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From food to clinical medicine — nutraceuticals as clinical therapeutics for hematological malignancies

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Nutraceuticals are food-derived bioactive compounds with anti-cancer treatment potential. From a vitamin A metabolite (all-*trans*-retinoic acid) for acute promyelocytic leukemia (APML) to an edible mushroom extract (maitake) in Phase 2 clinical trial for myelodysplastic syndromes (MDS), nutraceuticals are found at all stages of clinical development for treatment of various hematological malignancies. Here, we report the advances in nutraceutical discovery and therapeutic relevance for these diseases.

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Introduction

Hematological malignancies are broadly classified by the World Health Organization under groups that include myeloid and lymphoid neoplasms [1]. The majority (60–80%) of patients suffering from these malignancies consume some form of an over-the-counter dietary supplement [2,3]. There is limited clinical evidence supporting the benefits of self-medicating with nutraceuticals; however there is a large body of ongoing research attempting to define the clinical validity of these compounds. Nutraceuticals are the physiologically active components in food, which are formulated to reach concentrations that are unattainable by consuming the conventional food product [4]. They are a subset of natural health products and differ from food because they are not used as a source of energy.

Nutraceuticals, a term coined in the 1980s, represent a large portion of the health care market due to their perceived safety and therapeutic reach [5]. Garlic, for example, has long been used for its medicinal properties in addition to flavoring food. Garlic has been shown to lower blood pressure, enhance the immune system and induce apoptosis of lymphocytic leukemia cells in culture [6,7]. The bioactive component of garlic is allicin, however, it is not clinically marketed for any therapeutic intervention. This is the case with many nutraceuticals, as many do not proceed past rigorous pre-clinical evaluation and even fewer pass clinical trial stages.

Mutation events, which are distinct between tumor types, are largely responsible for cancer cell development [8,9]. Several reports have suggested dietary choices (e.g. red meat and fiber intake) can prevent cancer development; however, the focus of this review is not on cancer prevention but on nutraceuticals as therapeutics. Table 1 summarizes nutraceuticals that have undergone clinical evaluation for their potential anti-cancer treatment benefit. However, of the estimated 25 000 different types of nutraceuticals [10], relatively few have been tested clinically and even fewer have survived the very high attrition rates of clinical trial.

Nutraceuticals and leukemia

Leukemia is a cancer of the blood resulting from abnormal hematopoiesis (Figure 1). Under normal circumstances, a hematopoietic stem cell differentiates into a myeloid or lymphoid progenitor cell which will then terminally differentiate giving rise to mature blood cells. In leukemia, myeloid or lymphoid progenitor differentiation is blocked leading to the accumulation of immature, non-functioning myeloid or lymphoid cells (i.e. blasts) [11]. Acute leukemia occurs when there is a rapid accumulation of these blasts, which occurs in bone marrow but eventually spills over into the blood system, whereas chronic leukemia involves partially differentiated cells that do not function as well as normal cells.

Myeloid leukemia

Myeloid cell leukemia (acute myeloid — AML; or chronic myeloid — CML) results from a block in differentiation of cells from the myeloid lineage. As such, patients with AML and CML present with reduced numbers of granulocytes, erythrocytes, megakaryocytes, and/or monocytes/macrophages, which are all examples of terminally differentiated myeloid cells (Figure 1) [12,13].

A review on hematological malignancies and nutraceuticals would be incomplete without discussing the pioneering work on the use of all-*trans*-retinoic acid (ATRA) for the treatment of acute promyelocytic leukemia (APML),

Table 1

List of ongoing and completed clinical trials for nutraceuticals in various cancers. Criteria included: study completion date after 2012.

