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REVIEW

Metabolic bone diseases in patients after allogeneic hematopoietic stem cell transplantation: Report from the Consensus Conference on Clinical Practice in chronic graft-versus-host disease

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[Correction added after online publication July 25, 2011: Lorenz Hofbauer was changed to Lorenz Christian Hofbauer]

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Summary

With improved outcome of allogeneic stem cell transplantation (allo-SCT) for hematologic malignancies, long-term complications gain greater importance. Skeletal complications such as osteoporosis or avascular necrosis (AVN) occur frequently in allogeneic recipients with a cumulative incidence of diminished bone mineral density of 24–50% between 2 and 12 months after allo-SCT and a cumulative incidence of AVN in as many as 19% of patients 3 years after allo-SCT. Here, we present a review as part of the German, Austrian, and Swiss Consensus Conference on clinical practice in chronic graft-versus-host disease, held 2009 in Regensburg. The Consensus Conference aimed to achieve a consensus on the current evidence of diagnosis, prevention, and therapeutic options of late complications after allo-SCT summarizing and discussing the literature on these topics. In this report, we provide recommendations for metabolic bone diseases agreed upon by the working party. This includes guidelines for diagnosis, prevention, and therapeutic options in patients with low bone mass or AVN.

Introduction

With improved outcome of allogeneic stem cell transplantation (allo-SCT) for hematologic malignancies, long-term complications gain greater importance. This literature review was presented as part of the German, Austrian, and Swiss Consensus Conference on clinical practice in chronic graft-versus-host disease (GVHD) held 2009 in

Regensburg, which summarized the currently available evidence for first-line, second-line, and topical therapies and provided practical guidelines for the use of supportive treatment modalities [1–4]. This conference was a joint initiative by German, Austrian, and Swiss hematopoietic stem cell transplantation centers. The consensus conference was organized under the auspices of the German working group on bone marrow and blood stem cell transplantation (DAG-KBT), the German Society of Hematology and Oncology (DGHO), the Swiss Blood Stem Cell Transplantation Group (SBST), the Austrian Stem Cell Transplant Working Group of the Austrian Society of Hematology and Oncology and the German-Austrian Pediatric Working Group on SCT (PÄD-AG-KBT).

The evaluation of evidence and the subsequent recommendation was classified according to the system used in grading of supportive care published by Couriel *et al.* [5] (Tables 1 and 2). Based on the US NIH Consensus recommendations, the focus of this report was to provide an update and more detailed guidance in prevention and treatment of metabolic bone diseases after allo-SCT. All strength of recommendation and evidence levels were based on a PubMed-based literature search with subsequent rating by an expert panel followed by rating and approval of the recommendations by all participants of the consensus process. Abstracts from the Bone Marrow Transplantation Tandem meetings, the European Bone Marrow Transplantation meetings and the American Society of Hematology meetings were cited but were not included in the evidence rating. Reference lists from the articles retrieved were also evaluated for relevant information.

Table 1. Strength of recommendation.

Strength of recommendation level	Definition of recommendation level
A	Should always be offered
B	Should generally be offered
C	Evidence for efficacy is insufficient to support for or against, or evidence might not outweigh adverse consequences, or cost of the approach. Optional
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. Should generally not be offered

Table 2. Quality of evidence supporting the recommendation.

Quality of evidence	Definition of evidence level
I	Evidence from one or more properly randomized, controlled trial(s)
II	Evidence from one or more well-designed clinical trial(s) without randomization, from cohort or case-controlled analytic studies (preferable from >1 center), or from multiple time series or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports from expert committees

Qualifier for categories I-II: a-evidence derived directly from study(s) in patients after allogeneic stem cell transplantation; b-evidence derived indirectly from study(s) in analogous or other pertinent diseases (especially glucocorticoid-induced osteoporosis).

Osteoporosis is the most important metabolic bone disease and is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (Consensus Development Conference, 1993) [6]. The WHO Working Group estimates the degree of osteoporosis according to measurements of bone mineral density (BMD) using dual energy X-ray absorptiometry (DXA). Osteoporosis is defined as a bone density *T*-score at or below 2.5 standard deviations (SD). Osteopenia is defined as a *T*-score between −1.0 and −2.5 SD.

