Differentiation-inducing liposoluble vitamin deficiency may explain frequent secondary solid tumors after hematopoietic stem cell transplantation

Minireview

G. GEDIKOGLU[1*], M. A. ALTINOZ[2*]

[1]ggedikoglu@superonline.com; [2]Institute of Health in Halic University, Halic Universitesi (Golden Horn University) Merkez Kampus, Mecidiyekoy- Buyukdere Cd. No: 101, 34394, ISTANBUL- TURKEY, e-mail: maltinoz@gmail.com

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Secondary cancers are among the most threatening long-term health problems of hematopoetic stem cell- transplant (HSCT) patients. There are several lines of evidence indicating the possibility of a prolonged Vitamin A deficiency for solid tumor-type secondary cancers: I- Solid tumors such as oral cavity, head/neck region squamous carcinomas, skin cancers and melanomas, where lowered Vitamin A concentrations and chemo-preventing activity of its derivatives (retinoids) are most explicitly proven, arise much more frequently than others. II- Early monitorings: A significant retinol deficiency in HSCT patients is detectable along with a severity of mucositis and the vulnerability to infection. III- Monitoring of other liposoluble vitamins: Vitamin D, a differentiation-inducing vitamin like Vitamin A, showed a sustained decrease. Another similarity of these two vitamins is that they also depend on intestinal absorption and are decreased due to bowel injury by conditioning agents and chronic graft-versus-host disease. IV- Peroxidative reactions and inflammation can directly exhaust retinol levels despite sufficient intake. Considering the similar inhibitory role of Vitamin D analogs (deltanoids) on squamous carcinomas, skin tumors and melanomas, we propose that animal studies and extended vitamin surveillance studies in HSCT patients may unfold a preventive strategy against long-term complications.

Keywords: Bone marrow transplantation, secondary cancer, Vitamin A, e-mail: maltinoz@gmail.com

The Problem of Secondary Cancer after Hematopoetic Stem Cell Transplantation. Extended survivals following hematopoetic stem cell transplantation (HSCT) increased the importance of late complications such as secondary neoplasms. Secondary cancers are cancers arising from clones different and independent from the cells causing the primary disease [1]. Early secondary cancers are generally myelodysplastic syndromes or B-cell lymphomas seen after only a few months to approximately two years after transplantation, whereas late cancers are generally solid cancers which peak years after transplantation, and tend to accumulate 10 to 15 years after HSCT [1–15]. According to the pathological type and the emergence period of the novel malignant clones, secondary neoplasms can be classified as follows [1]: 1- Early post-transplant period B-cell lymphoproliferative syndromes associated with Epstein-Barr viral genome activation and diffused large-cell lymphomas mostly with a donor-cell origin. 2- Early post- transplant period myelodysplastic syndromes and leukemias, which could be classified into neoplasias having donor- or host-origins. 3- Late post-transplant T-cell lymphomas. 4- Late post-transplant Hodgkin and non-Hodgkin lymphomas, 5- Solid tumors, mostly likely to be seen in late post-transplant periods, but may also rarely emerge in earlier stages, especially if the recipient bears an inherent genetic instability (1). General risk factors relevant for all secondary cancers following HSCT are: I- Total body irradiation. II- Genetic Instability Syndromes. III- Acute Graft versus Host-Disease (GvHD) more severe than Grade II, and more importantly, the existence of chronic GvHD. IV- HLA mismatch [1, 2].

