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Vitamin D and Acute Myeloid Leukemia

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1. Introduction

The clearest role for vitamin D in human is in bone health as a regulator of serum calcium and skeletal homeostasis. Additional roles of vitamin D have been suggested, which include differentiation, apoptosis, angiogenesis and immunoregulation. Prevalence of vitamin D level

Vitamin D analogue	Chemical description	Comments
Vitamin D_1	Compound of ergocalciferol with lumisterol (stereoisomer of ergosterol) 1:1 ratio	
Vitamin D_2	Ergocalciferol (made from ergosterol)	
Vitamin D_3	Cholecalciferol (made from 7-dehydrocholesterol in the skin)	
Vitamin D_4	22-dihydroergocalciferol	
Vitamin D_5	Sitocalciferol (made from 7-dehydrositosterol)	
Vitamin D_6	Calciferol	
25-(OH) Vitamin D	Calcidiol or calcifediol; indicates no distinction between D_2 and D_3 forms. When relevant, forms are distinguished as 25(OH)D_2 and 25(OH)D_3	Vitamin D with one hydroxyl group added equivalent to liver activation.
Ercalcitriol	1,25$(OH)_2$ D_2	
Calcitriol	1,25$(OH)_2$ D_3	Vitamin D with two hydroxyl groups added equivalent to renal activation.
Doxercalciferol	1α(OH)D_2	
Alfacalcidiol	1α(OH)D_3	Vitamin D with one hydroxyl group added equivalent to renal activation

Table 1. Vitamin D Analogues

monitoring has significantly increased as the awareness of its potential importance to health has increased. Also, the readily available supply of vitamin D allows for intervention.

Vitamin D is generated in the skin from the non-enzymatic conversion of pro-vitamin D_3 to pre-vitamin D_3. Dietary intake of vitamin D is usually limited to selective foods, with the exception of certain kinds of fish which contain sizable amounts; supplements are commonly used. Vitamin D is either stored in adipose tissue or converted in the liver by the enzyme 25-hydoxylase to 25(OH) vitamin D_3, the most stable metabolite of vitamin D that reflects solar and dietary exposure (Binkley, Ramamurthy et al. 2010). There are many different analogues of vitamin D as shown in table 1.

Vitamin D body stores are reflected in the measurement of the serum level of the relatively stable (half-life approximately 3 weeks) surrogate marker 25 (OH) vitamin D_3 [25(OH)D_3]. Enzyme-linked immunosorbant assay (ELISA) is the most commonly used methodology in the United States (Hollis 2007); however, there are more sensitive and costly methods to measure vitamin D levels, e.g. mass spectroscopy (Yuan, Kosewick et al. 2011). Currently, the Institute of Medicine (2011) has put forth a guideline on recommended daily allowance and appropriate levels but this issue still remains controversial (Toner, Davis et al. 2010). In this paper, we will use the following definitions for vitamin D levels (Ross, Manson et al. 2011): Vitamin D deficiency as <10ng/ml (<25nmol/L) of 25(OH)D_3 in the serum. Vitamin D insufficiency as serum 25(OH)D_3 between 10-32ng/ml (25-75 nmol/L) (Rosen 2011). Subnormal vitamin D levels as less than 32 ng/ml of 25(OH)D_3 (Lee, HJ 2010). There are currently no standards of measurement or methods to measure vitamin D levels in the clinical setting. There have been numerous publications regarding vitamin D, but no consensus has yet been reached as illustrated in Table 2.

Author	*Year*	*Normal*	*Insufficient*	*Deficient*
Holick (Holick 2007)	2007	≥ 30 mg/ml	21-29 ng/ml	< 20 mg/ml
Lee (Lee, Eisman et al. 2009)	2009	> 25 ng/ml	12-24 ng/ml	< 12 ng/ml
Vashi (Vashi, Trukova et al. 2010)	2010	≥ 32 ng/ml	< 32 ng/ml (suboptimal)	N/R
Napoli (Napoli, Vattikuti et al. 2010)	2010	≥ 30 ng/ml	20-29 ng/ml	< 20 ng/ml
Drake (Drake, Maurer et al. 2010)	2010	≥ 25 ng/ml	< 25 ng/ml	N/R
Fedirko (Fedirko, Bostick et al. 2010)	2010	≥ 32 ng/ml	20-31.9 ng/ml	< 20 ng/ml
Rosen (Rosen 2011)	2011	> 30 ng/ml	10-30 ng/ml	< 10 ng/ml
Choo (Choo, Mamedov et al. 2011)	2011	≥ 30 ng/ml	< 30 ng/ml	N/R
Shanafelt (Shanafelt, Drake et al. 2011)	2011	≥25 ng/ml	< 25 ng/ml	N/R
Fiscella (Fiscella, Winters et al. 2011)	2011	N/R	N/R	< 20 ng/ml
Chadha (Chadha, Fakih et al. 2011)	2011	N/R	N/R	< 20 ng/ml