Metabolic bone diseases, such as osteoporosis with a high risk for fractures, or avascular necrosis (AVN) occur frequently in patients after allo-SCT. Transplant-related bone loss is a multifactorial, rapidly evolving, and possibly long-lasting disorder [7,8]. A diminished BMD (*T*-Score <−1.5) is diagnosed in 24–50% of the patients between 2 and 12 months after allo-SCT [9–11]. The cumulative incidence of AVN ranges between 6% and 19% 3 years after transplantation [9,12–15] (Table 3). Unfortunately, the currently available studies regarding prevalence and incidence applied different end points and definitions impairing joint evaluation. Moreover, the number of patients and the observation period vary considerably. Further long-term observational trials including a representative number of patients are required to determine the prevalence and incidence of osteoporosis and AVN after allo-SCT.

Osteoporosis

Risk factors

Risk factors for bone loss after allo-SCT include chemotherapeutic agents (especially high-dose regimes), calcineurin-inhibitor type immunosuppressants (e.g. cyclosporine A, tacrolimus), hypogonadism [8], age, and low body mass index (BMI) or rapid weight loss, and prolonged immobilization [16–18]. Studies including patients after allo-SCT

Table 3. Frequency of osteopenia, osteoporosis, and avascular necrosis in patients after allo-SCT.

References	*N*	Frequency		
		Osteopenia	Osteoporosis	Avascular necrosis
Abou-Mourad *et al.* [9]	429	24.4% osteopenia/ osteoporosis ≥2 years after allo-SCT		
Wiesman *et al.* [15]	272			6.3% 11.8% in long-term survivors
Schulte and Beelen [12]	255			6.1% (4-year cumulative incidence rate)
Tauchmanovà *et al.* [13]	207, 100 after allo-SCT, 107 after autologous SCT			10% in patients after allo-SCT
Petropoulou *et al.* [11]	146		>50% 2 months after allo-SCT	11% (3-year cumulative incidence rate)
Stern *et al.* [14]	104		osteoporotic fractures in 10.6% (3-year cumulative incidence rate)	9.6% (3-year cumulative incidence rate)
Yao *et al.* [10]	102	<6 months after allo-SCT: 13/27 (48%) with osteopenia/osteoporosis >6 months after allo-SCT: 9/19 (47%) with osteopenia/osteoporosis		
Savani *et al.* [19]	79	41.8% beyond 2 years after allo-SCT	31.6% beyond 2 years after allo-SCT	

allo-SCT, allogeneic stem cell transplantation.

identified prolonged immunosuppression, age, and the cumulative dose of glucocorticoid therapy as independent risk factors for osteoporosis [14,19]. The role of hypogonadism, low BMI, and prolonged immobilization have not been evaluated in patients after allo-SCT but are derived from studies in postmenopausal women [20,21]. The most important risk factor for osteoporotic fractures, however, might be the long-term use of corticosteroids in association with acute or chronic GVHD [17,19,22–24]. The risk for osteoporotic fractures is elevated when a daily dosage of 5 mg prednisolone is used for longer than 3 months. The fracture risk increases with a higher dosage of corticosteroids, especially for vertebral fractures. The fracture risk decreases 1 year after stopping the treatment of corticosteroids. Diabetes mellitus, chronic renal failure, and malabsorption (especially in GVHD of the gut), resulting in vitamin D deficiency, are associated with significant bone loss after allo-SCT, as well.

Moreover, the rapid and profound changes of cytokines after transplantation have been hypothesized to be major factors for bone loss. The release of certain cytokines appears to activate osteoclasts and to decrease the number and blunt function of osteoblast precursors [7,25]. Enhanced release of granulocyte-macrophage colony-stimulating factor, IL-6, IL-7 and TNF-α was observed after allo-SCT. Furthermore, an alteration in the balance between the receptor activator of the nuclear factor-κB ligand (RANKL) and osteoprotegrin (OPG) contributed to the pathogenesis of osteoporosis. Baek *et al.* described an increase in soluble OPG and soluble RANKL within 3 months after transplantation [26].

