Clin Pharmacokinet (2015) 54:1091–1093
DOI 10.1007/s40262-015-0300-4

COMMENTARY

How to Improve the Safe and Effective Use of Doxorubicin in Children with Cancer

John N. van den Anker[1,2]

Published online: 28 June 2015

Doxorubicin, one of the anthracyclines, is a chemotherapeutic agent widely used to treat several pediatric cancers such as acute lymphocytic leukemia, acute myeloid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, soft-tissue sarcoma, bone sarcoma, Ewing sarcoma, neuroblastoma, and Wilms tumor. As such, this drug has contributed substantially to the dramatic improvement of the 5-year survival rates for many of these childhood cancers [1].

However, a major potential adverse event of the use of doxorubicin is its cardiotoxicity. More than 50 % of patients will develop asymptomatic cardiac dysfunction, whereas one in six will result in clinical heart failure due to cardiomyopathy [2]. The exact causative mechanism of this devastating adverse event is, despite the fact that doxorubicin has been used for decades in many patients, not fully elucidated. There is more or less consensus about the important role of reactive oxygen species causing cardiac cell damage, progressive myocyte loss that ultimately will result in a decreased cardiac contractility [3].

To date, several clinical risk factors have been linked to the development of doxorubicin-induced cardiotoxicity and these are a higher single as well as total cumulative dose, cardiac irradiation, short infusion time duration, younger age, longer time since the treatment, and female sex [4]. In addition, much more recently, the potentially important role of genetic factors as predictors of doxorubicin-induced cardiotoxicity has been brought to our attention [5]. Multiple genetic variants in several genes associated with this cardiotoxicity have been identified [6]. However, until now, the currently available knowledge about both the clinical as well as the genetic risk factors has never resulted in sufficient discriminatory power to divide patients into groups with a high or low risk of developing cardiotoxicity.

In this issue of the journal, Völler and colleagues have described a population pharmacokinetic model of doxorubicin in children in which they have used a power function to describe the relation between doxorubicin clearance and age [7]. They were able to show, for the first time, that the pharmacokinetics (PK) of doxorubicin in infants and children with cancer are age dependent. Clearly, this finding might eventually assist in designing a more tailored, safe, and effective dosing regimen for the use of doxorubicin in children with cancer.

However, before this demonstrated lower clearance of doxorubicin in infants and children younger than 3 years of age will be able to change the currently used dosing regimens in pediatric patients with cancer, there is an absolute need to not only consider developmental PK but also, and probably more importantly, developmental pharmacodynamics (PD). At first glance, based on the demonstrated lower total body clearance, it seems that we need less doxorubicin in this group of young patients to reach the same amount of doxorubicin exposure as compared with older children and adolescents. However, what do we really know about the dose-concentration-effect relationship in children with cancer between 1 and 18 years of age? In other words, there is an urgent need to better

This commentary refers to the article available at doi:10.1007/s40262-015-0272-4.

✉ John N. van den Anker
jvandena@cnmc.org

[1] Division of Pediatric Clinical Pharmacology, Children's National Health System, 111 Michigan Ave, NW, Washington, DC 20010, USA

[2] Department of Paediatric Pharmacology, University Children's Hospital Basel, Basel, Switzerland

understand the PK/PD relationship of doxorubicin in infants, children, and adolescents before we are able to optimize and tailor the use of doxorubicin in these pediatric patients with cancer.

This is especially important in light of the fact that it has been shown that higher median plasma concentrations of doxorubicin resulted in more pediatric patients with acute myeloid leukemia going into complete remission [8]. This finding indicates that a decreased clearance of doxorubicin, resulting in these higher plasma concentrations, is directly linked to a more effective induction.

As such, we have to be careful not to adjust our dosing regimens purely on the basis of the developmental changes in PK that have been so elegantly shown by Völler and colleagues in this issue of the journal. We need to perform prospective studies to investigate the dose-concentration-effect relationship of doxorubicin in infants and children with a primary focus on both developmental PK as well as developmental PD.

Despite the fact that the etiology of anthracycline-related cardiac damage is not fully understood, the importance of preventing this damage by avoiding overexposure to doxorubicin is of great importance especially in light of the fact that the majority of the treated patients will survive and will live on to develop symptoms and signs of their cardiac damage.

How to find the optimal solution will depend on linking the aforementioned clinical risk factors with genetic predictors of increased or decreased potential toxicity. In their paper, Völler and colleagues also looked at the potential role of several of these genetic predictors and concluded that in their relative small group of patients there was no role for the investigated genetic factors.

