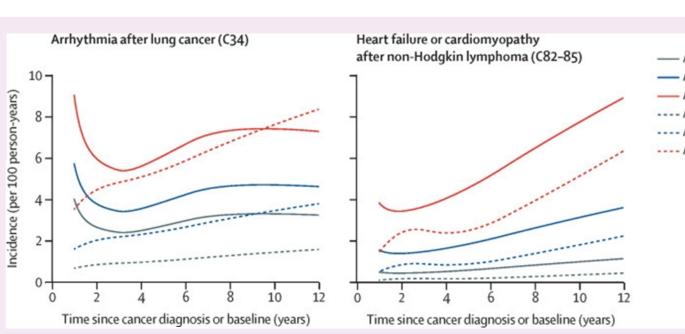
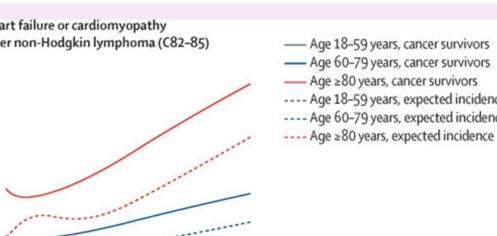
# Cardiotoxicity of Cancer Treatments

Microencapsulated Liposomal Doxorubicin with Erythropoietin

### Evidence of the problem

Cancer treatments come with a whole host of side effects that no one would ever want to experience, from fatigue to hair loss to recurrent infections and more, but the effect on the heart is often overlooked. Over one in ten cancer patients do not die from the cancer itself but from associated heart and blood vessel problems instead and, for some cancers, like breast, prostate and thyroid cancer around half will die from cardiovascular diseases (CVDs). Among the 3,234,000 cancer patients diagnosed between 1973 and 2012 in the USA, 11% died from CVDs, and 76% of these deaths were due to heart disease. Doctors also believe that between 5-15% of cancer patients will develop heart failure after they survive cancer (not accounting for those who develop other heart-conditions such as high blood pressure or atrial fibrillation). The National Institute of Cancer states that, for cancer patients, 'the risk of having [a heart attack or stroke] was more than twice that seen in people without cancer' - this shows how alarming a problem this is. Surprisingly, unless the cancer is of the heart itself, it is actually the treatment of the cancer that is causing these high levels of CVDs.



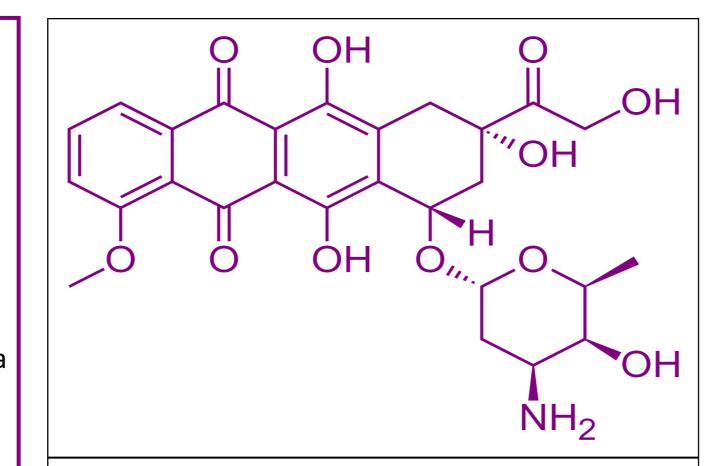


The graphs show that the incidence of arrhythmias after lung cancer and the incidence of heart failure or cardiomyopathy after lymphoma (both of which are treated with doxorubicin) are over twice as high in the first year of diagnosis compared to what is expected of the general population. The incidence of both heart conditions in cancer patients (compared to noncancer patients) is higher post-diagnosis for all ages, with the only exception being arrhythmias in patients aged 80 and over. However, the chance of this age group developing arrhythmias is still higher than the general population for up to 9 years since their diagnosis, after which it falls to below the expected trajectory. The graph supports the conclusion that there is a strong correlation between cancer and cardiotoxicity, both in the short term and the long term.