Abbreviations: N/R, not reported

Table 2. Various Definitions of Vitamin D Levels (25-Hydroxy Vitamin D_3)

1.1 Initial observation

An epidemiologic study estimated that one billion people worldwide have subnormal vitamin D levels due to decreased exposure to sunlight or dietary inadequacy (Holick 2011). Many studies suggest the detrimental effect of vitamin D insufficiency on heart, kidney, dermatologic, endocrine, and autoimmune diseases (Gueli, Verrusio et al. 2011). The well-established target organs of vitamin D are the intestines, kidney and bone, but several other

tissues also express vitamin D receptors (VDR), including normal and neoplastic hematopoietic cells (Haussler, Whitfield et al. 1998). In the early 1980s, *in vitro* data showed the ability of 1α,25-dihydroxy vitamin D_3 to differentiate acute myeloid leukemia (AML) [HL-60] into mature myeloid cells (Miyaura, Abe et al. 1981).
Vitamin D is a potentially exciting therapy for AML investigators due to its promising *in vitro* data and its safety (Trump, Deeb et al. 2010). The appropriate patient population selection and the development of optimum dosing and delivery schedule will maximize its clinical effect.

2. Epidemiologic evidence for vitamin D and leukemia

The epidemiology of vitamin D levels have not been extensively studied in AML as it has in other solid tumors (Toner, Davis et al. 2010). However, a study in northern Finland, where colder temperatures discourage extensive outdoor activities and minimize UV exposure during the winter months, found that majority of acute leukemia cases were diagnosed during the winter months of the year, rather than during the summer months (Timonen 1999). A possible explanation for this increase may be seasonal variation in levels of $25(OH)D_3$. It is estimated that $25(OH)D_3$ levels can vary by 8 to 12 ng/ml from the mean population during different seasons. Therefore, winter months can significantly increase the percentage of the population with low levels of $25(OH)D_3$, possibly increasing the risk of leukemia (Bolland, Grey et al. 2007). In addition, a large epidemiological study (Boscoe and Schymura 2006) using data from the North American Association of Central Cancer Registries and the National Cancer Institute's Surveillance, Epidemiology and End Results database found an inverse relationship between ultraviolet-B exposure and the incidence of leukemia; however, this study did not examine vitamin D levels and would make it difficult to conclude that vitamin D played a role in increased incidence of leukemia.
Similarly, a study in the United Arab Emirates (UAE) found that acute leukemia was more common among adult females than among adult males, despite the fact that the population of the UAE consists of more males than females, and acute leukemia is widely known to be more common in males. The authors' hypothesis was that the women's deprived sunlight exposure, due to their conservative clothing, may have contributed to their higher incidence of acute leukemia (Hassan, Islam et al. 2009). It would be difficult to conclude that vitamin D played a role in the increased incidence due to lack of dietary information on the populations.
However, these observations lend credibility to the association between AML and vitamin D.

2.1 Vitamin D and solid tumors

Initial observation by Garland et al. (Garland, Comstock et al. 1989) demonstrated higher mortality rates of colon cancer in the northeast when compared to the south and southwest United States, which suggested an association between sunlight exposure and cancer outcome. This finding led to several epidemiologic observations linking subnormal vitamin D levels to increased risk of breast (Garland, Garland et al. 1990), colorectal (Jenab, Bueno-de-Mesquita et al. 2010) and prostate cancers (Barnett, Nielson et al. 2010).
Giovannucci et al. performed a large prospective observational cohort study composed of 51,529 U.S. male healthcare providers and illustrated that low levels $25(OH)\ D_3$ (<25nmol/L) were associated with increased cancer incidence and mortality in men. Strongest association was seen with gastrointestinal cancers (Giovannucci, Liu et al. 2006).
On the contrary, a large randomized double blind controlled trial of 2,686 men and women aged 65 to 85 years of age from Oxford, England showed that supplementation of vitamin

