56 (38%) vs. 39 (53%)]; $P = 0.044$], Grade 2 or worse [35 (24%) vs. 30 (41%); $P = 0.012$] and Grade 3 or worse [9(6%) vs. 12 (16%); $P = 0.026$] was significantly less common with SC than with IV administration. SC administration was locally well tolerated.

THALIDOMIDE AND CYCLOPHOSPHAMIDE

The rationale for using thalidomide was based on its antiangiogenic properties because increased microvessel density in MM has been inversely correlated with survival. However, thalidomide has multiple modes of action, including immunomodulatory effects. This initial experience generated great enthusiasm and a large number of Phase 2 trials were conducted. A systematic review of 42 trials comprising >1600 patients confirm that the response rate is 29% with an estimated 1-year OS of 60%.

The well-known teratogenicity of thalidomide is not a major concern in patients with MM because of patient age, but still justifies careful informing of patients to avoid drug exposure in women with childbearing potential. The major toxicities of thalidomide are peripheral neuropathy, fatigue, somnolence and constipation, which are related to the daily dosage and treatment duration. The overall incidence of peripheral neuropathy is 30% but may be higher if treatment is prolonged for >1 year. Because this complication may be disabling and sometimes irreversible, patients should decrease the dose or stop treatment if significant numbness occurs.

CYCLOPHOSPHAMIDE, THALIDOMIDE AND DEXAMETHASONE THERAPY

The MRC Myeloma IX trial was a large-scale, multi-center Phase 3 study conducted in the United Kingdom. This trial investigated the efficacy of treatment with cyclophosphamide, thalidomide and dexamethasone (CTD) as well as with its attenuated regimen (CTDa) for induction therapy, in comparison with the combination of cyclophosphamide, vincristine, doxorubicin and dexamethasone (CVAD) and MP

therapy. In transplant-eligible patients with NDMM, the CR rate after induction therapy was 13.0% in the CTD group vs. 8.1% in the CVAD group ($P = 0.0083$), and the CR rate after transplantation was 50.0 vs. 37.2%, respectively ($P = 0.00052$) (23). CTD therapy was superior to CVAD therapy at every time point, but PFS and OS did not differ significantly between the two groups (PFS, $P = 0.56$; OS, $P = 0.29$).

In transplant-ineligible patients, the ORR ($\geq$PR) of the CTDa group was ~2-fold higher than the MP group ($\geq$PR, 63.8 vs. 32.6%, $P < 0.0001$; CR, 13.1 vs. 2.4%, respectively). PFS was extended significantly with CTDa therapy compared with MP therapy (13.0 vs. 12.4 months, $P = 0.01$, respectively), whereas OS did not differ between these two groups (33.2 vs. 30.6 months, $P = 0.24$, respectively) (24). Therefore, a CTD regimen would be considered an efficacious oral regimen. Furthermore, dose adjustment for elderly patients would lead to an improvement in their treatment tolerability, as demonstrated in those given CTDa therapy.

BORTEZOMIB, THALIDOMIDE AND DEXAMETHASONE THERAPY

The MMY-3006 study led by the GIMEMA Italy compared bortezomib, thalidomide and dexamethasone (VTD) to TD as induction therapy followed by VTD vs. TD as consolidation therapy after tandem transplantations for transplant-eligible patients with NDMM. The CR rate after induction therapy was 22.5 vs. 5.6% (VTD vs. TD, $P < 0.0001$) and 48.7 vs. 40.4% ($P = 0.131$) after tandem transplantations, indicating the superiority of VTD therapy. Furthermore, the estimated 3-year-PFS rate was 60% in the VTD group vs. 48% in TD group ($P = 0.043$)(25). AEs (Grade 3/4) that occurred at a higher frequency in the VTD group (compared with TD) during the induction therapy were skin rash ($P = 0.0001$) and peripheral neuropathy ($P = 0.0004$). Incidence rates of constipation ($P = 0.45$), deep-vein thrombosis ($P = 0.53$) and infection excluding herpes zoster ($P = 0.35$) were comparable between the two groups (26).

The above findings suggest promising potential of VTD therapy for induction therapy prior to transplantation based on its greater CR rate and a longer PFS compared with TD therapy. However, reduced-dose VTD (V, 1.3 → 1.0 mg/m²; T, 200 → 100 mg/day) is an imperative point in order to prevent the appearance of peripheral neuropathy upon administration of both bortezomib and thalidomide with slightly reduced efficacy (27).

LENALIDOMIDE

Lenalidomide is one of the immunomodulatory derivatives of thalidomide and has more potent biologic activities, such as direct anti-myeloma effects, via the production of IL-2 and IFN-γ, which lead to the activation of cytotoxic T cells and natural killer (NK) cells and inhibition of IL-6 and TNF-α production for the survival of MM cells (28).

Recently, cereblon, which is composed of E3 ubiquitin ligase complex, has been identified as the target molecule of lenalidomide and required for both direct anti-myeloma activities and the induction/inhibition of cytokines/growth factors from T cells and bone marrow stromal cells. Lenalidomide especially down-regulates the expression of IRF-4, which is critical for the survival of MM cells and the knock-down of cereblon leads to the down-regulation of IRF-4 and apoptosis in MM cells (29,30). As seen in *in vitro* growth inhibition and apoptosis of MM cells by lenalidomide, the administration of lenalidomide is effective in patients with high IRF-4 expression who have a poor prognosis in comparison with those with low IRF-4 expression (31).

Two randomized Phase 3 trails (MM-009/010) compared lenalidomide plus high-dose dexamethasone and high-dose dexamethasone monotherapy in patients with relapsed/refractory multiple myeloma (RRMM). Lenalidomide showed better efficacy for response rate, time to progression (TTP) and OS (32,33). A pooled analysis of these two studies showed that ORR and CR rates were improved for patients who received lenalidomide over those who did not (ORR: 60.6 vs. 21.9%, $P < 0.001$; CR: 15 vs. 2.0%, $P < 0.001$, respectively). A significant increase in OS was also seen in the lenalidomide treatment group after a median of 48 months of follow-up (median 38.0 vs. 31.6 months), despite the crossover of 47.6% of the placebo group to the lenalidomide treatment group after disease progression (34). The most frequent AEs were neutropenia, thrombocytopenia and thromboembolic events.

Lenalidomide plus high-dose dexamethasone (RD: lenalidomide 25 mg d.1–21, dexamethasone 40 mg d.1–4, 9–12, 17–20, every 4 weeks) is highly efficacious in RRMM patients, but is associated with a high incidence of thromboembolic complications and severe AEs (SAEs). Therefore, an adopted regimen of lenalidomide plus low-dose dexamethasone (Rd: lenalidomide 25 mg d.1–21, dexamethasone 40 mg d.1, 8, 15, 22, every 4 weeks) was evaluated for efficacy and safety compared with RD in NDMM (35). The ORR of Rd was lower (70%) than that of RD (81%), but PFS and the 1-year OS of Rd was longer (PFS, 25.3 months; OS, 96%) than that of RD (PFS, 19.1 months; OS, 87%). These results seemed to be associated with treatment-related toxicities. The Rd regimen is an effective treatment with acceptable toxicity and the early mortality of Rd was lower (0.5%) than that of RD (5%).