### The Cancer Treatment: Doxorubicin

Doxorubicin is one of the most effective cancer treatments to date against a substantial number of cancers, including certain types of breast, lung, stomach, ovarian and bladder cancers, as well as Hodgkin's lymphoma, non-Hodgkin's lymphoma, certain types of leukaemia and more. It is an anthracycline drug, which means it is extracted from the Streptomyces species, and is used among other chemicals during chemotherapy. It works by slowing or stopping the growth of cancer cells by blocking an enzyme called topoisomerase II, which is required by cancer cells to grow and divide. It can be taken in two main ways:

- L. Straight into the bloodstream commonly through a long plastic tube (central line) that goes into a large vein in the chest but can also be through a shorter, thinner tube (a cannula) that goes into a vein in the arm
- . Into the bladder used to treat cancer of the bladder lining and the drug is directly given to the bladder



Doxorubicin molecule

## The two main pathways of doxorubicin: cancer cells cardiomyocytes cell death cell death cardiotoxicity regression treatment

### <u>Issues with Doxorubicin Treatment: Cardiotoxicity and Anaemia</u>

Doxorubicin has been in use since 1974, due to its high efficacy. However, what is often overlooked is that it is one of the most cardiotoxic anthracyclines (with an irreversible effect) in chemotherapy. It is believed to lead to loss of heart muscle cells (cardiomyocytes) through two distinct cell death pathways: apoptosis (death of cells in a normal/controlled way) and necrosis (death of cells due to disease, injury or lack of blood). Its cardiotoxicity can be clearly recognised due to the fact that the drug causes a significant drop in the red blood cell count in the bone marrow. As well as this, the cardiomyocyte injury or death can leads to left ventricular dysfunction and even heart failure in around 5% of high-risk patients.

Anaemia: a disorder characterised by a lower-than-normal red blood cell count and insufficient haemoglobin levels. It affects approximately 25% of the population or 1.6 billion people worldwide. The number of visits to emergency departments with anaemia as the primary diagnosis are 890,000.

Left Ventricular Dysfunction: occurs when the left ventricle is either defective or damaged, so it becomes too stiff to properly relax during diastole so cannot be filled again to a normal end-diastolic volume. Over time, the heart muscles become thicker and weaker and the walls stretch in order to accommodate more blood. Generally, 50% of patients with left ventricular dysfunction do not go on to live beyond 5 years after being diagnosed. Unfortunately, there is no current cure for severe LV dysfunction, which is a life-threatening problem since in many cases it leads to heart failure.

Regular lab tests are needed before and during treatment with doxorubicin, in order to monitor heart function and check the red blood cell counts - this is essentially a precaution taken so that treatment can be stopped in patients whom are showing signs of heart-damage; however, a more worthwhile solution would be to prevent cardiotoxicity before the treatment begins. Therefore, for our project, we are going to take an approach to prevent/treat both anaemia and left-ventricular dysfunction (two large side-effects on the heart due to treatment by doxorubicin) from occurring in the first place, by targeting its major cause.

### Our Approach - researching how we could combat the problem:

After we identified our problem (cardiotoxicity of cancer treatments with doxorubicin), and two of the main ways in which the drug damages the heart and blood (anaemia and left-ventricular dysfunction), we began to do research into ideas for how we could prevent or treat these specific side-effects.

### Preventing Left-Ventricular Dysfunction:

The damage doxorubicin causes to the heart itself is a result of the drug physically entering the heart and damaging the muscles. Therefore, in order to protect the heart, we researched ways in which the drug could be prevented from entering the heart.

1. Researchers have identified an experiment drug, called BAI1, that could help protect the heart fron doxorubicin-induced damage. The drug has thus far been tested in mice - the results showed that th BAI1 successfully managed to prevent heart damage, whilst not interfering with doxorubicin's ability to kill cancer calls (reported in *Nature Cancer on March 2*). It works by binding to a protein called BAX, which is the protein required for the death of heart cells in mice treated with doxorubicin. When it is activated by doxorubicin, BAX initiates both apoptosis and necrosis (both of which cause the heart cells to die). However, the research showed that BAI1 blocks both.

2. Another way in which the drug could be prevented from reaching the heart would be through the use of <u>liposome</u> which is a fatty covering that can be used to coat the drug. This makes it much larger and so it cannot accumulate in organs like the heart. In 2015, groups of trials of 2889 breast-cancer patients found that using liposomal doxorubicin (compared to the regular drug) caused a significant reduction in the risk of cardiotoxicity, as well as an improvement in the overall response rate.