Dominance of Ectodermal Malignancies: Abundance of Head and Neck Tumors, Skin Cancers, Melanomas and Brain Tumors among Secondary Solid Tumors following HSCT. Head-neck tumors, skin cancers, melanomas and brain tumors following allogeneic HSCT were frequent. To show this clearly, we found all serial analyses between 1968 and 2006 on secondary solid cancers following HSCT via PubMed. This data is shown in Table 1. The purpose of the table is to show the tendencies of tumors rather than to provide a meta-analysis, since we were not sure whether or not the later reports of the same groups re-included

* Corresponding authors

Table 1. Solid tumor number and distribution

Serial Analysis Reports on Secondary Solid Cancers Following Bone Marrow Transplantation					
Pure Allogeneic	**Head-Neck Cancers**	**Melanomas**	**Skin Tumors**	**Glial Tumors**	**(TP) – TNST**
1- Deeg HJ, 1984 (3)	1	–	–	2	6
2- Socie G, 1991 (12)	4	–	–	–	4
3- Kolb HJ, 1992 (4)	2	5	9	2	33
4- Socie G, 1993 (5)	5	–	–	–	7
5- Pierga JY, 1994 (6)	5	–	–	–	5
6- Lowsky R, 1994 (10)	2	1	2	–	8
7- Deeg HJ, 1996 (13)	11	–	6	–	18
8- Curtis RE, 1997 (14)	33	11	1	11	80
9- Duell T, 1997 (7)	2	–	–	3	8
10- Socie G, 2000 (16)	5	4	–	9	25
11- Favre-S., 2000 (23)	–	–	–	–	5
12- Au WY, 2004 (26)	2	–	–	–	9
13- Hasegawa W, 2005 (27)	5	1	10	–	31
Total Numbers – Ratios	**77 – 32.2%**	**22 – 9.2%**	**28 – 11.7%**	**27 – 11.3%**	**(64.4%) 239**
Allogeneic+Autologous					
1- Withers. RP, 1989 (11)	2	3	1	3	13
2- Bhatia S, 1996 (2)	–	3	3	2	17
3- Kolb HJ, 1999 (15)	7	2	12	3	53
4- Bhatia S, 2001 (22)	6	–	9	1	29
5- Baker KS, 2003 (25)	5	8	19	4	137
6- Shimada K, 2005 (29)	7	–	–	–	19
Total Numbers – Ratios	**27 – 10.1%**	**17 – 6.3%**	**44 – 16.4%**	**13 – 4.9%**	**(37.6%) 268**
Pure Autologous					
1- Fetscher S, 1997 (8)	–	1	–	–	10
2- Oddou S, 1998 (9)	–	–	–	–	5
3- Forrest DL, 2003 (24)	1	–	–	2	16
4- Brown JR, 2005 (30)	**–**	**–**	***39***	***3***	***81***
Total Numbers – Ratios	**1 – 3.2%**	**1 – 3.2%**	**0 – 0%**	**2 – 6.4%**	**(12.8%) 31**

The numbers and sum ratios of particular tumor types and the total number of observed solid tumors were extracted from the serial analyses of secondary cancers found in PUBMED publications between 1968 (the date of the first marrow transplant in Minnesota due to a severe combined immunodeficiency) and September 2006. Given ratios represent the sum ratios of particular tumor types to the **TNST**- **T**otal **N**umber of **S**olid **T**umors in the last column. **TP** indicates the **T**otal **P**ercentage of the ectoderm and neuroectoderm malignancies (the sum of head and neck, brain, skin cancers and melanomas) among the TNST. Serial analyses were included in the table, if they reported the existence of solid tumors among their observed secondary cancers (some only mentioned secondary lymphoproliferative malignancies); and also if there is no clear indication that the discussed cases are exactly the same as in a previous publication of the same study group. However, since large serial analyses on these cases were mostly originated from a few groups around the world, it should be emphasized, that there exist more than one report in the table published by the same groups. Thus, it could not be clearly extracted from their papers, whether or not the given case numbers in their later reports reflect different patients. Moreover, patient age, causes of transplantation and median follow-ups differed among such reports leading to difficulties for finding clear comparisons. Hence, the ratios of the above table will be given to roughly represent the tendencies of the particular cancer types, rather than to establish precise overall estimates for these cancers. Some recent publications, which reported only squamous cancer numbers after HSCT were not included in the table, since their data would not support comparing relative ratios of different cancer types. Among the studies classified as pure allogeneic, there were only a few which also included autologous cases among their follow-ups, but these cases were nearly the same or lesser than 5% of the total patient number. The reason for transplantations were heterogenous (eg. malignancies, aplastic anemia, and a small percentage of metabolic diseases), but to a certain degree similar to ratios found in different publications. However, the report of *Brown (2005)* written in italic in the last line reported autologous transplants purely performed due to non-Hodgkin lymphomas. They also reported that, these cases seem to have a unique pattern of increased secondary malignancies in comparison to other autologous transplants. Therefore, the ratios of autologous transplants were given as ratios of the three previous serial studies with similar heterogeneity of patient profiles.