ZOLEDRONIC ACID (ZOMETA) AND DENOSUMAB: PREVENTION OF SKELETAL-RELATED EVENTS

Interactions between myeloma cells and bone marrow stromal cells are fundamental to the excessive activation and proliferation of osteoclasts causing localized bone destruction (36). Myeloma cells also secrete factors that inhibit osteoblasts, blocking the repair of osteolytic damage. The resulting bone lesions place patients at risk of skeletal-related events such as pathological fractures, the need for surgery or

palliative radiation to the bone and spinal cord compression. Bisphosphonates (BPs) and denosumab were developed mainly to impair malignant osteolysis, thereby breaking the cycle of bone destruction and cancer growth that can result in skeletal-related events. By blocking the growth-factor release from the bone matrix, BPs can indirectly impede myeloma growth. BPs, such as zoledronic acid (Zometa), inhibit osteoclast-mediated osteolysis and are the pharmacological standard of care for patients with myeloma bone disease (37). BP or denosumab therapy for MM is generally well tolerated (38). Potential AEs from BP therapy for MM include inflammatory reactions at the injection site, acute phase reactions following IV use, hyperthermia and hypocalcemia. Additionally, renal impairment and osteonecrosis of the jaw are infrequent but serious complications that can result from BP therapy.

MAINTENANCE THERAPY FOR MULTIPLE MYELOMA

Post-transplant consolidation/maintenance with novel agents can become an important step forward. Thus, it has recently been reported that post-transplant consolidation with thalidomide, lenalidomide or bortezomib increases the CR rate.

After induction treatment, two to four cycles of consolidation therapy are followed by maintenance, which is continuous therapy with a single agent with reasonable balance between maximum benefits and minimum toxicities until the time of disease progression (39).

Introduction of ASCT and novel agents into therapeutic regimens for MM have improved patients' response rates and survival rates markedly. However, the majority still experience disease recurrences, which have led to particular importance being placed on maintenance therapy. In this setting, several clinical studies are underway to evaluate maintenance therapies using mainly thalidomide, lenalidomide or bortezomib. Among those, the studies investigating thalidomide for its efficacy as maintenance therapy are foremost.

Attal et al. of IFM conducted the IFM 99-02 study. All subjects received tandem ASCT therapy followed by one of the three maintenance arms: no maintenance; pamidronate or pamidronate plus thalidomide. The first two arms were found to be inferior to the last arm in the response rate ($\geq$VGPR) (55 vs. 57 vs. 67%, respectively). Furthermore, an additional analysis combining first two group (no-thalidomide) against the thalidomide-maintenance group revealed a significant improvement in event-free survival (EFS) and OS for the thalidomide group (EFS, $P = 0.003$; OS, $P = 0.04$) (40). Moreover, Spencer et al. of Australia conducted the ALLG MM6 study to investigate the consolidation therapy post-single ASCT by comparing a thalidomide plus prednisolone group with a prednisolone-alone group. This study also demonstrated superior efficacy of the combined therapy with thalidomide based on its elevated response rate and significantly prolonged PFS and OS (PFS, $P < 0.001$; OS, $P = 0.004$) (41).

To evaluate the efficacy of bortezomib solely for maintenance therapy, a study involving this agent only in the maintenance therapy needs to be conducted, since the previous studies with bortezomib include it in both induction therapy as well as maintenance therapy.

I prefer disease control as a treatment goal, except in selected high-risk patients in whom an aggressive approach to achieving CR may be the only option for long-term survival. The disease control approach involves targeting VGPR (minimal residual disease) rather than CR by using limited, less intense therapy first and moving to more aggressive approaches as the need arises (sequential approach). This allows patients to help determine the timing and number of transplants.

We performed a prospective pilot study of sequentially registered subjects to determine the significance of BD maintenance therapy for long-term survival with good QoL. From September 2008, we continued an exploratory study of the effects of bortezomib on the ability of patients with relapsed, refractory, MM to continue maintenance therapy (42). Long-term survival with good QoL is the most important goal for elderly/low genetic risk MM patients. BD maintenance is a good and available option for this group (24/43 cases) over 20 months, especially in the cases where the total delivery dose is >40 mg.

Lenalidomide is an attractive agent for maintenance after induction therapy. The use of lenalidomide in combination with dexamethasone enhances its anti-myeloma activities, but inhibits the immunomodulatory effects of lenalidomide (43). Therefore, single-agent use of lenalidomide seems to be a logical option to enhance cytotoxic $CD8^+$ T-cell and NK-cells activity for immune surveillance. The effects of continuous lenalidomide monotherapy in ASCT-eligible and -ineligible patients have been investigated in three randomized Phase 3 studies (44,45). In ASCT-ineligible elderly patients, MPR-R resulted in better PFS compared with the MP or MPR regimens (MPR-R vs. MPR vs. MP: 31 months, 14 months ($P < 0.001$) and 13 months ($P < 0.001$), respectively. (46) In a landmark analysis, lenalidomide maintenance significantly prolonged PFS from the start of lenalidomide monotherapy compared with the MPR regimen (median PFS: 26 vs. 7 months). However, there were no differences in OS among these three regimens.

Two trials investigating lenalidomide maintenance for ASCT-eligible patients (CALGB100104 and IFM 2005-02 trials) were performed with or without consolidation (44,45). The consolidation with lenalidomide in IFM 2005-02 resulted in an increased CR rate from 14 to 20% ($P < 0.001$). The three-year PFS in the maintenance arm was 66% in CALGB100104 and 59% in IFM 2005-02 compared with those in the placebo arm, which were 39 and 35%, respectively, indicating that lenalidomide maintenance significantly improved PFS. On the other hand, the CALGB100104 trial showed significant improvement in OS (85 vs. 77% of patients were alive at the time of analysis, $P = 0.03$) despite crossover from the placebo arm to the lenalidomide

maintenance arm. However, second primary malignancy (SPM) is a serious event and the risk of SPM must be identified (47). The impressive benefits of lenalidomide maintenance must be weighed against the incidence of SPMs (48).

TANDEM AUTOLOGOUS TRANSPLANTATION AND AUTOLOGOUS PLUS REDUCED-INTENSITY CONDITIONING ALLOGENEIC TRANSPLANTATION

High-dose melphalan with autologous stem cell support has been an integral part of MM therapy for more than 20 years, either as salvage therapy or as consolidation of an initial remission. Tandem autologous transplantation (TA) and autologous plus reduced-intensity conditioning allogeneic transplantation (AR) in the management of NDMM has a defined role in the upfront treatment of MM, but nearly all patients may relapse. AR is associated with a higher chance of achieving CR but also with a 3-fold increase in transplant-related mortality (TRM) when compared with TA in the upfront management of MM (49). However, there was a long-term survival among the 40–50% of patients who achieved molecular remission. Substantial innovative measures are necessary to either reduce the TRM and/or enhance the graft-vs.-myeloma effect before allogeneic transplantation can be reassessed in the upfront management of MM.