D3 100,000 IU every 4 months versus placebo had a preventive benefit of reduced fracture in the vitamin D3 group after follow-up of five years. However, the cancer incidence was not statistically significant with relative risk (95% CI) 1.09 (0.86-1.36) (Trivedi, Doll et al. 2003). On the other hand, a study from Creighton University (Lappe, Travers-Gustafson et al. 2007) where they performed a population based, double blind, randomized placebo-controlled trial showed the opposite. Eligible subjects were >55 years and free of known cancer prior to entering study. Subjects were randomly assigned to take daily dosages of 1,400-1,500 mg supplemental calcium, 1,400-1,500 mg supplemental calcium plus 1,100 IU of vitamin D3, or placebo. Patients were prospectively followed for 4 years and the study showed that the calcium plus vitamin D group had a 60% reduction in cancer risk compared to placebo. The reasons for these differences are not clear but may be related to the supplementation offered and the subjects' pre-treatment vitamin D levels.

Further, the Nurses' Health Study, consisting of 32,826 participants, showed that the odds ratios for colorectal cancer were inversely associated with the 25(OH) D_3 serum levels (Feskanich, Ma et al. 2004). Similarly, Garland et al. (Garland, Garland et al. 2006) showed, in a meta-analysis of 980 women, that high dietary vitamin D intake was associated with significant reduction in developing breast cancer when compared with low vitamin D intake.

Various VDAs have been extensively tried as cancer therapeutic agents, but so far no ideal agent or delivery schedule has been clearly delineated. The most promising data was calcitriol in combination with docetaxel in prostate cancer; however, the phase III trial was halted by the data safety monitoring board because the survival rate in the vitamin D group was lower than the placebo group (Trump, Deeb et al. 2010). Among the concerns about the trial were that it included two different variables between the two arms; the control arm used docetaxel every three weeks, while the experimental arm, which included the addition of vitamin D, used docetaxel weekly. Second, there was limited rationale for calcitriol dose, which was probably inadequate, and the dose used was well below the calcitriol human maximally tolerated dose. This trial further highlights the need for continued exploration to define the appropriate dose and schedule to study in therapeutic and preventative trials.

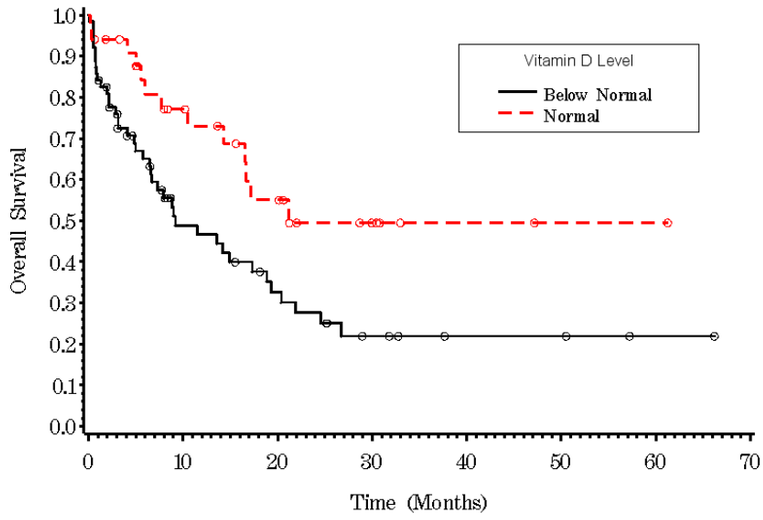
2.2 Vitamin D and hematologic malignancies (NHL, CLL)

A prospective Mayo Clinic study of 983 newly diagnosed NHL patients found that vitamin D insufficiency (<25 ng/ml, as determined by liquid chromatography-tandem mass spectrometry) was associated with inferior event free survival (EFS) and overall survival (OS) in diffuse large B- and T-cell lymphoma patients (Drake, Maurer et al. 2010). Similarly, the Mayo Clinic also examined 543 newly diagnosed CLL patients and found vitamin D insufficiency at diagnosis to be associated with decreased time until initiation of treatment (Shanafelt, Drake et al. 2011). These results lend credence to the possible correlation of adverse clinical effect of vitamin D insufficiency in newly diagnosed hematological malignancies.