Interestingly, the pattern of bone loss after allo-SCT is somehow different from other forms of osteoporosis (such as primary osteoporosis), being more persistent and severe in cortical bones, such as the femoral neck (FN), than in trabecular bones, such as the spine [14,27,28]. So far, no data exist regarding the frequency of vertebral fractures and hip fractures in patients after allo-SCT. In patients with glucocorticoid-induced osteoporosis the risk for vertebral fractures is considerably higher than for hip fractures [21,29]. Glucocorticoid exposure causes predominantly spinal bone loss and, thus, particularly increases the risk of vertebral fractures (to a greater extent than estrogen deficiency).

Diagnosis of osteoporosis

Dual energy X-ray absorptiometry scan which measures the areal BMD by X-ray absorption is the most widely used test because of its accuracy, convenience and

noninvasiveness. The FN and lumbar spine (L1–L4) are usually assessed by DXA where the lowest measurement of BMD has been proven to be a good predictor for the risk of future bone fracture [21,30].

Measurement of the BMD should be offered to every patient within the first year after allo-SCT (base-line measurement) (recommendation level A I). Patients developing a complication like acute or chronic GVHD requiring glucocorticoids (≥5 mg of prednisolone equivalent daily for >3 months) [31] should have a DXA scan shortly after starting glucocorticoid therapy as rapid bone loss has been reported within the first months of glucocorticoid administration [32,33]. The joint recommendation of EBMT, CIBMTR, and ASBMT for screening and preventive practices for long-term survivors after hematopoietic stem cell transplantation suggested a screening of BMD 1 year after allo-SCT [34].

Baseline BMD pre-SCT is recommended if risk factors are present [e.g. acute lymphoblastic leukemia (ALL), high dosage of steroids before allo-SCT]. In elder patients (>60 years), it might be useful to perform a measurement of BMD prior to allo-SCT depending on pre-existing risk factors such as other underlying diseases (e.g. rheumatoid arthritis), special medication (e.g. glitazones, anticonvulsant drugs), history of maternal hip fracture, or the propensity to falls. The indication for measurement of BMD might be adjusted according the DVO guidelines [21]. Patients with a *T*-score <1.5 SD pre-SCT should be followed closely and receive treatment as early as possible after allo-SCT. In addition to DXA, baseline measurement of serum levels of calcium, phosphate, and 25-hydroxy-vitamin D should be performed in all patients after allo-SCT.

If additional endocrine causes of osteoporosis such as primary hyperparathyroidism, hyperthyroidism, or hypogonadism are clinically suspected, the patient should be evaluated by an endocrinologist.

Prevention

Vitamin D and calcium

An adequate intake of calcium (800–1200 mg/day) via dietary intake or supplements is recommended. Vitamin D supplementation (at least 800 IU/day) is recommended as vitamin D deficiency has a high prevalence and, in addition to various adverse extraskeletal effects, may contribute to low bone mass and increase the propensity to falls [35]. In addition, the efficacy of anti-osteoporotic drugs has only been demonstrated in the presence of vitamin D and calcium supplementation. Therapy should be titrated with doses that result in serum 25-hydroxyvitamin D concentrations of at least 30 ng/ml and normocalcemia. All patients who receive a treatment with glucocorticoids should receive a prophylactic supplementation with 1000 IU vitamin D 3 (cholecalciferol) and, if the dietary intake is not sufficient, 1000–1200 mg calcium. Patients without glucocorticoids should receive a replacement of vitamin D 3 (cholecaliferol) and calcium only in deficient states (A I b) [5,21]. The American Society of Bone and Mineral Research has issued a statement and recommends the use of a combined vitamin D and calcium supplementation instead of only calcium supplementation because a recent meta-analysis raised concerns that calcium supplementation may be associated with an increased risk of cardiovascular events, although this has not been shown for allo-SCT patients [36].

Calcium and vitamin D alone are not a sufficient treatment for patients with manifest osteoporosis [37,38]. Preventive measures include regular weight-bearing physical activity (A I b) [39], a healthy life style, smoking cessation and measures to prevent falls (e.g. eye examination, exercise to improve proprioception).

Bisphosphonates

Several studies with patients after allo-SCT showed a significant increase in BMD with the use of bisphosphonates [22,23,40,41]. Table 4 shows the randomized controlled trials using bisphosphonates in prevention of bone loss in patients after allo-SCT.

