**Title: Cardio-Oncology A-Z: CAR-T Cell Cardiotoxicity With Dr Daniel Chen**

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**Dr Daniel Chen**

- My name's Dr. Daniel Chen. I'm one of the cardiologists with an expertise in cardio-oncology at the University College of London Hospitals in London, UK.

**What is CAR-T cardiotoxicity?**

So, the most widely described cardiovascular complications, in early paediatric populations receiving CAR-T cell therapy, were initially tachycardia and profound hypertension requiring the use of vasopressors and ICU support. However, hypertension and tachycardia can also be independent features of cardiovascular toxicity, but are also likely to be the hemodynamic consequences of cytokine release syndrome. Since then, we've had a better understanding of what CAR-T cardiotoxicity is, and it's a much broader spectrum of cardiovascular complications that is emerging through retrospective data over the last couple of years. And this can include asymptomatic serum troponin elevations, atrial and ventricular arrhythmias, pericardial disease, congestive cardiac failure with or without associated left ventricular systolic dysfunction, myocardial infarction, and cardiovascular death. Certainly from pharmacovigilance data from the FAERS database in the U.S.A., the most common cardiovascular events or complications noted within the CAR-T therapy space are arrhythmias and heart failure. Fortunately, to date, cardiotoxicity in the context of CAR T-cell therapy seems to be an early phenomenon and a transient phenomenon with good recovery and good longer term prognosis. And certainly, follow-up beyond one year by Cordero and her group in her 86 patient cohort has demonstrated an absence of any cardiovascular complications, suggesting that longer term and late onset cardiovascular complications are infrequent.

**Are there risk factors that predispose patients to this problem?**

 So the retrospective data sets have tried to pick up the groups of patients most at risk of developing cardiovascular complications. And so far, our current understanding is that risk factors for cardiotoxicity include preexisting cardiovascular disease and a high burden of haematological disease. But, cytokine release syndrome or CRS remains the strongest predictor of cardiovascular complications, and this is certainly in keeping with our clinical experience on the ground.

**How common is this issue?**

So cardiovascular complications were first noted in safety data of early pivotal trials and subsequent retrospective data sets have continued to expand on our understanding of cardiotoxicity in the context of CAR-T, but there's no prospective data just yet. The incidence of cardiovascular complications, based on contemporary series, puts this at around 10 to 20% in the adult CAR-T patient cohorts. Pharmacovigilance data from the FAERS registry suggest that cardiovascular complications are the second most common system specific adverse effects, and cardiovascular complication makes up about 1/5 of the reported AEs with a mortality rate of patients who do develop cardiovascular complications around 30%. And, these data sets emphasise the importance of ensuring that we understand the cardiac implications of CAR-T therapy.

**Should be screened before treatment or monitored during or after treatment for this?**

All patients being considered for CAR-T therapy should have a baseline cardiac assessment and that should include reviewing their history for preexisting cardiovascular disease or a high cardiac risk profile, based on accumulation of cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and smoking. It is important to note, particularly as these patients have relapsing and refractory disease and CAR T-cell therapy is a late line treatment, that they will have exposure to other potential cardiotoxic cancer treatments such as anthracyclines, tyrosine kinase inhibitors, immune checkpoint inhibitors or mediastinal radiation, amongst others. And subsequently, the cardiac assessment should also include a baseline ECG, serum cardiac biomarkers which include troponins and an NT-proBNP, and left ventricular assessment with either a transthoracic echo or a cardiac MRI, which can be helpful and have previously been recommended by esmolol patients about to receive a potentially cardiotoxic cancer treatment. Once the CAR T-cells have been infused, we would suggest that daily weights are measured and compared with their baseline weights as a surrogate for fluid accumulation. Regular clinical review to assess for their fluid status. Rechecking biomarkers within the first week to gauge for myocardial injury and the extent of fluid accumulation. And, rechecking the ECG to exclude the presence of arrhythmias. These suggestions are in keeping with the best practise recommendations of the EBMT, JCI and EHA, which my colleagues and I published in last year in 2021.

**How can it best be managed?**

So in the setting of a cardiovascular complication - high grade cytokine release syndrome or other clinical deterioration, we found that aggressive and early CRS treatment with the use of Tocilizumab and/or the use of steroids to be helpful in relation to preventing and minimising cardiac sequelae. Repeat cardiac tests and imaging with the biomarkers are helpful both for diagnostic purposes and to chart recovery. Left ventricular assessment with echocardiography and cardiac MRI are important diagnostic tools. And, early involvement of your local cardio-oncology or cardiac team to provide support is very helpful as well.