THERAPY FOR RRMM

There are few effective salvage regimens available for patients with disease resistant to novel agents. The salvage therapy of MM is shown in the NCCN guidelines 1.2013.

Table 1. SPMs: incidence of MDS/AML from the diagnosis of myeloma

	95% confidence interval		
	Estimate (%)	Lower (%)	Upper (%)
The cumulative incidence of second MDS/AML (95% CI) at 12 years from the time of diagnosis of MM			
1 year	1	0	5
8 years	3	1	9
12 years	7	2	19
The cumulative incidence of second MDS/AML (95% CI) after commencing len-based regimens			
1 year	1	0	5
2 years	4	1	9
3 years	9	4	12

1-, 8- and 12-year cumulative MDS/AML incidence by the conventional drugs were the same with the incidence of MDS/AML from the initiation of lenalidomide 1-, 2- and 3-year cumulative incidence.
Adapted from Reece et al. *Blood* (ASH Annual Meeting Abstracts) 2010;116 (Abstract 1877).

BORTEZOMIB RETREATMENT IN RELAPSED MULTIPLE MYELOMA

Retreatment with bortezomib appears to be a feasible treatment approach in patients with relapsed MM. A retrospective survey of patients with MM in 36 centers in Germany and Switzerland showed an ORR of 63% when retreating patients with bortezomib monotherapy or a combination of bortezomib with dexamethasone. At retreatment, 27 patients (64.3%) received concomitant dexamethasone and 47.6% of patients received other concomitant medications during bortezomib retreatment, including 14.3% who received concomitant anti-neoplastic or immunomodulating agents. Out of the 28 patients who had PR on initial treatment, 2 responded with nCR and 13 responded with PR on retreatment (50). The response rate was examined according to first treatment-free interval (TFI) ($\leq$6 vs. >6 months) and use of concomitant dexamethasone with bortezomib retreatment (yes vs. no). The response rate to bortezomib retreatment in the subgroup with first TFI >6 months was higher than that in the subgroup with first TFI $\leq$6 months (74.1 vs. 46.7%). The median time to response with bortezomib retreatment was 2.8 months. The median second TFI after bortezomib retreatment was 5.7 months. The median TTP after bortezomib retreatment was 10.5 months.

ANALYSIS OF SPM

Another important issue in MM is the risk of developing SPMs due to patients living longer after diagnosis. Long follow-up analyses of MM-009/010 in RRMM shows that the long-term use of lenalidomide did not increase the incidence of SPM compared with all patients and the incidence of SPM with the long-term use of lenalidomide was within the expected range (median treatment duration, 46.2 vs. 9.8 months; incidence of myelodysplastic syndrome (MDS), 0 vs. 0.4; solid tumor, 1.8 vs. 1.3; non-melanoma skin cancer, 2.3 vs. 2.4) (51). It was concluded that the benefits continue to outweigh the risks and that as a consequence the benefit/risk balance of lenalidomide is positive under normal conditions of use. Population studies show that MM patients have an increased risk of acute myeloid leukemia (AML). Some MM therapeutic agents are particularly associated with an elevated risk of SPMs and melphalan is associated with an increased risk of secondary acute leukemia.

By summarizing the data to date, the incidence of all/invasive SPM is significantly increased in lenalidomide treatment arms, driven by hematologic SPM ($P < 0.001$). The overall benefit–risk profile of lenalidomide in NDMM remains positive (Table 1) (52). Risk factors for SPMs with lenalidomide by univariate and multivariate analyses in IFM 2005 may be treatment duration >24 months, male, age >55 years, International Staging System (ISS) stage III and previous exposure to alkylators.

In a report on a retrospective analysis of 325 Japanese MM patients from 1998 to 2010 (13 years), we showed that t-MDS/AML developed in 17 (5.2%) patients. The median

time to onset was 60 months in *t*-AML and 88 months in *t*-MDS. All patients with *t*-AML died within 8 months, and were suspected to be treated with melphalan; none had been given lenalidomide (53). There appears to be an increased risk for secondary cancers, especially with melphalan administration and lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.

RENAL DYSFUNCTION IN MULTIPLE MYELOMA

The timing of treatment initiation in MM is dependent on the existence of organ dysfunction. When bone symptoms, renal dysfunction, anemia or hypercalcemia is observed, symptomatic MM is diagnosed and treatment should be started. Renal dysfunction in MM is one of the

Table 2. Complete response (CR) renal

Renal response	CC based (*n* = 32)	IMiDs based (*n* = 47)	Bortezomib based (*n* = 17)
CR renal (%)	41	45	71
	47	45	82
≧MR renal (%)	59	79	94
Time to response (months)	1.8	1.6	0.69
Stages		GFR (ml/min/ 1.73 m^2)	
1	Kidney damage with normal or elevated GFR	Over 90	
2	Kidney damage with mild reduction of GFR	60–89	
3	Moderate reduction of GFR	30–59	
4	Severe reduction of GFR	15–29	
5	Renal failure	Below or hemodialysis	
Response	Baseline eGFR (ml/min/1.73 m^2)	Best CrCl response (ml/min)[a]	
CR renal	<50	≥60	
PR renal	<15	30–59	
MR renal	<15	15–29	
	15–29	30–59	

CR may be attained by a bortezomib-based regimen not only the high levels percentage but also time to response. Five stage is divided as the figure. The table is adapted from M. Roussou et al. *Leukemia Res* 34, 1395–1397, 2010.
[a]Must be maintained for ≥2 months.

complications that require the most careful attention and occurs via various mechanisms. Of these, the most frequent is cast nephropathy, also known as myeloma kidney, in which excessive light chains of M protein [Bence Jones protein (BJP)] secreted by proliferated plasma cells form casts and deposit themselves in renal tubules. In addition, hypercalcemia associated with osteolysis by myeloma cells, deposition of amyloid in glomeruli, hyperviscosity syndrome, hyperphosphatemia and renal infiltration of myeloma cells are also causes of renal dysfunction. Care must also be given to recurring urinary tract infection, drugs and dehydration that may act as exacerbating factors. According to the Japanese Society of Myeloma, ∼15% of NDMM patients have a renal dysfunction complication and the rate increases as the disease progresses. BJP and immunoglobulin D (IgD) types of myeloma excrete high amounts of BJP into the urine and show a high frequency of renal dysfunction.

It has been reported that renal dysfunction remains reversible when serum creatinine is <4 mg/dL, Ca <11.5 mg/dL and urine protein ≤1 g/day (54). Although these are the data before the introduction of novel agents, in the 423 patients with NDMM, patients with renal dysfunction (22%) showed significantly shorter survival time compared with patients with normal renal function (8.6 vs. 34.5 months).