### Preventing/Treating Anaemia:

The anaemia caused by doxorubicin is another large problem, with the moderate form affecting over 59% of patients. Since the drug must be inserted into the blood in order to be effective, it would be difficult to prevent the problem and so we looked into ways to

1. Erythropoietin (EPO) is a glycoprotein hormone that is naturally produced by the kidney cells. Its function is to stimulate red blood cell production, specifically in the bone marrow. On top of this, it also acts on the red blood cells themselves to protect them from being destroyed. Though it is usually produced by the body naturally in response to low-oxygen levels, the hormone (or an erythropoiesis-stimulating agent) can also be taken orally or as an injection. This would help stimulate the production of red blood cells, hence helping to

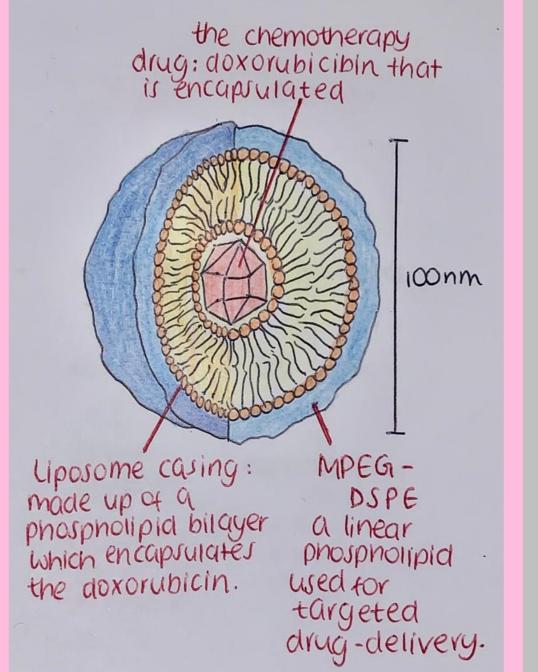
2. Another way to help increase the red blood cell count would be through the use of a **blood transfusion**. This is generally a very safe procedure and it involves having blood given to you through an IV line in one of the blood vessels. Getting a correct match can often be quite difficult, especially if the patient has a rare blood type. There are also complications regarding allergic reactions, fevers and more.

# Our Final Solution:

Liposomal Doxorubicin - to prevent LVD by ensuring the blood does not reach the heart

We decided to use liposome as opposed to the BAI1 drug in order to prevent lef ventricular dysfunction, mainly due to the fact that using the BAI1 drug would result in a much more expensive overall treatment, despite the liposome having been proven to be just as effective in reducing cardiotoxicity. Moreover, the study we looked at regarding liposomal doxorubicin showed that the adapted treatmen even made the cancer treatment more effective as its additional outer coating results in the drug remaining in the bloodstream for much longer.

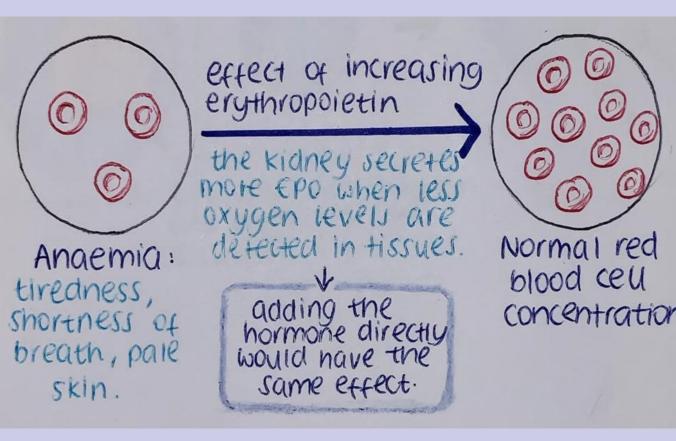
Due to the liposomal doxorubicin's larger size, it cannot accumulate as much in organs with a tight endothelium, such as the heart Since the drug cannot reach the coronary arteries in the heart, cardiovascular function is maintained and the heart is not damaged while the tumour itself is still being targeted It is a red liquid that is taken every 1-4 weeks. Moreover, as mentioned before, it can be taken into the bloodstream (via a cannula or a central line) or into the bladder However, we have decided to narrow our solution down so that it can only be administered through the blood as this allows for the treatment of a wider range of



