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The anthracyclines: When good things go bad

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In the era of targeted therapy the anthracyclines, which were discovered almost half-century ago, may appear to be too old to be good. While it is certainly true that the prototypic anthracyclines have been around for many years, there are robust clinical facts to confute that their time is over. These drugs continue to play an undisputed role in the treatment of many forms of cancer, including hematological malignancies and solid tumors. Unfortunately, however, their main side-effect remains: a life-threatening cardiotoxicity which became apparent at the beginning of anthracyclines' clinical use. In addition to this long-standing problem, we are now discovering that new combination therapies often cause a higher than expected incidence of cardiotoxicity, as if the newly designed drugs make the heart more vulnerable to the old one. Altogether, however, an overwhelming amount of clinical evidence suggests that anthracyclines are too good to be old. Yet, they would look much better if they caused less harm to the heart when administered as either single agents or in combination with otherwise promising new drugs.

This special issue of *Cardiovascular Toxicology* introduces a collection of papers based on lectures and discussions at the "International Workshop on Anthracycline Cardiotoxicity: Molecular Mechanisms and Clinical Correlates," held on October 20–21, 2006 in the scenic environment of Villa Olmo (Como, Italy). The meeting was co-sponsored by the Department of Drug Sciences & Center of Excellence on Aging, G. d'Annunzio University School of Medicine, Chieti (Italy) and the Menarini Foundation. We are indebted to their commissionaires for exceptional support both financially and logistically. The Workshop was aimed at bringing clinicians, public health workers, pharmacologists and laboratory scientists together to discuss and challenge their views on the mechanisms and clinical manifestations of anthracycline cardiotoxicity. To our knowledge this was the first meeting of this kind and it was received with great enthusiasm by all participants. The Workshop underlined things we had in common: a belief that antracyclines are here to stay and that one urgently needs to find ways to make them safer. On the other hand, this gathering pointed to significant gaps which exist between different groups of people who have to deal with issues of anthracycline cardiotoxicity. These include oncologists, who use anthracyclines to save their patients' life, versus cardiologists who are trying to help patients to recover from them; clinicians who, by the nature of their work, develop a pragmatic approach to these issues versus basic scientists who can afford a more speculative, long-term attitude toward possible mechanisms. One of the main goals of the Como's meeting was to initiate a dialog between these different groups.

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The Workshop was structured to overview anthracycline cardiotoxicity from its Clinical Aspects to Molecular Mechanisms and finally to Cardioprotection, and so is the order of articles in this special issue. The first article summarizes the current clinical indications of anthracyclines and the benefit/risk ratio of combining them with targeted drugs [1], followed by the review of the pharmacokinetic/pharmacodynamic foundations [2] and the clinical manifestations of cardiotoxicity induced by anthracyclines alone or in combination with taxanes or Trastuzumab [3]. The Clinical Aspects section concludes with an overview of liposomal formulations of the drug [4] and the third generation of anthracyclines that hold the promise of a reduced cardiotoxicity [5].

The second section, Molecular Mechanisms, starts with an overview of the metabolic determinants of anthracycline cardiotoxicity [6], followed by a description of how anthracyclines can target phospholipase A_2 [7] and a brief summary of how iron and oxygen radicals conspire at inducing cardiotoxicity [8]. The following three contributions describe how cardiomyocytes can be protected from [9], or succumb to anthracyclines at mitochondrial [10] and extramitochondrial sites [11]. This section concludes with an overview of the molecular and cellular mechanisms of anthracycline cardiotoxicity, with emphasis on proteins of the cell cytoskeleton and contractile machinery [12].

In the third section and the last section, the aforesaid research themes are recapitulated under the general concept of Cardioprotection. It starts with an in-depth update on implications for long-term monitoring of anthracycline cardiotoxicity [13]. The following contribution illustrates how the individual risk of cardiotoxicity might be identified and quantified on the basis of polymorphisms of genes of oxidative stress and anthracycline transport and metabolism [14]. The experimental models for probing the cardiotoxicity of anthracycline analogs and the safety or toxicity of different treatment schedules are then described [15]. The section continues with an in-depth update on the clinical efficacy and new applications of dexrazoxane, the only iron chelator approved by the FDA for use in anthracycline-treated patients [16], and reports on the development and biochemical mode of action of new iron chelators [17,18]. The section concludes with an overview of the efficacy and advantages of flavonoids in both preclinical and clinical settings [19] and an article about a new class of antioxidants for cardiac protection [20].

The tetracyclic ring of anthracyclines still buries as many biological mysteries as delocalized electrons, so not all the issues raised at the Workshop could be put in a cohesive picture. In fact some controversies became even more controversial, including an open challenge to what was considered to be rather established issues. The latter include oxidative stress as a main culprit of anthracycline cardiotoxicity, the need to establish universal guidelines for the drugs' maximal dose or the mechanism of cardioprotection offered by iron chelators. The articles presented in this Special Issue reproduce the different views and positions of the speakers and discussants as they surfaced at the Meeting; the discrepancies between one article and another are therefore unavoidable. We trust that this will be perceived as a strength, not as a weakness of this collection.

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Figure.
The International Workshop “Anthracycline Cardiotoxicity: Molecular Mechanisms and Clinical Correlates” Como (Italy), October 20–21, 2006, gathered over 100 participants from many European countries, United States, and Canada