IMPROVEMENT OF RENAL FUNCTION AND TREATMENT STRATEGY FOR MULTIPLE MYELOMA

An improvement in patient's MM is the best remedy for their complicating renal dysfunction. Since 2005, the treatment strategy for MM has significantly changed due to the successful introduction of novel agents. The three drugs, including a proteasome inhibitor (bortezomib) and two immunomodulatory drugs (IMiDs) (lenalidomide and thalidomide), are referred to as novel agents, and each drug has characteristic efficacy and safety profiles. While all of these agents can be expected to restore renal function due to the improvement in the primary disease, bortezomib, with a strong antitumor effect, is reported to rapidly improve renal function (Table 2). The renal response rate is (minor response and better) based on improving creatinine clearance and time to response. The creatinine clearance improvements and times to response were 59% and 1.8 months (chemotherapy); 79% and 1.6 months in (IMiDs) and 94% and 0.69 month (bortezomib) (55).

PERSONALIZED THERAPY IN MM ACCORDING TO PATIENT AGE AND VULNERABILITY

Most patients with NDMM are >65 years old with 30% >75 years. Elderly patients are more susceptible to side effects and are often unable to tolerate full drug doses (56). For these patients, lower dose-intensity regimens improve the safety profile and thus optimize treatment outcome. The

occurrence of serious hematological and non-hematological AEs during treatment should be carefully taken into account to adjust doses and optimize outcome.

CONCLUSION

As mentioned above, the therapy and treatment strategy of MM have largely changed in recent years. Ongoing efforts to improve the treatment paradigm even further include using oncogenomics to better characterize molecular pathogenesis and to develop refined patient stratification and personalized treatment in MM using immune-based therapies including monoclonal antibodies, cytokines and novel immunocytic (NK, DC and γδT cells) strategies (57). At the same time, it is becoming more important to control the disease in a long-term fashion, maintaining the QoL of the patient because it is still difficult to cure this disease. The increased number of treatment options means that personalized medicine which selects a treatment corresponding to the systemic condition of the patient, and the purpose of the treatment will be more important. For this purpose, early diagnosis and timing of initiation of treatments are important. Moreover, understanding the characteristics of novel agents and using them in combination with existing drugs appropriately for the individual patient is critical. In addition, collaboration with renal medicine is essential to avoid the introduction of dialysis. And finally, we should be considering how we can help patients through the treatment to live long, active lives.

Conflict of interest statement

None declared.

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Comparison of Autologous Hematopoietic Cell Transplantation and Chemotherapy as Postremission Treatment in Non-M3 Acute Myeloid Leukemia in First Complete Remission

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Abstract

Randomized trials of acute myeloid leukemia (AML) in first complete remission (CR1) showed that autologous hematopoietic cell transplantation (auto-HCT) improves relapse-free survival (RFS) but not overall survival (OS), compared with chemotherapy. Using a database of 2518 adult patients with AML in CR1, we conducted a 5-month landmark analysis and found that auto-HCT improves 3-year RFS but not OS compared with chemotherapy.
Introduction: A number of randomized trials in patients with AML in CR1 have been conducted and they showed that auto-HCT improves RFS but not OS, compared with chemotherapy. However, because these trials have had compliance problems, the value of auto-HCT still has not been clearly established. **Patients and Methods:** Using a database of 2518 adult patients with AML in CR1, we retrospectively analyzed the outcome of auto-HCT and compared it with intensive nonmyeloablative chemotherapy using landmark analyses. **Results:** In 103 auto-HCT recipients, OS and RFS at 3 years from treatment were 65% and 57%, respectively. Multivariate analysis showed that unfavorable risk cytogenetics and entry into CR1 after 2 courses of induction treatment predicted a poor outcome. Because the median time interval between CR1 and auto-HCT was 153 days, landmark analyses at 5 months after CR1 were performed to compare 1290 patients who received chemotherapy alone (median age, 52 years; range, 16-70) with 103 who received auto-HCT (median age, 48 years; range, 16-67). Auto-HCT improves 3-year RFS (58% vs. 37%; $P < .001$) but not OS compared with chemotherapy alone. Among patients with unfavorable risk cytogenetics or those who required 2 courses to reach CR1, there was no significant difference in RFS between the 2 groups. **Conclusion:** Auto-HCT can be considered as a postremission therapy for AML patients with favorable or intermediate risk cytogenetics who achieve CR1 after a single course of induction treatment.

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Introduction

Autologous hematopoietic cell transplantation (auto-HCT) has been investigated as a potential therapeutic option to improve the outcome in acute myeloid leukemia (AML) patients. However, its value in the treatment of adults in remission has not been clearly established. Compared with allogeneic hematopoietic cell transplantation (HCT), auto-HCT offers the possibility of performing the same myeloablative regimen without the risks associated with graft-versus-host disease. Though the toxic death rate in auto-HCT is much lower than that in allogeneic HCT, the relapse rate remains higher[1-6] because of either graft contamination by malignant cells[7] or the absence of a graft-versus-leukemia effect by donor lymphocytes. To date, randomized trials in patients with AML in first complete remission (CR1) have been conducted to compare the postremission strategies of intensive chemotherapy, allogeneic HCT, and auto-HCT.[8-19] All of these trials analyzed the outcome on an intention-to-treat basis, and only 66% of patients actually underwent the intended auto-HCT treatment.[2-4,20] This can clearly pose problems in interpretation when a significant proportion of patients do not actually undergo the intended treatment.[19] On the other hand, despite the limitations of biases that might be difficult or impossible to identify and/or adjust for, observational databases contain information on large numbers of diverse subjects who have received diverse therapies, and can be analyzed to potentially provide answers that are more useful to clinicians than those obtained from randomized controlled trials.[21]

In the present study, we used a database of 2518 adult AML patients who achieved CR1 to retrospectively compare auto-HCT with intensive nonmyeloablative chemotherapy in AML patients in CR1.

Patients and Methods

Data Source

We created a nation-wide database of AML patients in CR1.[22] The targeted patients were adults aged 16-70 years who had been diagnosed with AML between 1999 and 2006, and who had achieved CR1 after 1 or 2 courses of induction chemotherapy. The diagnosis of AML was determined according to the World Health Organization classification fourth edition.[23,24] The National Cancer Center Hospital's institutional review board approved the protocol. Clinical data for more than 2600 patients were collected from 70 institutions between June and December 2008. Among them, patients with acute biphenotypic leukemia who were treated with chemotherapy for acute lymphocytic leukemia and those who had extramedullary AML without marrow invasion, or extramedullary lesions that did not totally disappear after remission-induction chemotherapy were excluded. In this study, patients with acute promyelocytic leukemia and those who received allogeneic HCT in CR1 were also excluded. Information about the disease risk at diagnosis, clinical course, and conditioning regimen for auto-HCT were collected.

Statistical Analysis

Data were retrospectively reviewed and analyzed as of April 2010. The primary end point of the study was overall survival (OS) with respect to either auto-HCT or CR1. The unadjusted probabilities of OS, relapse-free survival (RFS), and relapse rate were estimated using the Kaplan–Meier product limit method. OS, RFS, and the incidence of relapse were estimated as probabilities at 3 years after either auto-HCT or CR1. The log-rank test was used to compare the probabilities among different subgroups. The Cox proportional hazards regression model was used to estimate relative hazard ratios for OS, RFS, and the incidence of relapse. As covariates, we considered age, sex, conditioning regimen, interval from CR1 to auto-HCT, cytogenetic risks according to the Southwest Oncology Group (SWOG)[25], French-American-British (FAB) classifications,[24,26-29] number of courses of chemotherapy required to achieve CR1, white blood cell (WBC) count, and antecedent hematological disorders or dysplasia at diagnosis. We judged 2-tailed P values < .05 to be statistically significant. Statistical analyses were performed with SPSS software version 11.0.1 (SPSS, Chicago, IL).