### Microencapsulated liposomal doxorubicin and erythropoietin

### 2. Treating Anaemia - erythropoietin (EPO)

In order to tackle the reduction in the red blood cell count, we have decided to use EPO as opposed to blood transfusions. This is due to the fact that cancer patients, especially those experiencing some of the side effects of their different treatments, are often in a very vulnerable stage, and having blood transfusions has



multitude of possible side-effects (headaches, dizziness, fevers) as well as complications with rejections/matching. On the other hand, if the correct levels of EPO are administered, there are no negative side-effects, preventing the patient from feeling worse than they already do.

By giving more of this glycoprotein hormone to the body, the lack of red blood cells will be made up since the protein will stimulate red blood cell production as well as protect them against being destroyed. For chemotherapy-induced anaemia, the average dose of erythropoietin is 40,000 units weekly, sold commercially as Eprex, made of epoetin alfa which is a human erythropoietin produced in cell culture using recombinant DNA technology. Eprex comes in solutions of 4000 IU/ml (international units per millilitre) so 10ml of this solution would be required per week. Alternatively, the concentration of the solution could be increased so that a smaller volume of the solution is required to deliver the same number of units of erythropoietin.

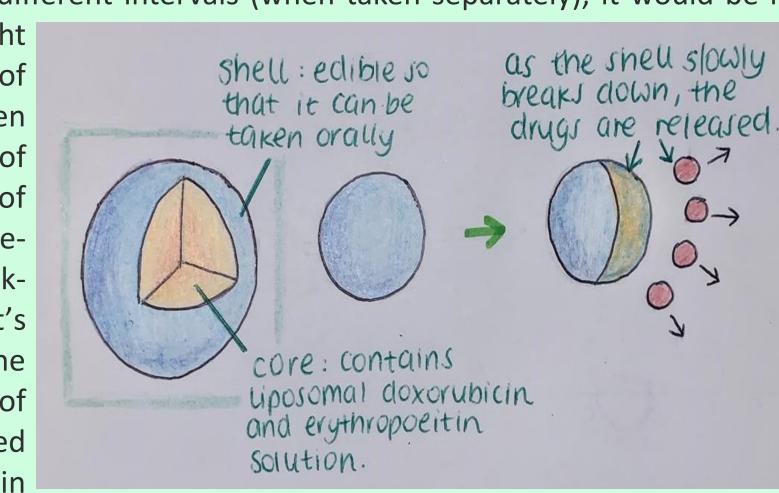
### 3. Microencapsulation:

Microencapsulation is a technique in which tiny particles or droplets are coated to give small capsules, resulting in them being released in a controlled way over a long period of time. The materials inside the capsules are known as the core (in our case, this would be the liquid liposomal doxorubicin and the protein solution of erythropoietin) while the outside coating is known as the wall or shell. This division ensures the core material is protected from the environment outside the wall and the chemicals can be released slowly by diffusion through the wall.

Clinically useful, injectable, sustained-release protein formulations can be achieved by using a nonaqueous, cryogenic (using very low temperatures) atomisation process involving the formation of protein microspheres, made of a biodegradable polymer, that releases the protein slowly. However, a solid form of the erythropoietin would not diffuse across the biopolymer wall as effectively - therefore, liquid solutions would be more effective. The erythropoietin solution and liquid liposomal doxorubicin can be injected into a biopolymer which slowly breaks down, enabling a long-term sustained-release system for drug delivery. Edible biopolymers, like a thin edible foil used for packaging products can be used as the biopolymer so that the medication can be sold as oral tablets (see oral tablet vs injection).

By using microencapsulation we can ensure that the correct dosage of both the drug and the hormone are administered in a safe manner. Since they are often taken at different intervals (when taken separately), it would be im-

portant to adjust the dosage or intake so that the right amount is taken each week. Therefore, the dosage of erythropoietin can be adjusted according to how often the patient takes their chemotherapy drug. The rate of release of the drugs would depend on the thickness of the biopolymer and so lab tests measuring the rate of release over time must be carried out to allocate a thickness that ensures the concentration inside the patient's body is neither too high nor too low. Increasing both the thickness of the biopolymer and the concentration of erythropoietin would mean the growth factor is released at the same rate for a longer period of time, resulting in less frequent administration of medication for the patient.