In one open uncontrolled study, the effect of a single 4 mg zoledronic acid infusion was evaluated in 12 patients with either osteoporosis (*T*-score <−2.5) or rapid bone loss after allo-SCT [40]. Most of the patients (nine of 12) received zoledronic acid within the first year after transplantation. Twelve months after the infusion, total hip BMD increased in 75% of the patients and femoral neck BMD increased in 11 of 12 patients. Spinal BMD increased only in four patients.

Most of these studies have small and often heterogeneous populations. Bisphosphonate therapy also has been used in the treatment and prevention of diminished BMD without considering the *T*-score before therapy. Although these previous studies have shown that bisphosphonates are well tolerated and improve BMD in these populations, more information is needed on which to base treatment recommendations.

As patients receiving steroids for chronic GVHD after allo-SCT are at high risk for osteoporosis, a prophylactic treatment with bisphosphonates regardless of the *T*-score in the DXA scan has been discussed during the conference and in the literature [7]. On the one hand patients after allo-SCT have two or even more risk factors for osteoporosis. Stern *et al.* showed that spine density did not predict fracture rate and that fractures may occur in patients with only slightly reduced *T*-scores [14]. Furthermore, loss of BMD may be very fast within the first

Table 4. Randomized controlled trials using bisphosphonates for prevention of bone loss in patients after allogeneic stem cell transplantation.

References	*N*	Duration (months)	Treatment regimen	Control regimen	Findings summary
Tauchmanovà *et al.* [41]	32	12	Zoledronic acid 4 mg i.v. administered at 1, 2, 3, 6, and 9 months after transplantation, calcium 500 mg/day and vitamin D 400 IU/day	Calcium 500 mg/day, vitamin D 400 IU/day	BMD: LS and FN BMD increased in zoledronic acid group (9.8% and 6.4%, respectively) and did not change in the control group at 12 months
Chae *et al.* [22]	53	24	Zoledronic acid 4 mg i.v. at 2 months after transplant and then every 3 months until 2 years	No treatment	Zoledronic acid significantly prevented bone loss in the FN and the spine
Grigg *et al.* [63]	116	24	Pamidronate 90 mg i.v. administered prior to transplantation and every month after transplantation for 12 months; calcium 1000 mg/dl; calcitriol 0.25 μg/day for 24 months	Calcium 1000 mg/day, calcitriol 0.25 μg/day	BMD: at 12 months, difference in bone loss from baseline was decreased at LS, FN, and TH in pamidronate group versus no infusion. At 24 months, the difference in bone loss from baseline was only significant at the TH (3.9%)
Kananen *et al.* [101]	99	12	pamidronate 60 mg i.v. administered prior to transplantation and 1, 2, 3, 6, and 9 months after transplantation; calcium 1000 mg/day; vitamin D 800 IU/day; estrogen, women; testosterone, men	calcium 1000 mg/day, vitamin D 800 IU/day; estrogen, women; testosterone, men	BMD: at 12 months, difference in bone loss from baseline at LS and TH was decreased in pamidronate group versus no infusion. No difference in bone loss from baseline at the FN
Tauchmanovà *et al.* [42]	34	12	Oral risendronate 5 mg/day 17–24 months after transplantation; calcium 1000 mg/day; vitamin D 800 IU/day	Calcium 1000 mg/day, vitamin D 800 IU/day	BMD: after 12 months, lumbar BMD increased significantly by 4.4% in the risendronate group and decreased by 4.3% in those without risendronate; at the FN, BMD did not change

FN, femoral neck; TH, total hip; LS, lumbar spine; BMD, bone mineral density.

months of glucocorticoid use. On the other hand, there are no long-term data whether the prophylactic use of bisphosphonates is able to decrease the rate of bone fractures. Savani *et al.* showed that bone loss was not associated with an increased fracture risk [19]. In summary, prophylactic use of bisphosphonates remains optional because of lack of long-term data. Osteonecrosis of the jaw (ONJ) remains a potential concern that has been associated with bisphophonates and invasive oral procedures. In Table 5, the recommendations of preventive measures are demonstrated.