Results

Patient Characteristics

We excluded 494 patients who had received allogeneic HCT in CR1 and 386 acute promyelocytic leukemia patients from the total of 2518 patients. Table 1 summarizes the characteristics of the remaining 1638 patients. Auto-HCT was used to treat 103 patients (auto-HCT group), and the other 1535 were treated with chemotherapy alone (chemotherapy group). Median follow-up times for the total test population and auto-HCT group were 50 months (0.2-116 months) and 60 months (6-115 months), respectively.

The proportions of patients in the auto-HCT group with favorable, intermediate, unfavorable, and unknown risk cytogenetics according to the SWOG criteria were 26%, 49%, 17%, and 9%, respectively. These values were not significantly different from those in patients who were treated with chemotherapy alone. As a remission induction therapy, 95% or more of patients in both groups had received standard-dose cytarabine and anthracycline (daunorubicin or idarubicin) -based regimen. Consolidation therapy was continued with cytarabine-based regimens with or without maintenance therapy at the discretion of physicians.

There was no significant difference in FAB subtypes, the number of remission-induction therapies, or the WBC count at the time of diagnosis between the 2 groups. However, the proportion of patients who had antecedent hematological disorders or dysplasia at diagnosis was significantly lower in auto-HCT patients than in chemotherapy patients (P = .011). Auto-HCT patients were significantly younger than the chemotherapy patients (P = .006).

Among auto-HCT patients, 62 (70%) received granulocyte colony stimulating factor (G-CSF) combined with BEA (busulfan/etoposide/cytosine arabinoside)[30,31] as a conditioning regimen: busulfan (4 mg/kg per day, 1 mg/kg per dose, 4 times a day [days −9 to −6], for 16 doses), etoposide (20 mg/kg on days −5 to −4), cytarabine (100 mg/m^2 on days −10 to −4, 3 g/m^2 every 12 hours on days −3 to −2), and filgrastim (200 µg/m^2 on days −12 to −4). The median time interval between CR1 and transplantation was 153 days (21-749 days). Only 8 patients (8%) received transplants within 100 days after reaching CR1, and approximately half of the patients (n = 55; 53%) underwent transplantation between 101 and 180 days after CR1.

Table 1 Patient Characteristics According to Treatment in CR1

Characteristic	Chemotherapy, n = 1535 n (%)	Auto-HCT, n = 103 n (%)	P
Age			.006
Median, years	52	48	
Cytogenetic Risk (SWOG)			.895
Favorable	360 (24)	26 (26)	
Intermediate	777 (51)	49 (49)	
Unfavorable	246 (16)	17 (17)	
Unknown	129 (9)	9 (9)	
FAB			.125
M1, 2, 4, 5	1345 (88)	94 (91)	
M0, 6, 7	104 (7)	3 (3)	
RAEB-t	32 (2)	3 (3)	
Unknown	54 (4)	3 (3)	
Remission Induction			.725
1 course	1276 (83)	87 (84)	
Standard-dose cytarabine with anthracycline	1455 (95)	101 (98)	
Low-dose cytarabine-based	65 (4)	1 (1)	
Others/data not available	15 (1)	1 (1)	
2 courses	259 (17)	16 (16)	
Dysplasia[a]			.011
No	1264 (83)	95 (92)	
Yes	268 (17)	8 (8)	
WBC			.351
≤ 20,000/μL	887 (61)	55 (56)	
> 20,000/μL	570 (39)	43 (44)	

Abbreviations: auto-HCT = autologous hematopoietic cell transplantation; CR1 = first complete remission; FAB = French-American-British; RAEB-t = refractory anemia with excess of blasts in transformation; SWOG = Southwest Oncology Group; WBC = white blood cell.
[a] Dysplasia contains patients with RAEB-t.

Outcomes of Auto-HCT

The relapse rate for 103 patients who received auto-HCT was 42% at 3 years from HCT (Figure 1A). There was only 1 case of nonrelapse mortality: a 38-year-old male who died of pulmonary hemorrhage 2.9 months after auto-HCT. The RFS and OS at 3 years after auto-HCT were 57% and 65%, respectively (Figure 1B and C).

The univariate analysis indicated that unfavorable risk cytogenetics according to the SWOG criteria and 2 courses of remission-induction treatment were associated with lower OS (P = .014 and P = .044, respectively) and RFS (P = .001 and P = .005, respectively), and a higher relapse rate (P = .001 and P = .004, respectively). The M0, 6, and 7 subgroups of the FAB classification, which are poor prognostic factors in the Japan Adult Leukemia Study Group scoring system,[32] were also shown to be significantly associ-

ated with lower RFS and a higher relapse rate (P = .018 and P = .018, respectively). Table 2 shows the results of multivariate analyses to determine independent prognostic factors. Although the M0, 6, and 7 subgroups of the FAB classification were associated with worse RFS and higher relapse rates in the univariate analysis, we excluded this factor from the multivariate analysis because of the small number of patients (n = 3). Unfavorable risk cytogenetics according to the SWOG criteria and 2 courses of remission-induction treatment were associated with lower OS and RFS, and a higher relapse rate.

The 3-year OS of patients with favorable, intermediate, and unfavorable risk cytogenetics were 84%, 60%, and 41%, respectively (P = .003, Figure 2A), and 3-year RFS were 77%, 63%, and 19%, respectively (P = .034, Figure 2B). Patients who required 2 courses of induction treatment to achieve complete remission (CR) had lower OS and RFS than those who required only 1 course of treatment (OS, 47% vs. 69%, P = .039; RFS, 34% vs. 62%, P = .002, Figure 2C and D).

In 89 patients for whom data regarding conditioning regimens were available, the 3-year OS did not differ between patients treated with G-CSF combined with BEA (74.5%, n = 62) and others (80%; n = 27; P = .834). Though the 3-year RFS was slightly higher in patients treated with G-CSF combined with BEA, the difference between the 2 groups was not statistically significant (69% vs. 59%) (P = .245).

When patients were divided into 4 groups according to the interval from CR1 to auto-HCT, there were no significant differences in the 3-year OS or RFS among the groups (Table 3). As shown in a multivariate Cox proportional hazard regression model (Table 2), there was no difference in survival rates when the groups were merged successively. Thus, we could not identify an appropriate cutoff point for the interval from CR1 to auto-HCT for OS and RFS. In the fourth group, the interval was rather broad, and ranged from 241 to 749 days. When we excluded this fourth group, the 3-year OS and RFS tended to be higher in subgroups with longer intervals.