old HSCT cases. We grouped the case analyses according to HSCT type. Most reports observed almost purely allogeneic cases or autologous transplants that were less than 5% of the whole group. These were grouped as 'Pure Allogeneic' section. A few case analyses examined groups with an equal dispersion of allogeneic and autologous transplants, or they at least contained a significant percentage of autologous cases among the whole group. These are grouped as 'Allogeneic+Autologous' in the table. Lastly, serial case analyses reporting groups with pure autologous transplants were grouped as 'Pure Autologous'. Ectoderm-origined cancers were reaching a very high ratio in the 'Pure Allogeneic' group, while the ratio was much lower among the 'Allogeneic + Autologous' groups, and even lower still among the 'Pure Autologous' transplants. Now, we will discuss the data of these serial analyses in a mostly chronological manner. Reports on secondary tumor following HSCT have indicated oropharyngeal, squamous skin cancers and glial tumors especially in patients receiving cranial radiation [3, 10]. In the IBMTR study 33 solid malignancies occurred among 9732 transplants, in which 9 were skin cancers, 5 were melanomas and 2 were brain/spinal cord tumors (4). In the EBMT-EULEP study, late effects were evaluated in 147 patients surviving 6 years and

in 79 patients surviving more than 10 years [4]. In the first group 4 new solid cancers were seen, in which 2 of them were squamous cancers. In the latter, 7 new solid cancers were seen, in which 4 of them were basal cell, 1 was squamous carcinoma of the skin, and 1 was a parotid gland mucoepidermoid cancer [4]. 7 new solid cancers were found among 748 HSCT patients and 5 of them were head and neck cancers [5]. 5 solid cancers were described among 147 patients receiving allogeneic HSCTs, and 4 of these were epidermoid carcinomas of oral cavity, and 1 was a parotid mucoepidermoid carcinoma [6]. Pure autologous HSCTs exhibited a different pattern of secondary cancer development. 8 new solid tumors in 500 autologous HSCT patients were reported, and each of these 8 tumors had a different histology, including only one melanoma, and no other existence of skin, head and neck, or brain cancers [7]. 5 secondary solid cancers were detected in 171 patients receiving autologous transplants after lymphoma chemotherapy, and again none of these included skin, head and neck, or brain cancers [9]. Allogeneic HSCT patients developed secondary cancers, which tended to group together in certain histological types rather than having a wide dispersion of different histologies. 8 secondary solid cancers were found among 798 marrow transplant patients of which, 2 of them were larynx and mouth carcinomas and 3 were brain tumors [8]. 7 new solid cancer cases were encountered among 557 allogeneic HSCTs. 3 of them were squamous carcinomas (tongue, oral cavity, and skin), 1 was a malignant melanoma, and 1 non- invasive basal cell carcinoma [10]. 35 secondary solid tumors were detected from 2145 HSCT patients, and these malignancies arose with a latency period ranging between 2.5 months to 14 years (median 4.6 years) [11]. In this report, squamous head and neck carcinomas, basal-cell skin carcinomas, melanomas, glial tumors and hepatomas were indicated in a respective order. Cause of secondary cancers by radiation was underlined; and azathiopurine treatment and chronic GvHD emerged as major risk factors [12, 13]. In a 28 years-prospective analysis, 80 secondary tumors were reported from 19220 HSCT patients. This study revealed an increased total risk of solid tumors by 2.8 fold in comparison to a normal population. Specific risk increases for buccal cavity, soft tissue, neural, thyroid tumors and melanomas occured by 11.1, 8, 7.6, 6.6, and 5-fold, respectively [14]. Radiation levels higher than 10 Gy in a single dose or 13 Gy in fractionation caused these tumors 3- to 4-fold more [14].