They looked at genetic variants in the following genes: NAD(P)H dehydrogenase, quinone 1 (NQ01), NAD(P)H dehydrogenase, quinone 2 (NQ02), ATP-binding cassette sub-family B member 1 (ABCB1), Solute carrier family 22, member 16 (SLC22A16), Carbonyl reductase 1 (CBR1), Carbonyl reductase 3 (CBR3), ATP-binding cassette sub-family C member 1 (ABCC1), Solute carrier family 28, member 3 (SLC28A3), and UDP-glucuronosyltransferase-2B7 (UGT2B7). From their paper it is not clear how many times they have found genetic polymorphisms in these genes, and as such, it is not possible to be certain that the fact that no influence was found of any of these genetic variants on the described population PK model had enough power to detect any impact whatsoever.

In the currently available literature in this important and rapidly emerging area, several candidate genes have been linked with doxorubicin-induced cardiotoxicity such as SLC28A3, ATP-binding cassette (ABC), NADPH, CBR, Sulfotransferase family cytosolic 2B member 1 (SULT2B1), Glutathione S-transferase (GST), UDP-glucuronosyltransferase-1A6 (UGT1A6), and Catalase (CAT). For only a few of these candidate genes (SLC28A3 and UGT1A6), this association has been replicated in independent patient groups [9]. These markers have been shown to improve risk prediction beyond established clinical risk factors [5, 6]. As a consequence, it seems that in the near future a more tailored approach will be possible by linking the impact of growth and development on the one hand with specific genetic markers on the other hand.

Looking back at the paper of Völler and colleagues it has become clear that the authors did an outstanding job in showing for the first time the age dependency of the total body clearance of doxorubicin, indicating that a more personalized approach might be possible and that younger kids probably need less doxorubicin to reach the same exposure. However, there are two major complicating factors, as outlined in this commentary, and these are the impact of developmental PD and the genetic background of the pediatric patients with cancer on finding the safest and most effective treatment regimen. The importance of both developmental PD and genetic variants in relevant genes needs to be prospectively investigated for both the effectiveness and toxicity of the relevant drugs. A very recent paper [10] shows that genetic variations in the ABCB1 gene might increase or decrease the risk of relapse in children with acute lymphoblastic leukemia on the one hand and variable liver toxicity on the other hand, showing the need to investigate drugs used to treat pediatric cancer with teams of clinicians, pharmacists, geneticists, and clinical pharmacologists. Only the use of this team approach will improve the short- and especially the long-term treatment outcomes of children with cancer.

Conflict of interest

The author declares no conflict of interest.

References

1. Ellison LF, De P, Mery LS, Grundy PE. Canadian cancer statistics at a glance: cancer in children. CMAJ. 2009; 180(4):422–4.
2. Van der Pal HJ, van Dalen EC, Hauptmann M, Kok WE, Caron HN, van den Bos C, Oldenburger F, Koning CC, van Leeuwen FE, Kremer LC. Cardiac function in 5-years survivors of childhood cancer: a long-term follow-up study. Arch Intern Med. 2010;170:1247–55.
3. Lipshultz SE, Adams MJ. Cardiotoxicity after childhood cancer: beginning with the end in mind. J Clin Oncol. 2010;28: 1276–81.
4. Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, Guerin S, Pacquement H, Aouba A, Hawkins M, Winter D, Bourhis J, Lefkopoulos D, Diallo I, de Valthaire F. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. J Clin Oncol. 2010;28:1308–15.

5. Visscher H, Ross C, Rassekh S, Barhdadi A, Dube M-P, Al-Saloos H, Sander G, Caron H, van Dalen E, Kremer L, van der Pal H, Brown A, Rogers P, Phillips M, Rieder M, Carleton B, Hayden M. Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. J Clin Oncol. 2011;30:1422–8.
6. Visscher H, Ross C, Rassekh S, Sandor G, Caron H, van Dalen E, Kremer L, van der Pal H, Rogers P, Rieder M, Carleton B, Hayden M. Validation of variants in SLC28A3 and UGT1A6 as genetic markers predictive of anthracycline-induced cardiotoxicity in children. Pediatr Blood Cancer. 2013;60:1375–81.
7. Völler S, Boos J, Krischke M, Würthwein G, Kontny N, Boddy A, Hempel G. Age-dependent pharmacokinetics of doxorubicin in children with cancer. Clin Pharmacokinet. 2015 **(in press)**.
8. Palle J, Frost B-M, Peterson C, Gustafson G, Hellebostad M, Kanerva J, Schmiegelow K, Lonnerholm G. Doxorubicin pharmacokinetics is correlated to the effect of induction therapy in children with acute myeloid leukemia. Anticancer Drugs. 2006;17:385–92.
9. Lee J, Aminkeng F, Bhavsar A, Shaw K, Carleton B, Hayden M, Ross C. The emerging era of pharmacogenomics: current successes, future potential, and challenges. Clin Genet. 2014;86:21–8.
10. Gregers J, Green H, Christensen IJ, Dalhoff K, Schroeder H, Carlsen N, Rosthoej S, Lausen B, Schmiegelow K, Peterson C. Polymorphisms in the *ABCB1* gene and effect on outcome and toxicity in childhood acute lymphoblastic leukemia. Pharmacogenomics J. 2015 **(Epub ahead of print)**.