Landmark Analysis Comparing Auto-HCT With Chemotherapy Alone

We next compared the outcomes for patients who received auto-HCT in CR1 (n = 103) with those for patients who did not receive either autologous or allogeneic HCT in CR1 (n = 1535). Because the median time interval between CR1 and auto-HCT was 153 days (21-749 days), landmark analyses at 5 months after CR1 were performed for all subgroups. We excluded 245 patients from the chemotherapy group who relapsed or died within 5 months after achieving CR1. The relapse rate in the auto-HCT group was significantly lower than that in the chemotherapy group (41% vs. 62% at 3 years from CR1, P < .001, Figure 3A). Nonrelapse mortality did not differ significantly between the auto-HCT and chemotherapy groups (1.1% vs. 1.4% at 3 years, P = .400). The 3-year RFS in the auto-HCT group was significantly higher than that in the chemotherapy group (58% vs. 37%, P < .001, Figure 3B). There was no significant difference between the auto-HCT and chemotherapy groups with regard to 3-year OS (68% and 64%, respectively, P = .169, Figure 3C).

By a subset analysis, patients with favorable and intermediate risk cytogenetics had the same trends in relapse rate, RFS, and OS

Figure 1 Outcomes of Autologous Hematopoietic Cell Transplantation (Auto-HCT) in Acute Myeloid Leukemia in First Complete Remission. Cumulative Incidence of Relapse (A), Relapse-Free Survival (B), and Overall Survival (C), After Auto-HCT are Shown
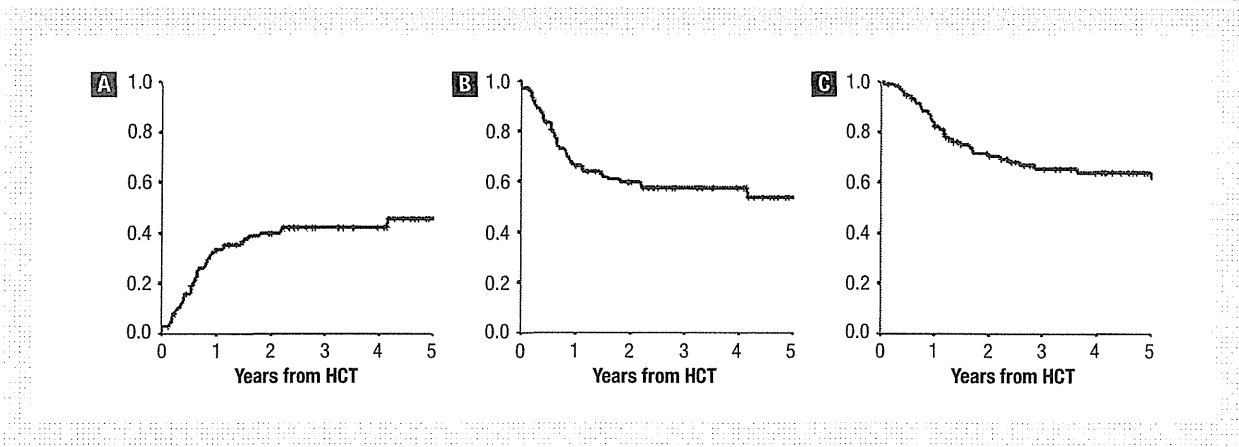

Table 2 Multivariate Analysis of the Auto-HCT Patients

Variables	OS		RFS		Relapse	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (Vs. ≤ 49)						
≥ 50	1.25 (0.60-2.60)	.549	1.17 (0.57-2.39)	.671	1.29 (0.62-2.66)	.495
Cytogenetic Risk (SWOG: Vs. Favorable)						
Intermediate	1.64 (0.59-4.55)	.343	1.51 (0.54-4.22)	.436	1.37 (0.48-3.87)	.558
Unfavorable	3.43 (1.14-10.36)	.028	4.24 (1.46-12.31)	.008	4.27 (1.47-12.42)	.008
Remission Induction (Vs. 1 Course)						
2 Courses	3.28 (1.37-7.86)	.008	3.55 (1.56-8.06)	.003	3.89 (1.69-8.95)	.001
Conditioning (Vs. G-CSF with BEA)						
Others	1.05 (0.47-2.33)	.902	0.74 (0.35-1.55)	.418	0.72 (0.34-1.51)	.378
Interval from CR1 to Auto-HCT (Vs. > 150 Days)						
≤ 150 Days	1.37 (0.66-2.83)	.398	1.34 (0.65-2.75)	.432	1.23 (0.59-2.56)	.578

Abbreviations: auto-HCT = autologous hematopoietic cell transplantation; BEA = busulfan/etoposide/cytosine arabinoside; CR1 = first complete remission; G-CSF = granulocyte colony stimulating factor; HR = hazard ratio; OS = overall survival; RFS = relapse-free survival; SWOG = Southwest Oncology Group.

as in the total population (Figure 4). Among patients with favorable risk cytogenetics, the 3-year rate of relapse in the auto-HCT group (n = 26) was significantly lower than that in the chemotherapy group (n = 335, 23% vs. 56%, 3 years from CR1, *P* = .002). The 3-year RFS in the auto-HCT group was significantly higher than that in the chemotherapy group (77% vs. 42%, *P* = .002, Figure 4A). There was no significant difference between the auto-HCT and chemotherapy groups with regard to 3-year OS (85% vs. 72%, *P* = .234, Figure 4B).

Similarly, in patients with intermediate risk cytogenetics, the relapse rate in the auto-HCT group (n = 49) was significantly lower than that in the chemotherapy group (n = 658, 36% vs. 59% at 3 years from CR1, *P* = .002). The 3-year RFS in the auto-HCT group was significantly higher than that in the chemotherapy group (63%

vs. 40%, *P* = .002, Figure 4C). There was no significant difference between the auto-HCT and chemotherapy groups with regard to 3-year OS (65% vs. 66%, *P* = .484, Figure 4D). In contrast, in patients with unfavorable risk cytogenetics, there was no significant difference between the auto-HCT (n = 17) and chemotherapy (n = 178) groups with respect to relapse rate (81% vs. 69%, *P* = .778), RFS (19% vs. 31%, *P* = .735, Figure 4E), or OS (41% vs. 49%, *P* = .787, Figure 4F).

Among patients who achieved CR1 after a single induction treatment, 3-year RFS and relapse rate in the auto-HCT group (n = 87) were significantly better than those in the chemotherapy group (n = 1100, RFS, 63% vs. 40%, *P* < .001, Figure 4G; relapse, 37% vs. 60%, *P* < .001). There was no significant difference in 3-year OS between these 2 groups (72% vs. 67%, *P* = .193, Figure 4H). In