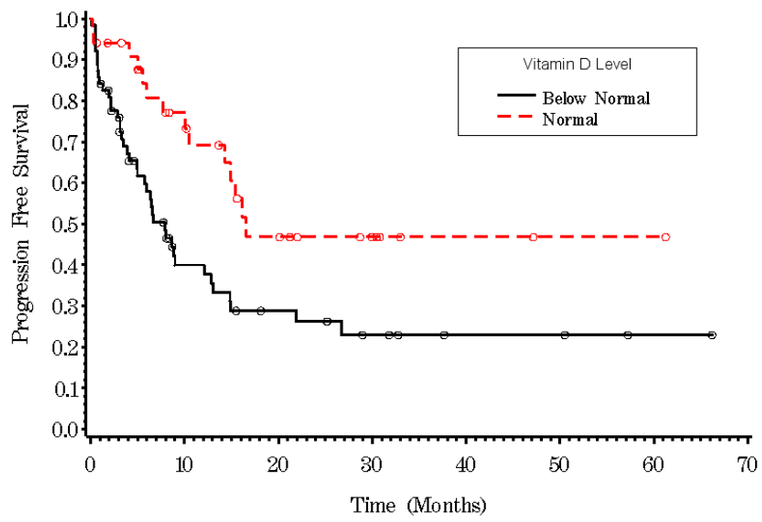
These studies illustrate observations that low vitamin D levels are associated with poorer clinical outcomes. Therefore, supplementation and corollary studies are needed to understand the effect of vitamin D on hematologic malignancies.

2.3 Vitamin D and AML

Lee et al. (Lee, HJ 2010) have recently reported 25(OH)D_3 levels at the time of diagnosis of AML and their association with survival. A cohort of 97 newly diagnosed AML patients treated on similar protocols showed that patients with subnormal 25(OH)D_3 (<32ng/ml) had significantly worse progression free survival (PFS) and OS when compared to those with normal 25(OH)D_3 levels (≥32ng/ml) (Figure 1).



(A)



(B)

Fig. 1. A: Overall Survival; B: Progression Free Survival

Therefore, one may hypothesize the benefit of supplementing AML patients with subnormal 25(OH)D_3 levels to see if they would benefit from 25(OH)D_3 normalization. There are several reports (Drake, Maurer et al. 2010; Lee HJ 2010; Shanafelt, Drake et al. 2011) indicating that low levels of vitamin D have been shown to be associated with worse clinical outcome; however, there are no prospective studies evaluating whether supplementation would improve outcome. It would be worthwhile to conduct a trial studying the effect of vitamin D supplementation in newly diagnosed AML patients.

2.4 Clinical trials with VDA in myelodysplastic syndrome and AML

Exploration of vitamin D as a possible therapeutic intervention for AML was propelled by the success of all-trans-retinoic acid (ATRA) treatment as a differentiating agent for AML

blasts (James, Williams et al. 1999). Vitamin D differentiates myeloid blasts to monocytes in vitro (Miyaura, Abe et al. 1981) and ex vivo (Lee, Kim et al. 1996), which prompted early clinical trials to investigate the anti-leukemic effects of VDAs in myelodysplastic syndromes (MDS) and AML (Table 3).

Author	Dx	#N	Median Age	Vitamin D	Chemotherapy	RR	CR
Petrich (Petrich, Kahl et al. 2008)	MDS	15	77	12.5 µg/d x 12 wks of doxercalciferol	Single agent	0%	0%
Siitonen (Siitonen, Timonen et al. 2007)	MDS	19	73	1 µg/d 1,25(OH)D_3	Valproic acid and 13 cRA	16%	0%
Mellibovsky (Mellibovsky, Diez et al. 1998)	MDS	19	75	266 µg 3xwk (calcifediol) 5 pts and 0.25-0.75 µg/d calcitriol 14 pts	None	58%	NA
Ferrero (Ferrero, Bruno et al. 1996)	MDS	53	74	1-1.5 µg/d calcitriol	cRA and intermittent	52%	NR
Slapak (Slapak, Desforges et al. 1992)	AML	29	73	0.25 µg oral Q12hrs Calcitriol	Cytarabine, hydroxyurea	79%	45%
Petrini (Petrini, Dastoli et al. 1991)	AML	21	67.5	20 mg BID AraC x 7d Q3w, 1 µg 1(OH)D_3	low dose ARA-C	62%	17%
Hellstrom (Hellstrom, Robert et al. 1990)	MDS, AML	69	NR	1 µg/d of 1α(OH)D_3	Low dose ARA-C	26%	NR