Since secondary solid tumors are the same type in pediatric group patients receiving single radiation due to non-HSCT reasons, radiation was indicated to be the sole cause for an increased risk of sarcomas, gliomas, thyroid, and salivary gland carcinomas. Atomic bomb survivors developed salivary gland cancers of all mucoepidermoid type as did radiation-receiving HSCT patients [18, 19, 20, 21]. The risk of secondary malignancies occurring in comparison to an aged- matched healthy population increased by 5 fold in 1036 allogeneic HSCT patients investigated (15). 53 cancers were seen, in which skin (14), oral cavity (7), uterus (5), thyroid (5), breast (5), and glial-tumors (3) were dominating (15). Oral cavity, thyroid and esophagus tumor incidences were found 10-fold more often than in comparison to an age-matched healthy population. Chronic GvHD was indicated to cause cancer by inducing repeated cycles of tissue degeneration and regenerating cell proliferations [15]. An analysis of 3182 patients which underwent allogeneic HSCT due to leukemia before the age of 17 revealed 20 post-transplant lymphoid diseases and 25 solid tumors [16]. Among 24 solid tumors, 14 were brain and thyroid cancers, of which 9 of these had received cranial radiation [16]. Tongue, salivary gland, thyroid cancers, melanoma, glioma, and soft tissue-sarcomas were found to increase 2765, 519, 126, 65, and 46-times, respectively [16]. In the combined NIH/IBMTR and FHCRC analysis, a total of 28884 allogeneic HSCT cases were investigated, which revealed increased risks of salivary gland, oral cavity, brain and skin tumors by 14.2, 11.6, 6, and 4.2-fold, respectively [1]. Purely hematologic cancers caused 2129 HSCT's to be investigated, and a 17.4-times increased risk of oral cavity cancers were found [22]. Among 3372 HSCT cases, in which 1193 underwent autologous transplants, 147 malignancies were identified in 137 patients [25]. 19 skin cancers including 8 squamous-type tumors, 8 melanomas, 5 oral cavity cancers (3 mucoepidermoid, 2 squamous) and 4 central nervous system tumors were found. It is revealed via standardized incidence ratios that the risks of melanoma, brain and oral cavity tumors were specifically elevated [25]. 615 allogeneic HSCTs were examined in Hong Kong and 9 solid cancers were detected, in which only 2 were head and neck cancers [26]. Here, it should be emphasized that the race and population-specific vulnerabilities to certain cancers also determine the risk of secondary cancers, since the remaining 7 solid tumors in this study were liver cancers in Hepatitis-C carrying patients, gastric and esophageal cancers and bronchogenic adenocarcinomas in female nonsmokers. These reflect common cancers among the Chinese population [26]. In 557 patients with allogeneic HSCTs 27 solid tumors were found, in which 10 were skin cancers, 7 oral squamous cell cancers, and 1 melanoma. A multivariate analysis defined that the age of the patient at transplantation was a significant predictor of solid cancers [27]. It is shown that the strongest risk factor of squamous cancers is chronic GvHD, particulary with the use of azathioprine [28]. Secondary cancers were analyzed among 1451 HSCTs and found 19 secondary solid cancers, of which 7 of them were buccal cancers and 3 squamous esophageal cancers [29]. 605 cases of autologous HSCTs were investigated and 81 solid tumors were detected, of which, 39 were skin cancers, 26 basal cell carcinomas and 13 squamous cell carcinomas [30]. For all these solid tumors post-HSCT, the exact molecular physio-pathology is unclear, yet it is shown that squamous cell carcinomas lack Herpes Virus-8, EBV, and papilloma genomes, which are their usual risk factors [1]. The only available data revealed the presence of p53 accumulations in post- HSCT solid tumors (p53 gene mutations increase the half-life of the p53 protein, and thereby its immuno- histochemical expression density) [1]. Here, it should be emphasized that p53 mutations are also hallmarks of the 'iatrogenic cancers', indicating tumors due to chemo-radiotherapy exposure in non-HSCT patients [17].