Figure 2 Overall Survival and Relapse-Free Survival After Autologous Hematopoietic Cell Transplantation (Auto-HCT) According to Cytogenetic Risks or the Number of Induction Treatment Courses Required to Reach First Complete Remission (CR1). Overall Survival (A and C) and Relapse-Free Survival (B and D) According to Cytogenetic Risks (A and B) or the Number of Induction Treatment Courses Required to Reach CR1 (C and D). P Values Were Calculated by the Log-Rank Test
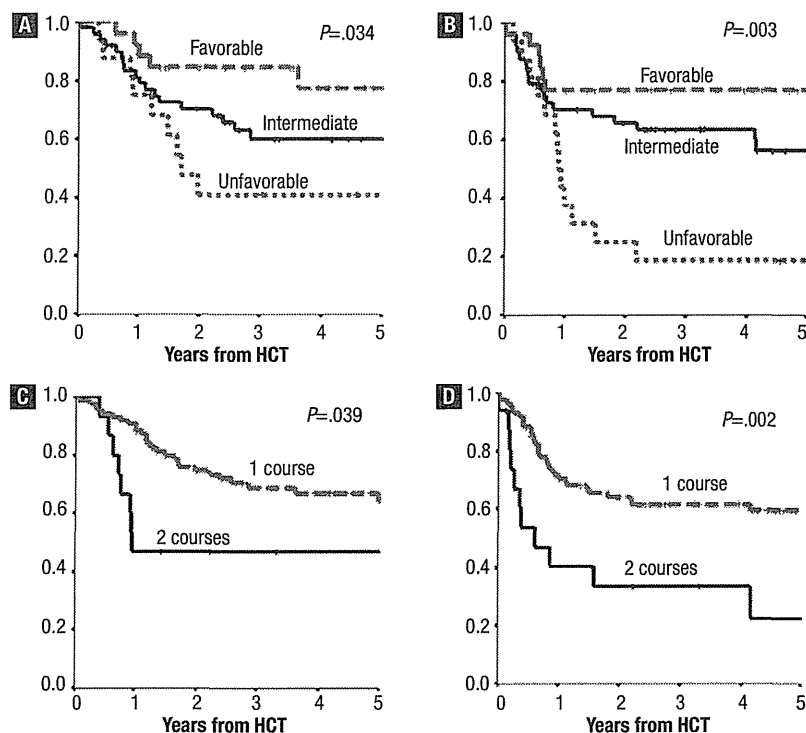

Table 3 Outcomes According to Interval from CR1 to Auto-HCT

Interval From CR1 (Days)	≤120, n = 21	121-150, n = 29	151-240, n = 30	≥241, n = 23	P
Relapse (%)	54.6	46.2	25.9	44.5	.37
RFS (%)	45.4	51.7	74.1	55.5	.32
OS (%)	59.1	61.5	73.9	63.2	.51

Outcomes are presented as the probability at 3 years from transplantation.
Abbreviations: auto-HCT = autologous hematopoietic cell transplantation; CR1 = first complete remission; OS = overall survival; RFS = relapse-free survival.

contrast, among those who received 2 courses of induction, there was no significant difference between the auto-HCT (n = 16) and chemotherapy (n = 190) groups with regard to relapse rate (66% vs. 75%, P = .414), RFS (34% vs. 24%, P = .367, Figure 4I), or OS (47% vs. 48%, P = .705, Figure 4J).

Among patients younger than 60 years of age, 3-year RFS and relapse rate in the auto-HCT group (n = 89) were significantly better than those in the chemotherapy group (n = 890, RFS, 60% vs. 38%, P < .001; relapse, 39% vs. 61%, P < .001). There was no difference

in 3-year OS between these 2 groups (68% vs. 67%, P = .545). In contrast, in patients aged 60 years or older, there was no difference between the auto-HCT (n = 14) and chemotherapy (n = 400) groups with respect to the relapse rate (52% vs. 63%, P = .294), RFS (47% vs. 36%, P = .237), or OS (77% vs. 59%, P = .224).

Discussion

In this study, we analyzed the outcomes in 103 AML patients who received auto-HCT in CR1. The 5-month landmark analyses indicated that auto-HCT improves RFS but not OS compared with chemotherapy alone. Our data are consistent with the findings of a meta-analysis of randomized studies of more than 1000 AML patients, which indicated that patients who received auto-HCT had a better RFS, albeit a similar OS, than those who received chemotherapy or no further treatment.[16-18] In addition, our findings were consistent with recently reported results of a randomized study in which more than 90% of randomized patients received their assigned treatment.[19]

We found that despite better RFS, auto-HCT did not improve OS in CR1 patients. Among the patients who relapsed after auto-HCT, the OS was only 21% at 3 years after relapse, although 46% of them received allogeneic HCT. We reported that, in patients who relapsed after receiving chemotherapy alone, the 3-year OS was 30% with
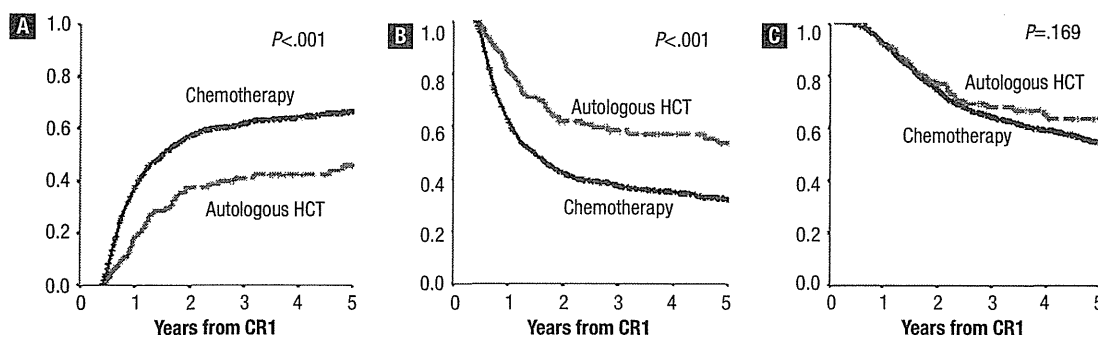
54% of them receiving salvage allogeneic HCT.[33] Thus, allogeneic HCT after relapse may have contributed to the improved OS in the chemotherapy group.

A European study[34] reported that a less favorable outcome was associated with a shorter interval from CR1 to auto-HCT. We found that, after excluding auto-HCT patients with an interval of > 240 days, a longer interval was associated with a better 3-year OS and RFS, although the differences were not statistically significant (Table 3). The better RFS with late transplants compared with early transplants might have resulted from the fact that patients who received transplantation later received more courses of chemotherapy, which also resulted in more intensive in vivo purging, as shown in previous studies.[35-37]

The WBC count at diagnosis has been reported to reflect the prognosis.[32,38] However, in the current study, a high WBC count did not have any prognostic significance. This suggests that myeloablative conditioning treatment might overcome the unfavorable nature of AML characterized by a high WBC count. In the current study, the influence of the source of stem cells was unclear, because the relevant data (peripheral blood [PB] or bone marrow [BM]) were not collected. However, our data were collected at a time when PB was commonly used for auto-HCT.

The number of induction treatments required to achieve CR1 has been reported to serve as a prognostic factor.[33,37] In this study, multivariate analysis for survival and relapse rates after auto-HCT showed that 2 courses of induction treatment to achieve CR1 were associated with a poor prognosis for auto-HCT patients. In patients who require a single induction, auto-HCT improved RFS compared with chemotherapy alone. In contrast, among those who required 2 courses of induction treatment, auto-HCT did not improve RFS compared with chemotherapy alone.