Abbreviations: NR: Not Reported, AraC: Cytosine Arabinoside, wk: Weeks, pts: patients, cRA: cis-retinoic acid, RR: Response Rate, CR: Complete Response

Table 3**.** Vitamin D Trials in Myelodysplastic Syndrome / Acute Myeloid Leukemia

Seven studies examined the effects of various VDAs in AML and MDS, either single agent or combined with other chemotherapy, including low-dose cytarabine, hydroxyurea, and valproic acid. All studies were small, ranging from 15 to 69 patients, and median age, when reported, ranged from 67.5 to 77. Overall response rates ranged from 0% to 79%, and complete response (CR) rates ranged from 0% to 45% when reported. Early results were mixed, as single agent VDA induced partial differentiation of myeloid blast cells in a few patients with a paucity of clinical improvements (Mellibovsky, Diez et al. 1998). Combination trials with VDA and chemotherapy resulted in mixed results in MDS/AML (Hellstrom, Robert et al. 1990; Petrini, Caracciolo et al. 1991; Petrini, Dastoli et al. 1991; Slapak, Desforges et al. 1992; Ferrero, Bruno et al. 1996; Siitonen, Timonen et al. 2007).

Slapak et al. (Slapak, Desforges et al. 1992) showed promising results in a study of 29 AML patients, who were treated with a regimen of low-dose cytarabine, hydroxyurea, and calcitriol (0.25µg, oral every 12 hours) begun on day 1 of cytarabine and continued until relapse or the patient went off study. Three patients died within 60 days, and of the remainder, the overall response rate was 79%; 45% achieved CR and 34% achieved partial remission (PR). The median overall survival was 14 months for those who responded and 12 months overall. Although all patients developed transient thrombocytopenia and

granulocytopenia and 20 patients required platelet transfusions transiently, the study nonetheless showed promise due to its high overall response rate and low induction death rate. Two patients experienced asymptomatic hypercalcemia (11.2mg/dl and 11.5mg/dl) but did not require treatment. The authors proposed that the favorable results might be due to the synergistic effects of cytarabine, hydroxyurea, and calcitriol, although they did not propose a specific mechanism (Slapak, Desforges et al. 1992),(Trump, Deeb et al. 2010).

Vitamin D was studied in 19 low-risk MDS patients with a median age of 75 years (Mellibovsky, Diez et al. 1998). Five patients received 266 mcg of calcifediol three times per week, and 14 patients received 0.25-0.75 micrograms per day of calcitriol. Of the patients treated with calcifediol, one responded, one progressed, and the other three patients did not respond. Of the 14 patients treated with calcitriol, 10 responded while the other four did not. The authors concluded that vitamin D_3 metabolites could be used to induce hematological responses in patients with low or intermediate risk MDS without the risk of hypercalcemia (Mellibovsky, Diez et al. 1998).

Petrich et al. (Petrich, Kahl et al. 2008) conducted a phase II trial of doxercalciferol (12.5 μg daily for 12 weeks) in 15 MDS patients. Only 9 of the 15 patients completed the whole 12 weeks, and no one responded. Stable disease was observed in six patients, and eight patients had disease progression, including two chronic myelomonocytic leukemia patients, who developed an increase in their monocyte count. Doxercalciferol was well tolerated; one patient experienced grade 3 rash, and one patient had grade 3 hypercalcemia and needed to be removed from the study. All toxicities resolved upon discontinuation of doxercalciferol. The authors therefore concluded that the study dose and scheduling of doxercalciferol appeared to have no efficacy in MDS patients (Petrich, Kahl et al. 2008).

