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Patient's Health: The Number One Priority in the Treatment of Cancer

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Most people think of cancer as a disease that does not follow an innate pattern of cell growth. With cancer, cells do not die after growing old or being damaged and the body creates new ones that are not needed. These cells that are formed without intent, in due time, become what one refers to as a tumor, which essentially is a clutter of tissue - it is these tumors that we think of that can be cancerous tumors that are known as malignant, meaning the tumors can metastasize to other areas of the body.

This paper will focus on leukemia, a cancer that does not form a solid tumor. Rather, leukemia is a cancer of the body's red blood cells by an increase in a person's white blood cells (leukocytes), cells that help fight infection.

One might be baffled by the very intricate, logical, pattern of this disease. Wouldn't the human body want more white blood cells to fight an infection? When a person has the flu, the body automatically produces, in a very controlled manner, a production of white blood cells to fight the infection. However, with leukemia, the switch made in our DNA triggers a change in the way our bone marrow produces white blood cells, red blood cells, and platelets. The bone marrow reads this switch and produces an uncontrolled pattern of white blood cells that are not able to work normally.

Acute leukemia progresses rapidly due to the shortage of healthy blood cells available to carry out innate processes (e.g. infection fighting processes), while chronic leukemia progresses slower because the body has the ability to carry out some innate processes since it has some cells that are able to do their job accordingly.

ALL and Doxorubicin

Acute Lymphoblastic Leukemia (ALL) is an acute form of leukemia that produces immature lymphocytes and progresses rapidly if not treated accordingly and in a timely fashion. It is the most common type of cancer found in children below the age of 18. According to The National Cancer Institute, symptoms include but are not limited to: fever, easy bruising or bleeding, bone or joint pain, painless lumps (located in the neck, underarm, and stomach), groin pain, fullness below the ribs, fatigue, looking pale, and loss of appetite.

One of the most common forms of childhood ALL treatment is doxorubicin - classified as an "anthracycline antibiotic," an anti-cancer drug that changes DNA (Cancer Treatment Centers of America 2018). Research has shown that doxorubicin therapy causes cardiotoxicity in children with ALL years after their treatment (Lipshultz et. al, 2005). Reported cardiotoxicity from doxorubicin-therapy include: left-ventricular (LV) abnormalities,[1] dilated cardiomyopathy and inadequate LV hypertrophy[2](Lipshultz, et. al, 2005). Symptoms discussed

1 Left-ventricular abnormalities refer to defects of the left ventricle found in the heart

2 Enlargement and thickening of the left ventricle

previously are indicators of cardiotoxicity, irreversible damage to the heart, and the progressiveness of this complication can lead to the need for invasive treatments.

When I understood the scheme of the treatment, I wondered why the treatment is being offered to treat ALL since it causes such irreversible effects. Some of this persistent treatment may come to light if I illustrate in more depth, through a hypothetical situation of a patient with childhood ALL.

Take a hypothetical patient, Jane Doe, a 4-year-old diagnosed with ALL whose assigned medical personnel and parents mutually decided that aggressive doxorubicin therapy would be the most effective course of treatment. Jane Doe has a 90% chance of going into remission (Inaba, Greaves, & Mullighan, 2013). After weeks of treatment that included doxorubicin therapy, Jane indeed goes into remission. Ten years later, now 14, Jane is considered cured from ALL.

Four years later, from her last visit with her oncologist, Jane Doe, now 18 years old, presents in her primary care physicians office for a routine checkup. Jane expresses unusual symptoms like chest pain and shortness of breath when doing strenuous work. Concerned, the physician orders a blood test, specifically focusing on Jane's brain natriuretic peptide (BNP), high levels of which indicate

possible heart complications that could be confirmed with an EKG (Hirata et. al, 2001). The physician indeed orders an EKG to confirm Jane's diagnosis. Jane has higher than normal levels (>400 pg/mL) and her EKG confirms LV failure. Skeptical as to why an 18-year-old girl who was just about to enter adulthood had LV failure, the physician consults her health history. Her health history was clear from pre-existing heart conditions but confirmed that her LV failure was likely caused by the doxorubicin therapy she was treated with for her diagnosis of ALL at the age of four.