Vitamin A and Retinoids as Differentiation Factors for the Ectodermal Layer and for the Tumors. It is indicated that retinoids (Vitamin A derivatives) exert therapeutic effects on (neuro)ectodermal and epithelial malignancies as an extension of their ability to induce differentiation in the ectoderm [31]. Many of the abnormalities in organ formation that result from the exogenous addition of Vitamin A derivatives during embryogenesis are related to the retinoid ability to change the expression of homeobox genes in the mammalian embryo [32]. The embryonic differentiation role of Vitamin A derivatives may extend from branchial arch morphogenesis [33] to anteroposterior axis specification [34, 35] in vertebrates. Retinoic acid receptors (RAR) and retinoic X receptors (RXR) are critical for the skin. In epidermis, RXRα and RARγ isoforms are highly expressed. In normal skin, RXRα is localized in the epidermis, sebaceous glands and hair follicles, while RARβ is detectable in melanocytes and in stratum granulosum [36]. Treatment of early melanocyte precursors with Vitamin A induce their differentiation to stage III/IV melanosomes with an increase of their apoptotic vulnerability [37]. The exposure of human melanoma cells to retinoic acid causes a decrease in the rate of cell proliferation with an increase in melanogenesis [38].

Proposing a Sustained Deficiency of the Differentiation-Inducing Liposoluble Vitamins as Etiological Factor Behind Secondary Solid Tumors after HSCT.

1 – A big proportion of the post-HSCT secondary solid tumors (head and neck tumors, squamous and basal skin cancers, melanomas and brain tumors) are malignancies derived from the ectoderm, as shown above. These are the cancers, where chemoprevention with Vitamin A is most highly indicated [31–38].

2 – Studies conducted at early intervals proved retinol-depletion in correlation with the GvHD-associated mucositis [39]. 68% of the studied 82 patients had plasma retinol concentrations ≤ 1.05 μM/L at least once during the peritransplant period, and 31% had at least one plasma concentration below the World Health Organization (WHO) definition of retinol deficiency (≤ 0.7 μM/L) [39]. 28% of the patients with hyporetinolemia developed Herpes Zoster (HZ) infections, whereas only 16% without hyporetinolemia developed them [39]. The authors have underlined that even if these observations may have occured due to acute phase reaction- associated changes, retinol replacement is significantly beneficial in conditions with acute phase reaction-associated transient hyporetinolemia. They mentioned that in patients with the measles, the plasma Vitamin A concentrations fall below the WHO criteria in 70% of the patients, even in US children with extremely low rates of underlying malnutrition. Administration of a single dose of Vitamin A is associated with normalization of serum concentrations, rapid recovery of diarrhea and pneumonia, and a lower mortality rate [39].

3 – With the increasing severity of GvHD, serum post-HSCT vitamin D concentrations decrease; and this has been linked with reduced intestinal absorption of liposoluble vitamins [40]. Long term monitoring of Vitamin D up to 75 months after HSCT due to osteopenic complications, showed this event to be constant [41, 42].

4 – There are overlapping pathways of Vitamin D and A intestinal absorption [43, 44]. Loss of the intestinal barrier function directly causes a permanent Vitamin A deficiency [45]. Serum Vitamin A concentrations depend on how well intestinal mucosa is functioning, such that a Vitamin A absorption test is used as a more sensitive method rather than a d-xylose absorption to monitor jejunal injury [46]. Gastro- intestinal tract injury by radiation in cervix cancer patients is measurable with the same test [47]. Diarrhea and malnutrition are synergistic, bidirectional, and compound a vicious cycle, in which, a small intestinal injury as a consequence of diarrhea, causes malnutrition, which in turn exacerbates the diarrhea [45]. The Vitamin A status is compromised in children who have a decreased villous surface area [45], and thyphlitis is severe diarrhea due to intestinal GvHD.

