Oncology Issues

ISSN: 1046-3356 (Print) 2573-1777 (Online) Journal homepage: https://www.tandfonline.com/loi/uacc20

A Review of ADR-529: A New Cardioprotective Agent

Joyce A. Filppi & Robert E. Enck

To cite this article: Joyce A. Filppi & Robert E. Enck (1990) A Review of ADR-529: A New Cardioprotective Agent, Oncology Issues, 5:4, 16-18, DOI: 10.1080/10463356.1990.11905012

To link to this article: https://doi.org/10.1080/10463356.1990.11905012

SPECIAL REPORT

A REVIEW OF ADR-529: A NEW CARDIOPROTECTIVE AGENT

by Joyce A. Filppi, Ph.D., and Robert E. Enck, M.D.

Joyce A. Filppi, Ph.D., is Director, Project Management, and Robert E. Enck, M.D., is Vice-President, Medical Affairs, Adria Laboratories, Columbus, OH.

The clinical usefulness of doxorubicin is often limited by its capacity to produce a dose-dependent, potentially life-threatening form of congestive cardiomyopathy.[1,2,3] Because of the prominence of doxorubicin in the treatment of a wide range of cancers, a long-term, broad-based approach has been conducted toward the elucidation of the mechanism responsible for the cardiotoxicity and its possible control.

ADR-529 (ICRF-187), a potent intracellular chelating agent, stands alone as the only agent to clearly demonstrate protection of mammalian cardiac tissue from the damaging effects of doxorubicin

Mechanism of Cardiotoxicity

It is postulated that the formation of free oxygen radicals produces damage to cardiac cells by lipid peroxidation. Support of this hypothesis is provided by the observation that ADR-529 can remove iron from the preformed iron-doxorubicin complexes,[4] which are responsible for free radical formation.

Cardioprotective Approach

ADR-529 (ICRF-187), a potent intracellular chelating agent, stands alone as the only agent to clearly demonstrate protection of mammalian cardiac tissue from the damaging effects of doxorubicin. Unlike other proposed cardioprotective agents, such as n-acetylcysteine, DMSO, Vitamin E, coenzyme Q, and carnitine,[5,6,7,8] the protective effect of ADR-529 has been demonstrated in a wide variety of species, including rats, dogs, mice, rabbits, miniature pigs, hamsters, and man.[9,10,11,12,13,14,15] It is postulated that the activity of ADR-529 responsible for this protection resides in the ability of the compound to cause a reduction in the formation of iron-doxorubicin complexes.[16] The reduced formation of iron-doxorubicin complexes, in turn, inhibits the ability of the complexes to generate free radicals and produce cardiac damage. ADR-529 can prevent doxorubicin-induced free radical formation in the perfused rat heart model.[17]

In addition, the diacid diamide hydrolysis product of ADR-529 can block the peroxidation of membrane lipids catalyzed by ferric complexes of doxorubicin.[18] Thus, ADR-529 exerts a protective effect not by scavenging oxygen radicals, but rather, by preventing their formation. The time frame in which ADR-529 is administered relative to doxorubicin is critical to the effectiveness of the compound.

Studies in mice utilizing the Bertazzoli cardiotoxicity model[19] show that *cardioprotective activity is achieved when* ADR-529 is administered by the intravenous route as early as two hours prior to, or as long as one hour after, doxorubicin treatment.[11] The optimal level of protection is conferred when ADR-529 is administered in a time ranging between 30 minutes prior to doxorubicin and up to 15 minutes post administration. Simultaneous dosing of doxorubicin and ADR-529 also provides optimal protection. A similar window of dosing has been reported in studies using dogs as the test species.[20]

In mice, the dose of ADR-529 which confers cardioprotection relative to a fixed dose of doxorubicin extends over a five-fold range. Studies in this species indicate protection is significant at doses ranging from 4 to 20 times the dose of doxorubicin.[11,21] More limited dose range studies in dogs show protection is achieved at ratios of 14:1 and 20:1.[10,20]

The potential of ADR-529 to influence the antitumor activity of doxorubicin has been examined both *in vitro* and *in vivo*. Early studies to evaluate the antitumor potential of ADR-529 alone indicated that the agent is capable of extending the life span of mice implanted with several experimental murine tumors. The optimal effect was achieved only after prolonged exposure or frequent daily dosing.[22,23] ADR-529, combined with doxorubicin *in vitro*, is reported to cause a synergistic decrease in the colony-forming ability and cell proliferation capacity of sarcoma 180 cells.[24] More recent studies conducted *in vivo* fail to support a broad spectrum, synergistic role for ADR-529. However, in no instance is a *diminution of the antitumor activity of doxorubicin* observed.[25]

SPECIAL REPORT

ADR-529 animal pharmacokinetic studies in mice indicate a terminal half-life in plasma of 35 minutes. There is a low volume of distribution, suggesting that the drug is not extensively distributed to tissues. The major route of excretion is renal[26,27]

Clinical Studies

To date, two studies[15,28] have been published evaluating the role of ADR-529 in preventing doxorubicin-induced cardiac damage. Belt[28] studied 12 adult cancer patients without heart disease to determine the efficacy of ADR-529 as a cardioprotective agent. The ADR-529 was given at a dose of 500mg/M² such that 250mg/M² was administered by intravenous push followed by 250mg/M² by infusion for one hour preceding the doxorubicin. Doses of 50mg/M² or 40mg/M² of doxorubicin were used either singly or in combination with cyclophosphamide/fluorouracil, vinblastine, or mitomycin/fluorouracil. Cardiotoxicity was monitored by serial MUGA scans obtained at cumulative doxorubicin doses of 0, 300mg/M², 450mg/M², and then every 100mg/M² or when patients were taken off study.