Table 5. Recommendations of preventive measures in patients after allogeneic stem cell transplantation.

Preventive measures	Recommendation	Evidence
Calcium and vitamin D replacement in deficient states, and high risk of deficiency (e.g. patients with glucocorticoids, prednisolone ≥5 mg/day > 3 months)	A	I b
Regular physical activity	A	I b
Bisphosphonates	C	II a

First-line therapies

Based on the experiences in prophylaxis of osteoporosis after allo-SCT and numerous trials in treatment primary and secondary osteoporosis, a specific therapy for osteopenia/osteoporosis is recommended in patients with a *T*-Score ≤−1.5 in the DXA scan or with prevalent osteoporotic fractures (A II a) [5,21].

Bisphosphonates

Currently, first-line therapy of osteoporosis consists of bisphosphonates together with vitamin D and calcium. Bisphosphonates given parenterally are associated with a lower rate of adverse effects and better long-term adherence. Oral treatment with bisphosphonates is possible in patients with good compliance, no malabsorption and no

diseases of the upper gastrointestinal tract. Oral bisphosphonates are contraindicated in immobilized patients, patients with dysphagia, or in patients with gastrointestinal GVHD. A positive effect of risedronate on the BMD has been reported only in one study, so far [42].

Zoledronic acid is contraindicated in patients with severe renal failure (GFR <45 ml/min). Rare side effects are ONJ, more frequently acute phase reactions and hypocalcemia are reported. ONJ is reported to be a severe complication with a significant impact on oral function that may lead to marked maxillofacial mutilation [43]. In the majority of the ONJ cases which developed post-transplant, the indication for SCT was multiple myeloma most likely due to the extended use of bisphosphonates prior to SCT. The estimated incidence was reported to be 4.5–15% following intravenous bisphosphonate therapy [44,45]. Intravenous bisphosphonates, cancer and anti-cancer therapy, dental extraction, duration of exposure to bisphosphonates, glucocorticoids, alcohol and/or tobacco abuse and pre-existing dental or periodontal disease are risk factors associated with ONJ [46,47]. The risk of ONJ in patients with cancer treated with high doses of intravenous bisphosphonates like patients after allo-SCT is clearly higher than in patients with primary osteoporosis, in the range of 1–10 per 100 patients [48]. Further information about the detailed management of ONJ is published by the Consensus Conference separately [4].

The optimal administration of bisphosphonates, and the frequency and duration of therapy are still unclear. A therapy with zoledronic acid 4 mg given at intervals every 3 months for at least 1 year has been tested in several studies with patients after allo-SCT [22,41]. Only one study, so far, investigated a single infusion of zoledronic acid [40]. It is important to mention that in primary osteoporosis and in glucocorticoid-induced osteoporosis a dosage of 5 mg zoledronic acid once a year is recommended [21,48,49]. Further studies to define the adequate dosage and duration of osteoporosis therapy for patients after allo-SCT are required. So far, no studies exist whether bisphosphonates can in fact reduce the fracture rate in patients after allo-SCT. Therefore, studies including the fracture rate as an end-point are urgently needed.

Hormone replacement therapy

Premature ovarian failure and hypogonadism are the most common long-term effects affecting young patients after allo-SCT. Ovarian failure occurred in 70–95% of young women after allo-SCT [8,50–53]. Estrogens inhibit osteoclast activity and promote osteoclast apoptosis. Androgens may directly affect osteoblast differentiation, and are also converted to estrogens. Endocrine parameters (LH, FSH, estradiol, and progesterone) should be assessed 3–6 months after allo-SCT. Estrogen/progesterone-based hormone replacement therapy (HRT) is generally recommended in patients with premature ovarian failure but several contraindications (e.g. thromboembolism, increased risk of breast cancer, cardiovascular events, and severe liver diseases) are to be recognized (A II a) [7,23].

Tauchmanovà *et al.* showed a decreased loss of BMD in young female patients receiving HRT in comparison with patients with no HRT [23]. However, no significant increase of BMD was achieved. Therefore, HRT alone seems to be an insufficient treatment of the multifactorial osteoporosis in patients after allo-SCT.