5 – We do not have concrete data on long term serum retinol concentrations after the HSCTs. Nonetheless, we have strong clinical indications of a sustained Vitamin A deficiency in these patients due to reports on:

I – Dry eye syndrome II – Corneal perforations. III – Occurence of rare skin diseases, which are treatable with retinoids and/or related to a Vitamin A deficiency. I- The dry eye syndrome (keratoconjunctivitis sicca) was seen in 82% of patients with chronic GvHD after allogeneic transplants, and in 33% of patients after autologous HSCT [48]. This eye disorder is more often caused by a squamous metaplasia of the ocular surface, rather than being related to an immune infiltration [49]. It is succesfully being treated with retinoic acid in chronic GvHD-suffering HSCT-survivors [50].

II – Cornea perforation is an event associated with a Vitamin A deficiency. This condition is rarely seen today, especially rare in more developed countries. In 2004, corneal perforation cases from Germany were reported and lowered Vitamin A serum concentrations were documented. Besides the cases of alcoholic cirrhosis and related hyporetinolemia, 1 was a chronic GvHD-ileitis following HSCT [54]. In 2005 and 2006, three more such cases were reported from Japan all associated with chronic GvHD after HSCT [51, 52, 53]. These cases further support the hypothesis of a clinical hyporetinolemia in a post-HSCT period.

III – Hyperkeratotic skin disorders with rare clinical presentations are reported following HSCT. These have either a direct ethiologic relation or could be treated with retinoids. Such a case of nipple ceratinization following HSCT is reported, which responsed to isotretinoin [55]. Porokeratosis of Mibelli is another rare skin disorder reported following marrow transplantation [56, 57] and also treatable with retinoids [58, 59]. Linear lichenoid eruptions following marrow transplantation [60] is treatable with Vitamin A [61]. Acquired ichtyosis cases following marrow transplantation [62, 63] and their direct temporal associations with hyporetinolemia attacks in cancer patients [64] are other similar examples. Lastly, akantosis nigricans is also a disorder observable in association with hyporetinolemia after marrow transplantation [65,

67, 68], which is treatable with synthetic retinoids [66] and Vitamin A [67].

Here, it is proper to mention the relationship of the differentiation agent retinoic acid and retinoids related to Vitamin A (retinol). Retinoic acid is formed via intracellular oxidation of diet-derived retinol and is recognized as a principal retinoid in nearly all of the non-visual functions of Vitamin A. The term retinoid is comprised of retinol and a large number of synthetic analogs with structural and/or functional relationships to retinol [76–79]. All organs examined were able to oxidize retinol, beta-carotene, or retinaldehyde to retinoic acid.

Oxidizing activity has been reported in both tissue cytosols and membrane fractions [77]. The function of Vitamin A is inseparable from its metabolism because the biogeneration of retinoic acid in the embryo is the first developmental step in the initiation of retinoic acid-regulated signaling pathways [79]. All of the physiologically important enzyme systems that regulate Vitamin A metabolism have been demonstrated in embryos [79]. Dietary Vitamin A, the essential precursor of tissue retinol is metabolized by sequential oxidations into two classes of retinoids: 11-cis retinoids, which function specifically for vision. Acidic retinoids (all-trans-retinoic acid and 9-cis-retinoic acid) regulate many processes via nuclear receptors, RARs and RXRs [76]. Retinoic acid supplied in a retinol-free diet has been shown to support all of the biological activities of Vitamin A except for some in male reproduction [78]. Recent studies showed a direct correlation between circulating concentrations of retinol, retinyl palmitate (a main depot of Vitamin A esterified in the liver) and retinoic acid in lung cancer patients [80]. Circulating endogenous retinoic acid concentrations among participants enrolled in a randomized placebo-controlled clinical trial of retinyl palmitate, are found to significantly increase following Vitamin A palmitate treatments [81]. Consumption of animal liver during pregnancy raised teratogenecity concerns, since the esterified Vitamin A elevates serum concentrations of 13-cis retinoic acids [82]. Thus, retinoic acid and retinoids in the above examples would not be illegitimate clues for our hypothesis.