The present study showed that in favorable and intermediate risk cytogenetics patients, auto-HCT provides better RFS than chemotherapy alone. The multivariate analysis revealed that unfavorable risk cytogenetics was associated with poor outcomes. The results of a meta-analysis of 24 prospective trials with 6007 AML patients showed that, compared with nonallogeneic HCT therapies, alloge-

neic HCT improved RFS and OS for intermediate- or poor-risk AML patients in CR1.[39] Compared with nonallogeneic HCT therapies, allogeneic HCT was reported to offer no survival advantage for favorable risk AML in CR1.[39-42] It has been reported that, because of the low CR rate after reinduction therapy and an inferior survival duration especially after relapse with t(8;21),[40] HCT is the postremission therapy of choice in patients with additional adverse factors.

At present, the indications for allogeneic HCT for patients diagnosed with intermediate risk AML have not been fully defined when unrelated donors are used.[43,44] The present findings suggest that auto-HCT can serve as an alternative option for AML CR1 patients with intermediate risk AML who do not have an appropriate sibling donor.

Our study has several limitations, and thus the results must be interpreted with caution. These limitations include the retrospective nature of the study, leaving room for selection bias or chance effect. The auto-HCT group included significantly younger patients and fewer patients with myelodysplastic syndrome related AML than the chemotherapy group. This imbalance might have influenced the results. However, this large retrospective analysis using landmark methods should have important implications in determining the indication of auto-HCT.

Conclusion

On the basis of our results, we believe that auto-HCT might be recommended as a first-line postremission therapy for favorable or intermediate risk AML patients who have achieved CR1 after a single induction. It remains unclear whether auto-HCT is more beneficial than high-dose cytarabine for AML patients with favorable risk cytogenetics. Moreover, it also remains to be seen whether auto-HCT is a better option for those with intermediate risk AML in CR1 when they do not have a suitable related donor. Our observation needs to be confirmed in a prospective study.

Clinical Practice Points

● A number of randomized trials in patients with AML in CR1 have been conducted and they showed that auto-HCT improves re-

Figure 4 Comparison of Autologous Hematopoietic Cell Transplantation (Auto-HCT) and Chemotherapy Alone Using a Landmark Analysis at 5 Months After First Complete Remission (CR1) According to Cytogenetic Risks or the Number of Induction Treatment Course Requiring CR1. Relapse-Free Survival (A, C, E, G, and I) and Overall Survival (B, D, F, H, and J), After Receiving Auto-HCT and Chemotherapy Alone are Shown in the Subgroups of the Southwest Oncology Group Criteria: (A and B) Favorable Risk Cytogenetics; (C and D) Intermediate Risk Cytogenetics; and (E and F) Unfavorable Risk Cytogenetics; or in the Subgroups of the Number of Induction Treatment Courses: (G and H) 1 Course; and (I and J) 2 Courses. P Values Were Calculated by the Log-Rank Test
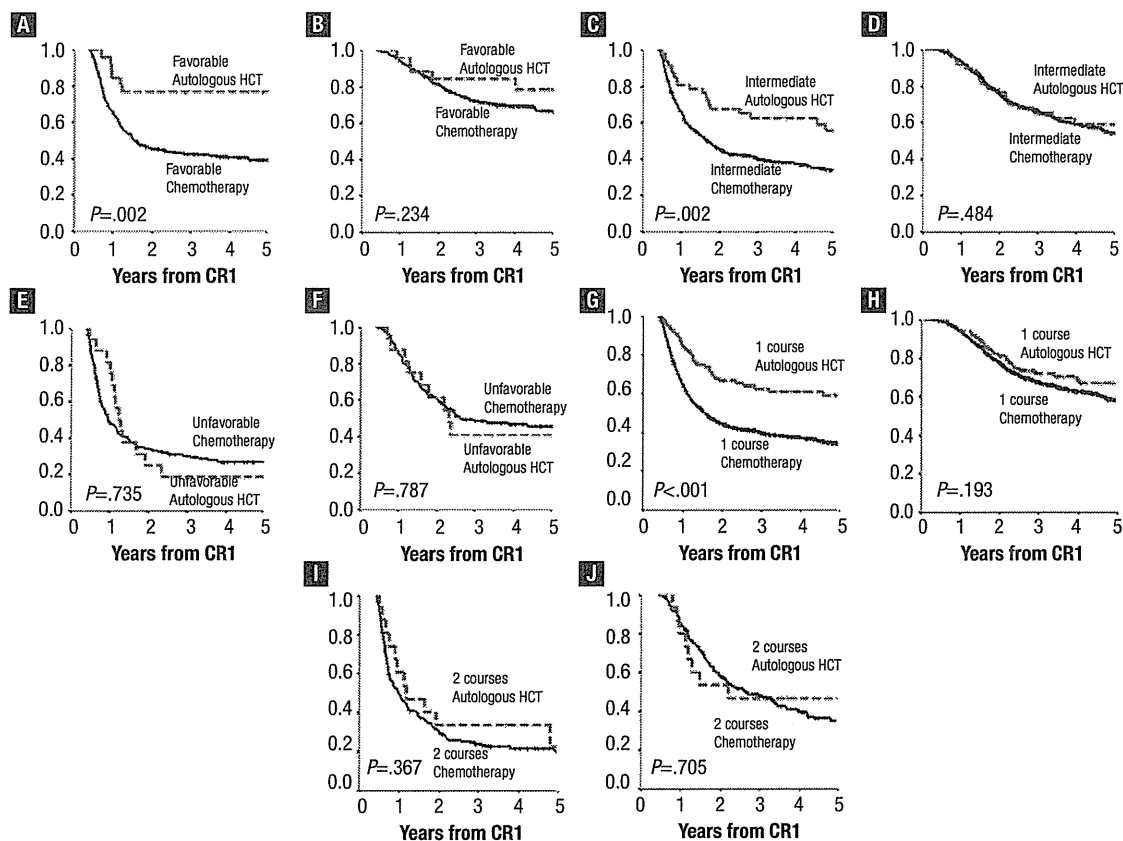
lapse-free survival but not overall survival, compared with chemotherapy.

- Because these trials have had compliance problems, the value of auto-HCT still has not been clearly established.
- To avoid this problem, we constructed a database of 2518 patients with non-M3 AML in CR1 collected from 70 institutions and conducted landmark analyses to compare the outcome of auto-HCT with intensive nonmyeloablative chemotherapy.
- In 103 auto-HCT recipients, multivariate analysis showed that unfavorable risk cytogenetics and entry into CR1 after 2 courses of induction treatment predicted a poor outcome.
- Because the median time interval between CR1 and auto-HCT was 153 days, landmark analyses at 5 months after CR1 were performed to compare 1290 patients who received chemotherapy alone with 103 who received auto-HCT. Auto-HCT improves 3-year RFS (58% vs. 37%; P < .001) but not OS compared with chemotherapy alone.

- Among patients with unfavorable risk cytogenetics or those who required 2 courses to reach CR1, there was no significant difference in RFS between the 2 groups.
- Auto-HCT can be considered as a postremission therapy for AML patients with favorable or intermediate risk cytogenetics who achieve CR1 after a single course of induction treatment.

Acknowledgments

Disclosure

All authors have no conflicts of interest.

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