All the clinical trials were conducted with very low doses of VDA. Also, there have been no pharmacokinetic studies examining whether supplementation was sufficient to observe clinical responses. In the future, studies of pharmacokinetic and novel markers (e.g. miRNA, methylation pattern of vitamin D responsive elements) may be used to select and properly dose populations that may benefit from VDA.

3. Molecular mechanism of vitamin D in AML

Cardinal features of AML are the inability to differentiate and the clonal expansion of myeloid blasts. Intensive biological research and clinical trials to eradicate AML cells with cytotoxic chemotherapy have yielded minimal improvements and have rarely led to cures, especially in those 60 years or older (Burnett, Wetzler et al. 2011). Vitamin D predominantly exerts its effects through binding to the cognate nuclear VDR; ligand bound VDR heterodimerizes with the retinoic X receptor (RXR) and binds to vitamin D responsive elements in the promoter regions of target genes, such as *CYP24A1*, *BGLAP* (osteocalcin) and cyclin dependent kinase inhibitor 1A (*CDKN1A,* $p21^{Waf1/Cip1}$), several protein kinase C (*PKC*) isoforms (Shimizu, Taira et al. 2002), the p42 extracellular regulated kinase (p42 *ERK*), p38-ERK and c-Jun N-terminal kinases (*JNK*) families of mitogen activated protein kinases (*MAPKs*) which are important in differentiation, metabolism and cell cycle (Wang and Studzinski 2001; Ji, Kutner et al. 2002; Hughes and Brown 2006; Marcinkowska, Garay et al. 2006; Studzinski, Garay et al. 2006). One of the main anti-proliferative and differentiating actions of vitamin D is the induction of cell cycle arrest by up-regulating anti-proliferative genes, such as p21, CCAAT/enhancer-binding protein α (*C/EBPA*) and interferon α-inducible protein 27 (*IFI27*, p27). Further, non-genomic actions of vitamin D through

increased activation of voltage gated calcium channels can alter the actions of Ras/Raf/mitogen-activated protein kinase (ERK) pathway as well as phosphoinositidine-3-kinase catalytic, alpha polypeptide (PI3K)/Akt pathway which have been shown to be activated in AML (Trump, Deeb et al. 2010). VDR is essential for vitamin D function. VDR is a highly conserved gene found in primitive organisms such as the sea squirt (*Ciona intestinalis*), a chordate invertebrate, showing that VDR was important even early in evolution (Reschly and Krasowski 2006). Calcium regulation is a key component to regulation of life itself, and vitamin D therefore is crucial to any system that relies on calcium for signaling. The VDR gene has been sequenced and compared among many different species, and now VDR polymorphism is an active area of research (Reschly and Krasowski 2006). VDR polymorphisms have been extensively studied in solid tumors and have been shown to have predictive value in cancer prognosis and recurrence (Kostner, Denzer et al. 2009). There are a limited number of studies of VDR polymorphisms in AML. In a French study (Rocha, Porcher et al. 2009), the investigators looked at VDR polymorphism (*Apa*I, *Taq*I and *Bsm*I), and demonstrated worse toxicity and survival after allogeneic transplantation in leukemia patients with VDR *Taq*I polymorphism. Binding affinity would be greatly affected by different VDR polymorphisms, given the structural variations induced by the polymorphism; hence, understanding structural and functional variations will allow for rational therapy design. Functional activity of VDR has been shown to be impaired by AML associated chromosomal translocations *PLZF-RAR* α, *PML-RAR* α and *AML-ETO1*; these fusion proteins interfere with VDR nuclear localization by binding to VDR (Puccetti, Obradovic et al. 2002).