6 – Inflammatory pathways directly reduce serum retinol, despite sufficient intake by blocking liver RBP (retinol binding protein) synthesis [83]; RBP behaves like an acute phase reactant, yet an ongoing lowering of RBP-retinol complex due to inflammation may limit the retinol availability to tissue [84].

7 – Peroxidative reactions caused by the HSCT conditioning induce direct exhaustion of anti-oxidants. This is especially true for the retinol precursor beta-carotene [85, 86]. In 20 patients, weekly measurements for a 6 week period after transplantation revealed highly increased TBARS (lipid peroxidation parameter) in inverse correlation with erythrocyte glutathione peroxidase levels. This was proposed by researchers as proof of a higher antioxidant requirement [87]. It was underlined that the antioxidants decrease intensely following radiolysis of cell water with γ-radiation and following robust membrane peroxidations induced with chemotherapy, especially with cyclophosphamide [87]. A more recent study has also proven the failure of parenteral nutrition to improve the antioxidant status with the consumption of antioxidants after HSCT [88]. Massive infusion of polyunsaturated fatty acids (about 26 g linoleic acid/day) in parenteral nutritions to HSCT patients may worsen the condition by rendering patients more susceptible to lipid peroxidation (85). For instance, 0.6 mg of Vitamin E is required per gram of linoleic acid consumed in normal conditions, and this exceeds the supplemented 9 mg/day of Vitamin E in the parenteral solutions [85]. During reconstitution and activation of peripheric granulocytes, oxidant stress may further increase, as well as antioxidant requirement.

8 – The GvHD-treatment drug cyclosporine decreases liver Vitamin A stores in Vitamin A-sufficient experimental animals [89].

9 – Parallel to animal studies [95], there is clinical evidence to show lowered plasma retinol for melanoma and squamous carcinoma in non-HSCT patients [90–94]. Similar relevance is present to show low plasma vitamin D concentrations in melanoma [96]. Deltanoids exert efficacy of skin cancer prevention [97] and act inhibitory on squamous head and neck tumors [98]. Retinoids and deltanoids synergize to suppress parathormon-related protein expression in oral cancer cells [99] involved in tumor growth.

10 – There are strong molecular cooperations between retinoid and deltanoid signalling at the level of receptor induction [100] such as, a direct interaction between nuclear signalling via VDR-RAR heterodimers [101]; and by a convergence of their signalling via overlapping nuclear receptor DNA binding [102].

11 – As will be discussed in detail later, Vitamin A prevents secondary- and radiation carcinogenesis [104–107] and Vitamin A and D synergize tumor differentiation via RAR and RXR signalling pathways [108]. 12- It was underlined several times before, that chronic GvHD is major risk factor for secondary cancers. Here, it is proper to mention that both retinoids and deltanoids alleviate GvHD in experimental animals [70, 71, 73] as well as in human patients [72, 74, 75]. Moreover, Vitamin D receptor polymorphism is a significant determinant of GvHD-severity [69].

Clinical Evidence of Lowered Plasma Vitamin A in Squamous Carcinomas and Melanomas. In 1980, a large prospective study indicated the Vitamin A in cancer prevention. This study stored serum samples from about 16000 men. Retinol concentrations of stored samples from 86 men who developed cancer were later measured, and compared with 172 controls who did not develop cancer [90]. Low retinol concentrations were associated with an increased risk of cancer, regardless of age and smoking habits [90]. The association was greatest for men who developed lung cancer (mean retinol concentration 5.6×10^{-4} g/l compared with 6.9×10^{-4} g/l for the controls, $p < 0.005$). The risk of cancer at any site for men with retinol concentrations in the lowest quintile was 2.2 times greater than the risk for men with concentrations in the highest quintile [90]. This association of lowered Vitamin A concentrations with a greater cancer risk also accounts for squamous cancers of the head and neck region. Significantly