Second-line therapies

Parathyroid hormone-derived peptides

In theory, second-line therapies of osteoporosis might be parathyroid hormone-derived peptides, such as human recombinant PTH peptide 1–34 (teriparatide) or the full-length human recombinant parathyroid hormone (hrPTH 1–84). Teriparatide is already approved for glucocorticoid-induced osteoporosis (B I b) [49]. PTH-analogs may be an alternative to the antiresorptive bisphosphonates because of their anabolic and stimulating effect on bone formation. PTH-analogs are contraindicated in patients with severe renal failure, hypercalcemia, radiotherapy of the bone, and malignant diseases of the bone. Therefore, it may not be used after total body irradiation or prior/after radiotherapy of bone structures which markedly limits its potential use. In addition, there is no experience with patients after allo-SCT. Although PTH-analogs might have a specific role after allo-SCT in stimulating mesenchymal stem cell (MSC) differentiation into the osteoblast lineage, clinical studies are required to test this hypothesis [54].

Selective estrogen receptor modulator

Another antiosteoporotic therapy is the selective estrogen receptor modulator raloxifene. This medication could be useful in patients with familiar risk of breast cancer but has to be evaluated more precisely [55]. Raloxifene is contraindicated in patients with thromboembolism, severe liver or renal failure and bleeding of the uterus of unknown causes. Raloxifene is only approved in primary osteoporosis and, so far, not in secondary osteoporosis. No studies exist in patients after allo-SCT.

Denosumab

Another new potential therapy for osteoporosis represents a humanized monoclonal antibody to RANKL (denosumab) [7,56,57]. The treatment is under development and seems to be promising in preventing bone loss after allo-SCT because its mechanism involves pathways disturbed by glucocorticoids, hypogonadism, and cytokines. Denosumab has been tested in two randomized

Table 6. Recommendations of therapeutic options in osteopenia/osteoporosis in patients after allogeneic stem cell transplantation.

Therapeutic options (*T*-score ≤−1.5 SD or osteoporotic fracture)	Recommendation	Evidence
Calcium and vitamin D	A	I b
Bisphosphonates	A	II a, I b
Hormone replacement therapy in deficient states	A	II a
Parathyroid hormone analogs	Experimental	I b
Raloxifene	Experimental	–
Denosumab	Experimental	II b

trials in postmenopausal women with low BMD [56,58] demonstrating a significantly reduced risk for hip fracture, vertebral fracture and nonvertebral fracture [58].

In a recent study of patients with rheumatoid arthritis, including some treated with glucocorticoids, denosumab increased spinal and hip BMD [59]. Attributes of denosumab in clinical studies include a rapid onset of action, sustained effects for several months after a single injection, and good tolerability (especially in patients with impaired renal function) [60]. Although denosumab has been applied in cancer patients for the treatment of skeletal metastasis, there is no experience with denosumab in patients after allo-SCT [61,62].

An important point to mention is that some antiosteoporotic agents are only approved for primary osteoporosis (e.g. raloxifene, hrPTH 1-84) and not for secondary osteoporosis. The recommendations of therapeutic options in osteopenia/osteoporosis are listed in Table 6.

Follow-up

After initiation of treatment with bisphosphonates, the value of DXA screening is less clear as bone density does not longer correlate with the risk of osteoporotic fractures. Therefore, follow-up DXA testing should be performed after 24 months [21].

It is still unclear how long a transplanted patient with osteoporosis should be treated and what happens after withdrawal of bisphosphonates [60]. Grigg *et al.* reported that bone loss reappeared at the spine and FN, but not at the total hip during the second year after withdrawal of high-dose pamidronate therapy [63]. Long-term studies are required to investigate the long-term effect of bisphosphonates.

Special aspects of osteoporosis in pediatric patients

In the pediatric setting, the measurement of BMD represents a complex problem because DXA reference values for the pediatric cohort of patients do not exist [64]. The bone size, skeletal maturity, and body composition of children should be considered when interpreting DXA measurements. In children the diagnosis of osteoporosis should not be made on the basis of densitometric criteria alone. It requires the presence of a clinically significant fracture history and a low BMD that is defined as a BMD *Z*-score less than or equal to −2.0, adjusted for age, gender and body size, as appropriate. A *Z*-score between −1.0 and −2.0 is defined as the low range of normality [65–67].