3.1 Leukemia, vitamin D and the effect on apoptosis

Programmed cell death may be aberrant in AML cells as they continue to proliferate uncontrollably without activating the apoptotic pathway. AML has been known to be deregulated in the FAS induced apoptosis as a means of avoiding death (Testa and Riccioni 2007). VDAs have been shown to increase the expression of the FAS ligand and activate caspase-2,-3,-6 and -9 (Chen, Huang et al. 2008). Further, Vitamin D has been shown to down-regulate telomerase activity in ovarian cancers, which are known to have the highest level of telomerase activity in solid cancers (Jiang, Bao et al. 2004). Vitamin D was reported to disrupt telomerase reverse transcriptase (*TERT*) mRNA, therefore inducing apoptosis through telomere shortening and ultimately resulting in down regulation of telomerase activity(Jiang, Bao et al. 2004). Since AML has been reported to have high telomerase activity (Capraro, Zane et al. 2011), it would suggest that vitamin D may have a similar effect in this disease as well. Indeed, *in vitro* exposure of the leukemic cell line, HL-60, known to have high telomerase activity (Capraro, Zane et al. 2011), to vitamin D, led to down-regulation of the telomerase activity. This down regulation was associated with induction of p21, PI3K/AKT/mTOR pathways which play a key role in differentiation (Seol, Kim et al. 1998; Yamada, Ozaki et al. 2008). In summary, vitamin D, can modulate several pathways that will lead to AML apoptosis and should be exploited in AML treatment.

3.2 Leukemia, vitamin D and the effect on proliferative signaling

The FMS-like tyrosine kinase 3 (*FLT-3*) is mutated (internal tandem duplication, ITD) in cells of approximately 25-30% of AML patients (Burnett, Wetzler et al. 2011), providing such cells with a proliferative advantage. FLT-3 exerts its proliferative effect through the activation of many different pathways, e.g., PI3K/AKT/mTOR, RAS/RAF/ERK and signal transducer

and activator of transcription (STAT). Ultimately, these signaling pathways will down-regulate pro-apoptotic signals, such as the B-cell chronic lymphocytic leukemia/lymphoma 2 (BCL2)-family of proteins, and repress tumor suppressive genes, such as p21 and breast cancer 1 (BRCA1) (Stirewalt and Radich 2003). Of note, AML cells with chromosome 7 deletion were extremely sensitive to VDA but FLT-3 positive AML cells did not differentiate in the presence of VDA (Gocek, Kielbinski et al. 2010). This raises the question as to whether a FLT-3 inhibitor would restore the ability of FLT-3-ITD positive AML cells to differentiate in response to VDA. The data also emphasizes potential importance of detailed molecular characteristics of patients' AML cells and VDA use only in certain AML subgroups.

3.3 Leukemia, vitamin D and the effect on tumor suppressor genes

Leukemia cells must avoid or turn off negative regulators in order to proliferate. One example is the tumor suppressor transcription factor p53, whose inactivation, rather than mutation, is observed in many cancer types (Bohlig and Rother 2011); p53 is negatively regulated by murine double minute 2 (MDM2). It was recently shown that vitamin D alone induced monocytic differentiation of two wild-type p53 AML cell lines as well as a p53-null AML cells. Combination of a small molecule inhibitor (nutlin-3a) of p53-MDM2 interaction and vitamin D accelerated programmed cell death (Thompson, Andreeff et al. 2010). Interestingly, MDM2 levels dropped significantly in the presence of vitamin D_3, possibly contributing to the apoptotic effect. Additional factors were found to contribute to the sensitization of the wild-type p53 cells to apoptosis when exposed to combinations such as BCL2, ERK and others. The authors suggested that vitamin D_3 recruits its co-activators to enable p53 to become more effective in inducing cell death. This illustrates only a small amount of the complexities of cellular cross-talk seen in the vitamin D signaling pathway.

3.4 Leukemia, vitamin D and the effect on the tumor microenvironment

The bone marrow microenvironment is known to provide a nurturing environment for the hematopoietic stem cells. Leukemic stem cells also start to exploit the bone marrow microenvironment for survival advantage from conventional chemotherapy. Conventional chemotherapy induction is able to clear peripheral blood of leukemic cells, but patients ultimately relapse due to leukemic stem cells in the protected bone marrow microenvironment. Clinical trials (Harousseau, Witz et al. 2000; von Lilienfeld-Toal, Hahn-Ast et al. 2007; Borthakur, Kantarjian et al. 2008) have attempted to use granulocyte colony-stimulating factor (G-CSF) in order to bring out leukemic stem cells from the bone marrow. However, this method has not been shown to be widely effective. The mechanism by which G-CSF mediates mobilization is by sympathetic nervous system suppression of osteoblasts and modulation of serum calcium in the endosteal proximity of the bone marrow (Metcalf 1985). A recent report by Kawamori et al. (Kawamori, Katayama et al. 2010) demonstrated the regulatory role of VDR on mobilization of hematopoietic cells by using VDR knockout mice; lack of VDR caused inability to mobilize hematopoietic cells. The authors demonstrated that VDR is important for calcium regulation in the endosteal proximity of the bone marrow. *RANK ligand*, a gene downstream of VDR, is also stimulated by the sympathetic nervous system and aids in the stabilization of VDR. Jeanson and Scadden (Jeanson and Scadden 2010) reported that VDR knockout mice had marked accumulation of hematopoietic stem cells in the spleen, which was reversed by dietary calcium supplementation, thus adding credence to the importance of calcium/VDR regulation of stem cell trafficking. These data suggest that low