reduced plasma concentrations of retinol and retinol-binding protein were found in 53 patients with head-neck squamous cell tumors of various size and metastases, than in tumor-free individuals and patients with laryngeal premalignant lesions [91]. Concentrations in tumor patients remained low after tumor resection and postradiation. Thus, the reduced plasma retinol concentrations were considered to be a supporting factor in tumor development [91]. Serum retinol concentrations of 19 patients with T1/T2 tumors of the larynx were compared with those of non- malignant smoking and non-malignant, non-smoking controls, matched for age, sex and weight. The cancer group had a significantly lower concentration of serum retinol than either control group. The unlikelyness was suggested that lower serum retinol concentrations may have occured due to tumor consumption of Vitamin A or smoking [92]. Relationships of Vitamin A serum concentrations in patients with head and neck cancer with and without second primary tumors were also studied, and statistically lowered concentrations were found in patients with secondary tumors than in the group with a single head and neck cancer [93]. Low plasma retinol concentrations accompanying cancer is also relevant for melanoma: Serum retinol and retinol binding proteins were measured in 22 cutaneous melanoma patients at diagnosis, and in 17 patients with 1 or more basal cell carcinomas of the skin recently removed. The indices measured were found to distinguish melanoma patients from non-melanoma patients with high accuracy [94], which is concordant with experimental animal evidence that high doses of retinol suppress melanoma growth [95].

Rationale of Vitamin A Prevention Against Secondary Radiation-Carcinogenesis. In the MD Anderson Cancer Center, 103 patients were prospectively studied, who were disease-free after primary treatment for squamous-cell cancers of the larynx, pharynx, or oral cavity [103]. After completion of treatment, patients were randomly assigned to receive either isotretinoin (13-cis-retinoic acid, 50 to 100 mg/m2 of body-surface area per day) or a placebo to be taken daily for 12 months. After a median follow-up of 32 months, only 2 patients (4%) in the isotretinoin group had second primary tumors, compared with 12 (24%) in the placebo arm ($P = 0.005$) [103]. Multiple second primary tumors occurred in 4 patients in the placebo arm; and of the 14 secondary cancers, 13 (93%) occurred in the head and neck, esophagus, or lung [103]. Cancer prevention with the use of Vitamin A may also specifically target radiation induced carcinogenesis. Vitamin A analogs are powerful preventive agents against radiation induced transformation in Hamster embryo cells [104, 105], which is supported by rat studies showing Vitamin A prevention against radiation induced soft-tissue and bone sarcomas [106]. An experimental breast carcinogenesis model was based on the production of free radicals in human breast epithelial cells induced by high linear energy transfer (LET)-radiation in the presence of 17β-estradiol [107]. In this model, 0.1% retinol significantly decreased H_2O_2 production in all breast cell lines following radiation exposure [107]. Retinol also significantly decreased invasive capabilities of oxidant-exposed cells across matrigel coated invasion chambers. It also reduced PCNA, Fra-1 and mutant p53 expression levels [107]. This makes sense, when remembering that p53-positivity constitutes a hallmark of HSCT cancers.

Summary and Suggestions for Further Studies. A prospective monitoring of HSCT patients may unveil an association between liposoluble vitamin deficiency and secondary solid tumors. The ratio of transthyretin to retinol binding protein [83, 84] at the time of tumor detection will give healthy clues about prolonged retinol status independent of inflammation. Diseaseas such as Wernicke encephalopathy has been described in HSCT patients at long term [109]; but this has been limited to the prolonged parenteral nutrition-associated carbohydrate load and the associated exhaustion of thiamin levels. Water-soluble vitamin deficiencies generally have more acute clinical manifestations, and none of them would constitute a well-matched differentiation pattern on solid tumors associated with HSCT. Therefore, focusing on Vitamin A and D serum concentrations would not be an illogical approach to illuminate micronutrient deficiencies behind the deadly complications of HSCT.

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