小児がんの既往者において遺伝子と薬物用量が心障害と関連している

小児がん既往者における心血管系の問題はある特定の遺伝子および化学療法剤の用量に関連している

Cardiovascular problems in childhood cancer survivors tied to specific gene and chemotherapy drug dose

第46回American Society of Clinical Oncology（ASCO）年次集会で発表されたスタディにおいて、CBR遺伝子の特定の変異を有し低用量のアントラサイクリン系抗癌剤による化学療法を施行された小児がん既往者は、この遺伝子型を有さず低用量化学療法を受けた者に比べ心疾患を発症する確率がはるかに高いことが示された。研究者らは心筋症を発症した小児がん既往者165人（診断時年齢中央値7.5歳）と心疾患を有さない小児がん既往者323人を比較した。その結果、心筋症を有する者のうち高用量のアントラサイクリン（250mg/m^{2}より高用量）で治療された患者においては、薬物が高用量のためにリスクがもとより高く、そのためCBR遺伝子の心疾患に対する影響は少なかった。しかし、心疾患を発症した者のうち低用量（250mg/m^{2}未満）で治療された患者においてはCBR1およびCBR3いずれの亜型も心筋症のリスクを増大させた。CBR1亜型を有する患者は低リスクの亜型を有する患者と比べ心筋症リスクが5.3倍高く、CBR3亜型を有する患者は3.1倍リスクが高かった。これらの結果から、一部の特定の小児がん患者におけるアントラサイクリン関連の毒性を予防するテーラーメイド治療法が導き出される可能性がある。

Full Text

A Children's Oncology Group study has shown that survivors of childhood cancer who carry particular variants of the CBR gene and who received low doses of anthracycline chemotherapy were much more likely to develop heart disease than those without this form of the gene who received low doses.

This finding may guide a more personalized approach to preventing toxicities associated with anthracycline chemotherapy among a specific subset of children with cancer. Prior to treatment, oncologists may be able to screen patients for these specific gene variants, and based on these results, to choose non-cardiotoxic alternatives.

"Although we depend heavily on anthracyclines for treating children with cancer, we are fully aware of their toxic effects to the heart. We also know that some patients -- despite being exposed to higher doses -- don't develop heart problems, while others with little exposure have considerable cardiac damage," said senior author Smita Bhatia, M.D., MPH, professor and chair of the department of population sciences at the City of Hope National Medical Center in Duarte, Calif. "Our results are a good example of how understanding a cancer patient's genetic makeup can help us better tailor individual therapies."

Nearly 80 percent of children treated for cancer survive, but many have health effects from treatment later in life. A major late effect of some chemotherapy drugs, such as commonly used anthracyclines, is cardiomyopathy, where the heart cannot pump efficiently. CBRs, or carbonyl reductases, are enzymes that help metabolize anthracyclines into substances that can damage the heart. Variants in two CBR producing genes, CBR1 and CBR3, are known to affect CBR activity. The researchers examined the potential effects of the CBR1 and CBR3 variants on cardiomyopathy risk.

In this case-control study, Dr. Bhatia and her colleagues compared 165 childhood cancer survivors who developed cardiomyopathy (the largest cohort of documented childhood cancer-related cardiomyopathy) and 323 cancer survivor controls with no heart disease. The participants were diagnosed between 1966 and 2008, with approximately 80 percent treated beginning after 1981. The children's median age at diagnosis was 7.5 years.

The researchers found that among those with cardiomyopathy who had been treated with high doses (greater than 250 mg/m^2) of anthracyclines, the CBR genes had little effect on heart disease risk, since the risk was already high because of the large dose of drug. But among those who developed cardiomyopathy and received low drug doses (less than 250 mg/m^2), both CBR1 and CBR3 variants increased the cardiomyopathy risk. Those carrying the CBR1 variant had a 5.3-fold increased risk for cardiomyopathy compared to those carrying the low-risk variant; those with the CBR3 variant had a 3.1-fold increased risk.

The researchers believe that at the lower doses, anthracycline cardiotoxicity is dependent on CBR gene metabolism, whereas at higher doses, toxicity is likely mediated by other mechanisms driven by high doses of unmetabolized anthracyclines.

This study was presented at ASCO's 46th Annual Meeting in Chicago.

Disclosures: Nothing to disclose.

ASCO2010特集