Jane Doe's treatment highlights the importance of the persistent treatment that urges the immediacy of finding ways to improve treatments for childhood ALL. I am aware that cancer treatments are evolving and though, in trials of research, it is unrealistic to discuss a "complication-free" treatment in this paper. Rather, I propose treatments that prioritize a patient's health during and thereafter treatment; such treatments ensure that Jane and children like her are protected of their innate rights to create a life for themselves.

Combination Therapy: Dexrazoxane and Doxorubicin

Dexrazoxane is a cardioprotective drug that is more commonly used in women with breast cancer as to similarly, with the treatment for ALL with doxorubicin, reduce the likelihood of cardiotoxicity (Swain et. al, 1997). The

same approach can be directed towards children like Jane, with ALL. Dr. Steven Lipshultz, a pediatric oncologist at the Wayne State University School of Medicine, and his team conducted a multi-drug therapy trial which consisted of dexrazoxane and doxorubicin, in which they evaluated levels of serum cardiac troponin T (cTnT), a cardiac biomarker (Lipshultz, et. al, 2006). cTnT detects myocardial damage and would allow the team to identify onset cardiotoxicity in pediatric patients. 76 out of 101 patients who were administered doxorubicin alone tested for high levels of cTnT and 85 out of 105 patients who were administered dexrazoxane thereafter their dose of doxorubicin found to have lower levels of cTnT.

Effectiveness of combination therapy is evident in this medical trial, but supplemental research must be conducted on this topic to examine a wide-range of plausible complications and consider the developing stages of children at the time of their diagnosis. Cardiotoxicity symptoms, as mentioned earlier, are not evident years after treatment, but implementing a treatment that concurrently evaluates the patient's cardiac biomarkers while undergoing combination therapy can serve as a pre-indicator for cardiotoxicity and allow medical professionals to assess the patient's care during and after treatment.

Tracking Cardiotoxicity with the Use of Other Cardiac Biomarkers

A biomarker is a measurable molecule inside the human body that can indicate normal or abnormal processes occurring in the body. Cardiac biomarkers like N-terminal pro-brain natriuretic peptide (NT-proBNP), is a substance released when the heart is stretched and can act as an indicator for heart failure, making it a pivotal cardiac biomarker to track as high levels indicate myocardial failure (Fallah-Rad et. al, 2011). Another cardiac biomarker pivotal for the detection of cardiotoxicity is cTnT, as mentioned earlier. Chronic inflammation is important in heart disease and tracking high-sensitivity C-reactive protein (hsCRP), because it can provide detailed results of an inflammatory response from the body, linking it to possible cardiotoxicity in the patient. CRP is synthesized in the liver as a response to cytokines, important proteins in cell signaling, released by damaged tissue. Logically, any indication of high levels of these biomarkers indicate myocardial injury and lower levels of these cardiac biomarkers indicate no evident forms of myocardial injury.

If the best course of treatment for the patient is doxorubicin, tracking cardiac biomarkers prior to and after treatment will allow for early detection of cardiotoxicity, as mentioned earlier. Lipshultz and his team conducted another clinical trial (Lipshultz, et. al, 2012), in which they used an identical methodology as the clinical trial that consisted of dexrazoxane and doxorubicin. This nearly

identical clinical trial continued with their multi-drug approach but focused on individual cardiac biomarker levels (NT-proBNP, cTnT, and hsCRP), mentioned above, for the recognition of onset cardiotoxicity in high risk ALL patients.

The team randomly analyzed 75 (doxorubicin alone) and 81 (doxorubicin-dexrazoxane) patients with high risk ALL. The team found lower levels of NT-proBNP (48% in the doxorubicin group and 20% in the doxorubicin-dexrazoxane group) after treatment with doxorubicin and dexrazoxane, and no differing numbers for hsCRP and higher levels of cTnT (12% in the doxorubicin group and 13% in the doxorubicin-dexrazoxane group) had high levels prior to and after treatment. The team concluded that NT-proBNP and cTnT can act as pivotal indicators of onset cardiotoxicity if closely tracked during doxorubicin therapy.

Asparaginase and Multiple-Drug Therapy

Defining the stage of ALL of the patient is important as to individualize an effective treatment for the patient based on certain risk factors at the time of the diagnosis.