In children, the main risk factor for osteoporosis is represented by hypogonadism (low estrogen and testosterone level) because of the direct toxicity of chemo- and/or radiotherapy on gonadal function (hypergonadotropic hypogonadism) or gonadal failure associated with cranial irradiation (hypogonadotropic hypogonadism). In girls, the age and pubertal status at the time of chemo- and/or radiotherapy have an impact on the rate of ovarian dysfunction, but the latter association can not be demonstrated in boys [64]. For this reason, the measurement of BMD is not necessary in all pediatric patients, but it is strongly recommended in young females and high-risk patients with a prolonged immunosuppressive treatment and/or low BMI and immobilization.

Treatment of osteoporosis in children includes increasing weight-bearing exercise, optimizing nutritional intake of calcium and vitamin D, nutrient supplementation if dietary intake is insufficient, and treatment of conditions that may exacerbate BMD deficits such as hypogonadism or GVHD [68].

The use of bisphosphonate therapy in pediatric patients remains controversial because of inadequate long-term efficacy and safety data. For this reason, many experts recommend limiting the use of these agents to those children with reduced BMD, recurrent peripheral fractures, and/or symptomatic vertebral collapse [67,69].

Intravenous pamidronate therapy is reported to reduce fractures and improve bone density in children affected by primary or secondary osteoporosis [70]. In particular, the experience with these drugs is related to children affected by osteogenesis imperfecta [71,72]. Recently, some studies reported that intravenous zoledronic acid in children is safe and similar effective to pamidronate [73]. Prospective studies are needed to evaluate the efficacy and safety of bisphosphonates in children after allo-SCT.

Avascular necrosis

Avascular necrosis is a late, often severe complication after allo-SCT which occurs 13 to 26 months after transplantation [13,15,74,75]. The cumulative incidence of AVN is

Table 7. Studies analyzing risk factors for AVN in patients after allo-SCT.

References	*n*	Findings summary	Statistical significant risk factors for AVN
Campbell *et al.* [82]	1346	Cumulative incidence of AVN at 10 years after transplant by 5.4% (matched related donor) and by 15% (unrelated donor)	Male sex, chronic GVHD, exposure to cyclosporine A, tacrolimus, prednisone, and MMF; especially patients with a history of ≥3 drugs with increased risk for AVN
Patel *et al.* [83]	1053	Only patients with ALL; incidence rate of AVN by 4.0% at a median of 2.2 years postdiagnosis; incidence of AVN by 29% at 10 years in patients <20 years old compared to 8% at 10 years in those >20 years	Younger age, prolonged chemotherapy
Schulte and Beelen [12]	255	4-year cumulative incidence rate of AVN by 6.1%	Diagnosis other than CML, steroid intake
Tauchmanovà *et al.* [13]	207	107 patients after autologous SCT: cumulative incidence of AVN by 1.9% at 180 months after SCT 100 patients after allo-SCT: cumulative incidence of AVN by 10% at 180 months after SCT	chronic GVHD cumulative dose of glucorticoid therapy decreased number of bone marrow CFU-F colonies *in vitro*
Jagasia *et al.* [84]	206	50 cases, 156 controls	In univariate analyses, unrelated donor, use of total body irradiation, systemic steroids to treat GVHD
Faraci *et al.* [99]	172	A case–control study conducted among pediatric patients (43 cases, 129 controls) 43 of 1091 (3.9%) patients developed AVN	In univariate analysis, older age at SCT, total body irradiation, chronic GVHD and duration of steroid treatment after SCT; in multivariate analysis remained age at SCT, TBI and chronic GVHD
Torii *et al.* [85]	100	19% osteonecrosis of the femoral head; diagnostic method: magnetic resonance imaging	Younger age at the time of transplant, chronic GVHD, cumulative dose of steroid, intravenous pulse therapy with methylprednisolone
McAvoy *et al.* [86]	74	Patients after autologous and allo-SCT	Cumulative dose of prednisone, especially a cumulative dose of >9735 mg prednisone with 8.6 times higher risk for AVN

ALL, acute lymphoblastic leukemia; AVN, avascular necrosis; CFU-F, colony-forming unit fibroblast; CML, chronic myeloid leukemia; GVHD, graft-versus-host disease; allo-SCT, allogeneic stem cell transplantation.

between 6% and 19% 3 years after transplantation. The most common localization is the femoral head, often on both sides [76]. Other localizations are knee, shoulder, ankle, and in rare cases metacarpal bones.