### Our Clinical Trials

### The Phases

The first tests that will be carried out regarding out product would be to decide It is crucial to have a control group in our on the dosage, based on how slowly the drug is released from its trial. They will be given a placebo, while the microencapsulation—following this, dosage will be tested again during the other group in the clinical trial will be given clinical trials.

Initially, we will begin with testing the microencapsulated drug using in-vitro (in a against the placebo's. We will carry out test tube or cell culture) and in-vivo experiments (in an animal), to test for double blind trial to eliminate bias, and all toxicity and efficacy. Following this, we will move on to clinical trials, using cancer participants will be selected randomly, using patients to find out more about potential side effects on humans, and comparing a randomised participant selection the liposomal doxorubicin with normal doxorubicin. We will also look at the patient's red blood cell count, to analyse the effect of erythropoietin on reducing anaemia. We will also need to test that the effectiveness of the cancer treatment is not reduced. As we progress through the different phases of the trials, we will we represent all data in a fair and unbiased gradually increase the number of patients involved.

### <u>Participants</u>

From the bar chart pictured aside, it is evident that lung cancer treatments have a severe effect on the heart. causing fatal heart disease in less than a year. Therefore, we will begin trials with lung cancer patients, to maximise the efficacy of our treatment. As well as this, testicular cancer has a high mortality rate from heart disease post-diagnosis, so it would be beneficial to include patients with testicular cancer in our trials, to accurately reflect the demographic we wish to utilise the drug in. Furthermore, we would need to ensure we have a range of age groups and sexes t reduce bias in our results.

Pros

Functionality: Since the drug cannot reach the coronary arteries in

still targeted, making the drug more suitable for patients.

reduces these symptoms.

remain in the bloodstream for longer).

the heart, cardiovascular function is maintained while the tumour is

Reduction in side effects: With normal doxorubicin, due to a drop in

red blood cells, this can cause symptoms such as fatigue, weakness,

breathlessness, and pale or yellowish skin. Due to the microencapsus

lation of erythropoietin, this increases the red blood cell count and

Response rate: Early studies show that the patients' response time t

the cancer treatment is faster, accounting for more rapid recovery

time after chemotherapy (because the liposome allows the drug to

**Effective use of resources:** Treating/preventing cardiotoxicity of doxo

rubicin treatments means the regular lab tests that doxorubicin-

taking patients usually undergo (to check for any heart damage)

would no longer be necessary – this saves resources and time

# <1 year</p> 1-5 years 5-10 years 10+ year

Cons

stages of clinical trials, and is therefore not very preva

lent in the medical field. As a result of this, liposoma

doxorubicin would be considerably more expensive

than normal doxorubicin in the short-term, but may

Possibility of allergic reaction: Signs of a reaction can

include shivering, a skin rash, dizziness and swelling of

the face or mouth. However, a reaction can be treate

immediately by medical staff if identified quickly.

Timeframe: Since trials must still be carried out, it car

not be established for certain when the procedure will

be able to be practiced clinically. Therefore, it may tak

some time before this solution can be implemented

This being said, when the procedure does start to be

carried out regularly, it will be very beneficial to the

patients.

save money in the long-term (see affordability).

Cost: liposomal adaptation of drugs is in very early

### Ensuring unbiased results

and liposomal adaptation is a modern and less commonly used technique. However, as manufacturing becomes more widespread on a larger scale, the cost of manufacture would be expected to decrease - this means the procedure will most likely become cheaper in the our microencapsulated drug. In this way, we can compare the drug's effectiveness Although the short-term costs are much greater, in the long term the benefits will undoubtedly outweigh the cost. This will be a result of fewer resources and less time being needed to test for cardiotoxicity throughout treatment. As well as this, fewer patients will suffe from left ventricular dysfunction and doxorubicin-induced anaemia, causing a reduction in treatment costs.

procedure. Having obtained the results, we

must carry out a meta-analysis of all the

data, not excluding any trials and ensuring

The microencapsulated drug would be taken as an oral tablet, as opposed to as an injection It would have to be ensured that the liposome is modified so that it is not broken down by the hydrolytic enzymes in the stomach. However, taking it as a tablet would make it consi erably cheaper.