Dr. Luis Clavell, a pediatric hematologist-oncologist, and colleagues (Clavell et. al, 2010), administered a course of treatment for patients based on risk factors that consisted of four systemic drugs:

> Patients at high risk (62 percent of the total) had one or more of the following risk factors: age below two or above nine years, a white-cell count of 20,000 per cubic millimeter or more, the presence of T-cell immunologic markers, radiologic evidence of a mediastinal mass, and involvement of the central nervous system. Patients in both standard-risk and high-risk groups were treated for two years, receiving intensive remission-induction therapy, central nervous systems prophylaxis, weekly administration of high-dose asparaginase, and multiple-drug continuation therapy (which in the high-risk group included doxorubicin and a larger dose of prednisone).

What sets aside this particular clinical trial from the others discussed in this paper is that the team rendered an approach that consisted of a 20-week period of high dose asparaginase therapy for both standard and high-risk patients. Asparaginase is an anti-cancer drug that is a bacterial-derived enzyme and is most commonly used for the treatment of ALL (Pieters et. al, 2011):

> The anti-leukemic effect of asparaginase is due to the fact that lymphoblastic leukemia cells are unable to synthesize adequate amounts of L-asparagine (Asn) and, therefore, depend on extracellular sources (Eagler, Ahuja, & Matloub, 2016).

Cells need to grow and divide, the antileukemic effects of asparaginase are at work when leukemic cells are unable to depend on asparaginase to grow and therefore turn to other sources to help them replicate. The results of the clinical trial highlight the importance of the drug in regard to treating childhood ALL.

Of the 110 standard-risk group in the Clavell study, 109 had a complete remission and of the 179 children under the high-risk category, 169 entered complete remission. All deaths from toxicity were due to infectious organisms like hypersensitivity to both *E. coli* and *Erwinia carotovora* and pancreatitis.

An important finding from this paper was that none of the patients had clinical evidence of congestive heart failure. The treatment implemented by Clavell and his team on childhood ALL can act as an alternate treatment for ALL, although other side effects were noted in his clinical trial. Implementing this form of treatment into the prognosis of a patient can reduce the likelihood of cardiotoxicity after a patient's treatment.

Similarities and Differences in the Above Clinical Trials

The distinguished clinical trials are similar in that they epitomize the idea of advocating for the patient's health during and after treatment: treating childhood ALL while improving the treatment of doxorubicin or proposing a new treatment that reduces the likelihood of cardiotoxicity in patients as to improve the prognosis of the patient. Lipshultz targets two pivotal cardiac biomarkers

that will help health professionals identify onset cardiotoxicity - NT-proBNP and cTnT and proposes combination therapy. While the study conducted by Clavell (Clavell et. al, 2010), treats childhood ALL using, pivotal to this paper, a 20-week high-dose asparaginase period that poses no congestive heart failure after treatment. These treatments described in this paper treat ALL while concurrently managing cardiotoxicity, a critical finding from this paper.

Continuation of Holistic Approaches in Cancer Research

An important question that I hope this paper brings about for discussion is what kinds of treatment options should medical professionals and those closely working with cancer research, focus on?

The question of whether doxorubicin treatment is able to carry out its antileukemic functions is not something of importance at this stage in childhood ALL research, as the statistics have reached a final conclusion - children who are diagnosed with ALL and treated with doxorubicin are reaching remission. But the treatment for cancer does not and should not end once a patient with cancer reaches remission, rather it extends even to their well-being years after treatment.

Minimal longitudinal research, that is 7-8 years after cancer treatment, that I am aware of, has been done on cancer patients that are undergoing chemotherapy with the use of doxorubicin or other drugs with similar side effects

have been conducted.

It is why I press onto those who closely work with cancer research to look beyond the said definition of cancer that has been universally known to this day (found on page 1), and focus their attention on searching for a treatment that not only works in attacking cancer cells, but one that, if and only if, the said correct means are provided - that is, the stage of cancer, current health of the patient, available treatments at the time of diagnosis are all permissible to the setting in which the patient might find themselves, protect a patient's health during and after the said treatment.

This definition then is what potential cancer treatments offered to patients battling with and not limited to childhood ALL, with side effects like cardiotoxicity, make promising as they do more than attain remission, like in the studies discussed above.

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