vitamin D levels can cause leukemic stem cells to hide in the protective layers of the bone marrow to avoid cytotoxic chemotherapy agents.
Further, anemia, bone marrow hypocellularity, and extramedullary hematopoiesis have been observed in vitamin D deficient rickets and have disappeared following vitamin D treatment. In two case reports, myelofibrosis and marrow dysfunction have been described secondary to vitamin D deficiency, and both improved following vitamin D supplementation (Balasubramanian, Varadharajan et al. 2005; Bhakhri and Debata 2010).
These results suggest that the interaction between the bone marrow microenvironment and the leukemia cells may be mediated, at least partially, by vitamin D.

4. Future directions

Three studies have shown the prognostic significance of vitamin D deficiency in hematologic malignancies, including CLL (Shanafelt, Drake et al. 2011), NHL (Drake, Maurer et al. 2010) and AML (Lee HJ 2010). There have been no studies evaluating the clinical significance of vitamin D supplementation on raising the $25(OH)D_3$ levels of patients with hematologic malignancies to normal. It would be worthwhile to carefully design a pharmacokinetic study to evaluate supplementation of vitamin D in AML patients. Following the pharmacokinetic study, the next question of whether vitamin D supplementation affects outcome will need to be separately evaluated in a large phase III clinical trial. At least two possibilities exist, either that the mere supplementation of vitamin D, with its multitude effects on bone and other tissues, is causing better outcomes or that vitamin D has a specific differentiation effect. The support for the latter is the preclinical finding that AML cells with chromosome 7 deletion are extremely sensitive to the VDA calcitriol, while FLT3-ITD positive cells are resistant to this differentiation therapy (Gocek, Kielbinski et al. 2010). There are other in vitro studies showing anti-proliferative, pro-apoptotic and differentiating properties of vitamin D on AML (Nowak, Stewart et al. 2009). Finally, the search for an ideal VDA that will not cause hypercalcemia is still on-going. A group from South Korea recently tested 11 VDAs and found that one compound had significant anti-leukemic activity with low proclivity toward hypercalcemia (Yoon, Kim et al. 2008). These new findings in the biology and improvements in VDAs will hopefully lead to an improved treatment option for AML patients.

5. Acknowledgments

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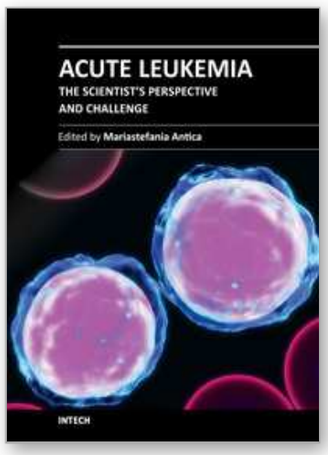
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This book provides a comprehensive overview of he basic mechanisms underlying areas of acute leukemia, current advances, and future directions in management of this disease. The first section discusses the classification of acute leukemia, taking into account diagnoses dependent on techniques that are essential, and thankfully readily available, in the laboratory. The second section concerns recent advances in molecular biology, markers, receptors, and signaling molecules responsible for disease progression, diagnostics based on biochips and other molecular genetic analysis. These advances provide clinicians with important understanding and improved decision making towards the most suitable therapy for acute leukemia. Biochemical, structural, and genetic studies may bring a new era of epigenetic based drugs along with additional molecular targets that will form the basis for novel treatment strategies. Later in the book, pediatric acute leukemia is covered, emphasizing that children are not small adults when it comes to drug development. The last section is a collection of chapters about treatment, as chemotherapy-induced toxicity is still a significant clinical concern. The present challenge lies in reducing the frequency and seriousness of adverse effects while maintaining efficacy and avoiding over-treatment of patients.

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