Affordability of proposed solution

The final predicted costs for our solution would be available later on in the process, due to the on going clinical trials and the fact that liposomal doxorubicin is still in early practice.

On one hand, the liposomal adaptation of doxorubicin is costly, as it is a relatively new drug,

### Ethics of the Process:

Patient care is at the core of everything in the healthcare industry, whether it is regarding patient interaction or treatments such as our idea. Since the proposed solution involves administering a drug to the patient, it would be essential that any participants in trials and any future patients are made aware of how the medicine works and any potential side effects there could be. This would ensure that 'informed consent' is obtained - allowing the patient to make their own decisions would be demonstrating 'autonomy' which is one of the four pillars of medical ethics. As well as this, since our proposed solution's aim is to help cure doxorubicin-induced cardiotoxicity, we are preventing heart failure and thus doing good to the patients - this is in line with another pillar: beneficence. Furthermore, by keeping the patients' health and safety at the centre of our decision-making process, the final solution ensures non-maleficence (it does not do harm to the patient). In order to achieve justice (ensuring fairness of treatment), we will ensure that, by the end of the process, the drug is made available to all hospitals globally in order to treat cancer with minimal cardiotoxicity Following these four pillars will be vital in earning public support and trust.

### Oral Tablet vs Injection:

The two most common ways for medication to be taken would be orally or via ar injection. However, we have decided that using an oral tablet would be more suitable. Firstly, pills have been shown to have a higher compliance rate than injections, so patients are more likely to take the necessary medications orally and improve their quality of life at a faster rate. Moreover, intramuscular injections can cause needle trauma in muscles, and patients would experience pain; therefore, having an oral tablet takes away such discomfort. As mentioned, this would be achieved by making the biopolymer for microencapsulation edible. Once the medication arrives in the stomach it would essentially be 'broken down' before passing through the liver and entering the bloodstream (like any other oral tablet).

### Potential for general availability

Since our solution is essentially a modified version of a commonly used cancer treatment, i would be administered by a cardio-oncologist physician. This way they would be able to measure the effect on the heart, as well as whether the cancer treatment is effective. By the end of the clinical trials, the aim would be for the drug to be given as part of a patient's chemotherapy course. Since it takes the form of an oral tablet, this would be quite easy to implement. Moreover, the drug does not need to be available to the general public as it is still a form of cancer treatment, and so should be given by a healthcare professional - this makes it easier to execute. This being said, ideally, after years of monitoring any long-term side effects, it would be beneficial if the patient could take the drug alone (since it is in tablet form) - this would save them a trip to the hospital every week as well as reducing costs of treatment.

### Degree of Public Acceptance:

Since our proposed solution is an alternative chemotherapy treatment, with increased benefits in cardio-oncology, we believe it will be widely accepted by the general public. It reduces the mortality rate from CVDs, especially from the symptom of heart failure, one of the most common causes of death globally. It should be welcomed by patients as, in the future, it will be easily taken as an easy-to-use oral tablet by the patient at home, improving patient independence and self-management. As far as we are aware (though it must be confirmed through clinical trials), there are no obvious negative implications of our proposed solution, and so it would most likely be accepted by the public - all of this makes us certain that our proposal will be seen as a strong benefit in the medical field.

### Feasibility of the Final Solution

In order to determine whether our proposed solution is truly feasible, we evaluated different aspects of our product, such as public acceptance, cost and general availability. When deciding on different features of our solution, the patients' health and safety was our top priority - this has led to our proposal being extremely safe with no obvious side-effects - it may have some of the same one as regular doxorubicin treatment but the severity and range of symptoms are significantly reduced. Also, by administering the drug as a tablet, we are not only making it a cheaper option for both the healthcare field and the patient, but we are also opening up th possibility of having the medication viable to be taken independently at home. Tablet medication is very commonly used and s having it in this form makes our product even more feasible. In terms of cost, though the short-term manufacturing costs as relatively high (mainly due to the use of the liposome), we believe that our solution has the potential to be batch-produced in th future, which would considerably reduce the cost, making the whole process more economical, and the product more feasible.

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By Lithikga Gobi, Rameen Nauman and Alisha Sri-Ram - The Henrietta Barnett School, Year 12