Cancers	Nutraceutical	Phase	Trial identifier	Aims
Leukemia				
APL	ATRA + ATO	3[a]	NCT00482833	Treatment of APL without chemotherapy
CMML	Dandelion root extract	1	OCT1226, DRE	Determine recommended dose of oral DRE
CLL	Polyphenon E	2[a]	NCT00262743	Reduced lymphocyte counts in CLL patients without imparting toxicity
	Curcumin + cholecalciferol	2	NCT02100423	Determine the response rate and tolerability in untreated stage 0-II CLL patients
MGUS	Green tea extract	2	NCT00942422	Determine efficacy of defined green tea catechins extract in treating MGUS patients
MDS	Maitake	2[a]	NCT01099917	Stimulates granulopoiesis by increasing G-CSF levels and restoring functional neutrophil counts
Colorectal	Pomegranate extract	1/2	NCT01916239	Evaluate the disposition of pomegranate phenolics and urolithins in tumoral vs. normal colon tissues
	Curcumin	1	NCT01859858	Determine benefit of co-administering with irinotecan vs. metastatic colorectal cancer
		1[a]	NCT01333917	Curcumin C3 tablet monotherapy
Prostate	Acai juice product	2	NCT01521949	Use of low risk natural antioxidant product to determine changes in PSA baseline
Liver	PHY906	1	NCT01666756	Determine doses for Chinese herbal formulation (PHY906) combined with sorafenib tosylate
	Resveratrol	1/2	NCT02261844	Determine if resveratrol improves metabolic profile of liver cells
Endocrine	Resveratrol	–	NCT01476592	Determine the effects of resveratrol's on Notch-1
Pancreatic	Curcumin	2	NCT00094445	Assess curcumin's efficacy vs. pancreatic tumors
	Vitamin C	2	NCT01555489	Evaluate the tumor response of high dose ascorbic acid treatment in combination with chemotherapy
Breast	Curcumin	2	NCT01740323	Determine NF-kB levels post curcumin intervention
	American ginseng root	2	NCT00631852	Observe changes in breast cancer tumor biomarkers vs. surrounding normal breast tissue
Other	Grape seed extract	1	NCT01820299	To identify phytochemicals that can reduce systemic inflammation

[a] Completed clinical trial.

a subset of AML. ATRA, or tretinoin, is the key active metabolite of vitamin A branded under the name 'Vesanoid' [14]. In the early 1980s, micromolar amounts of ATRA was shown to induce APML cell differentiation *in vitro* [15] and in 1987, ATRA was used successfully to induce complete remission in APML patients [14]. Since these seminal findings, ATRA has remained the main therapy for APML and 5-year survival rates have improved to over 90% since the adoption of ATRA therapy [13,16•].

A recent Phase 3 clinical trial (NCT00482833) of APML and arsenic trioxide (ATO) without traditional chemotherapy was conducted. Chemotherapy can cause many side effects, which limits dosing and restricts treatment options. The standard regimen for APML was to give ATRA (to promote differentiation) in addition to the chemotherapeutics daunorubicin or idarubicin with or without cytarabine [16•]. This Phase 3 study showed that ATRA + ATO without chemotherapy was more effective in causing complete remission than the traditional regimen [17••]. This provides a better treatment option for patients who are ineligible for treatment due to the associated dose-limiting toxicities of the conventional chemotherapeutics. The National Comprehensive Cancer Network now recommends that initial induction therapy for low-risk or intermediate-risk APML patients primarily be only ATRA + ATO [16•]. ATRA is an incredible success story and a prime example of the potential clinical utility of nutraceuticals.

Multiple case studies have reported AML patients achieving remission and sustaining low myeloblast counts by drinking dandelion root tea (DRT). These patients did not respond well to the standard chemotherapy regimen and self-medicated with DRT after news of its unusual efficacy (C. Hamm *et al.*, abstract 122:5216, ASH Annual Meeting Abstracts, December 2013). Since discovering this unique correlation in 2009, pre-clinical testing has shown dandelion root extract (DRE) induces caspase-8 mediated extrinsic apoptosis in human CML and melanoma cell lines [18••,19]. These results have led to the