Schulte *et al.* showed no increased risk for AVN in patients with low BMD or rapid loss of BMD [77].

Risk factors

Risk factors for AVN include GVHD, treatment with steroids, immunosuppressants (e.g. cyclosporine A, tacrolimus) with toxic effects on blood vessels [78], chemotherapy, and the underlying hematologic malignancies, especially ALL. Some studies showed an increased risk of AVN in patients with plasminogen activator inhibitor 1 (PAI-1) polymorphism [79–81]. Dysregulation of the lipid metabolism, drug-induced injury of the blood vessels with disrupted blood supply of the bone, and vasculitis have been identified as pathogenetic factors [13].

A summary of the literature regarding the risk factors is shown in Table 7 [82–86].

Diagnosis

Avascular necrosis is diagnosed by magnetic resonance imaging (MRI) which allows early detection and assessment of its severity [34].

Therapeutic options

One important therapeutic strategy is to taper corticosteroids as much as possible. Patients with high levels of cholesterol or triglycerides might require a medical

Table 8. Recommendations for avascular necrosis in patients after allogeneic stem cell transplantation.

Therapeutic options in avascular necrosis	Recommendation	Evidence
Pain relief	A	II a
Orthopedic measures to decrease pressure on the joint	A	II a
Surgical options (e.g. core decompression)	B	II a
Cellular-based therapies (e.g. BMSCs, MSCs)	C	III a

BMSCs, bone marrow stromal cells; MSCs, mesenchymal stem cells.

treatment, especially with statins. Experimental data showed that statins, e.g. lovastatin, can prevent the development of steroid-induced osteonecrosis in animal models [87–90]. Data regarding the role of statins in prevention of AVN after allo-SCT do not exist, so far. In patients after renal transplantation, the application of statins did not protect against AVN [91].

Pain relief (pharmacological or surgical measures) is the goal of recommended treatment. In an early phase of AVN, patients should use crutches or other supports to avoid weight load on the limbs [5,64]. Current treatment in advanced disease is surgical, and includes core decompression of the affected area and joint replacement (e.g. total hip replacement). In progressive and severe courses of AVN arthrodesis may be required.

Cellular-based therapies are under investigation and might be used in addition to, or instead of, invasive surgery in future. Bone marrow stromal cells (BMSCs) [92] and MSCs [93] may improve the efficiency of surgical treatment of AVN [94–96]. However, the results of first case reports and early experimental studies have to be evaluated more precisely in larger randomized controlled trials. Recommendations for AVN are listed in Table 8.

Special aspects of avascular necrosis in pediatric patients

In the pediatric setting, the role of steroids as a causative factor for AVN has been implicated in a few other reports involving children with leukemia treated with front-line therapy only. However, these studies reported a lower (1.1% to 1.8%) incidence of AVN [97,98]. A case–control study was conducted among Italian children treated with SCT and demonstrated an incidence of AVN of 3.9% [99]. This study revealed a significant correlation of older age at SCT, total body irradiation, chronic GVHD, and duration of steroid treatment after allo-SCT with AVN [99].

Like in adults MRI with an overall sensitivity of more than 90% is the most sensitive method for diagnostic detection and follow-ups of AVN [100]. Therapeutic options are similar to adult patients.

Conclusion

Metabolic bone diseases are an important, early, and potentially long-lasting complication after allo-SCT. Osteoporosis is more frequent than AVN in patients after allo-SCT. Several risk factors for diminished BMD are identified, including corticosteroids, GVHD, immunosuppressants, chemotherapy, cytokine release, and hypogonadism. As patients cumulate a number of risk factors, a reduced BMD is diagnosed in 24–50% between 2 and 12 months after allo-SCT. The presented consensus provides guidance for screening, prevention and treatment of osteoporosis and AVN in clinical routine. The low level of evidence for some of the suggested treatment options indicates the urgent need for further clinical trials including patients after allo-SCT.

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