Belt found no significant differences compared to the baseline in left ventricular ejection fractions for patients receiving ≥300mg/M² and ≥450mg/M² of doxorubicin. There were no cases of clinical congestive heart failure. ADR-529 did not affect the clinical activity of the doxorubicin in a variety of solid tumors, nor did it significantly increase toxicity. Belt concluded that further trials of ADR-529 in preventing doxorubicin cardiotoxicity were warranted.

In 1988, Speyer et al[15] published the results of their study on ADR-529 as a cardioprotector. This randomized trial at New York University Medical Center involved 92 female patients with advanced breast cancer who were treated with fluorouracil, doxorubicin, and cyclophosphamide (FDC) with or without ADR-529. The dose of ADR-529 was 1000mg/M² and represented 20 times the dose of doxorubicin. Thirty minutes before FDC treatment, the ADR-529 was administered intravenously over a period of 15 minutes. The intravenous fluorouracil (500mg/M²), doxorubicin (50mg/M²) and cyclophosphamide (500mg/M²) regimen was repeated every 21 days. Cardiac function was evaluated in all patients by MUGA scans and, in some cases, by endomyocardial biopsy.

Overall, the authors concluded that ADR-529 offered significant protection against cardiac toxicity caused by doxorubicin

The two groups of patients, that is, those who received FDC with or without ADR-529, were comparable in regard to prior adjuvant chemotherapy, cardiac risk factors, age, and performance status. Patients were taken off study either when cardiac toxicity developed or when disease progression occurred.

Overall, the authors concluded that ADR-529 offered significant protection against cardiac toxicity caused by doxorubicin. Clinical congestive heart failure occurred in 11 of the patients in the FDC arm who were taken off study, compared to only 2 of the patients in the ADR-529 arm. Furthermore, the mean decrease in the left ventricular ejection fraction showed a significant decrease with increasing doses of doxorubicin in the unprotected arm. The endomyocardial biopsy scores in those patients who were not randomized to ADR-529 were significantly worse than those patients who did receive ADR-529 protection. Antitumor activity of FDC was unaffected by ADR-529. The only toxicity appeared to be a slightly greater myelosuppression in the ADR-529 treated group.

In the unprotected arm, no patient received more than 700mg/M² of doxorubicin. By comparison, more than 700mg/M² were administered to 14 of 47 patients in the ADR-529 arm. In fact, two patients in the ADR-529 group were treated with 800 to 1000mg/M² of doxorubicin without meeting the criteria for cardiac toxicity. Combining the three parameters for cardiotoxicity, 38 percent of the patients in the FDC arm went off study due to cardiac toxicity compared to only 11 percent of the patients in the ADR-529 arm. In addition, 60 percent of the patients in the protected arm were taken off the

Hsiao's Relative Values Published

Managing Reimbursement in the 90s: The Original Physician's Reference to a Resource-Based Relative Value Scale, by Dr. William C. Hsiao and his associates at the Harvard School of Public Health, is now available from SysteMetrics/McGraw-Hill. The publication is being offered on an annual subscription basis to accommodate planned updates of the values as they become available.

The publication also provides an overview and discussions of the legislation that established a resource-based relative value scale of payment for physicians; a list of geographic modifiers; a guide for estimating the annual impact on fees during the five-year, phase-in period; and worksheets to estimate reimbursement levels using the new relative value scales.

The publication is available for an annual subscription price of $149. Orders may be placed by calling 800/544-8168. For more information regarding this and other relative value products sold by McGraw-Hill, contact Marjorie Wolper at 800/544-8168.

study because of progressive disease, whereas only 26 percent of the patients in the unprotected arm discontinued the study because of disease progression. Thus, the majority of patients in the FDC arm went off study because of cardiotoxicity.

Conclusions

ADR-529 represents a significant advance in the area of chemotherapy toxicity modifiers. Hopefully, in the future, there will be additional modifiers available that allow oncologists to treat their patients with optimal drug doses. Such modifiers offer patients a better opportunity for cure or, at least, enhanced palliation without burdensome side effects. ■

The endomyocardial biopsy scores in those patients who were not randomized to ADR-529 were significantly worse than those patients who did receive ADR-529 protection

References

1. Carter, S.K., "Adriamycin-A Review." *J. Natl. Cancer Inst.* 55:1265-1274, 1975.
2. Lenaz, L., Page, J. "Cardiotoxicity of Adriamycin and Related Anthracyclines." *Cancer Treat. Rev.* 3:111-120, 1976.
3. Von Hoff, D.D., Layard, M., Basa, P., *et. al.* "Risk Factors for Doxorubicin-Induced Congestive Heart Failure." *Ann. Intern. Med.* 91:710-717, 1979.
4. Hasinoff, B.B. "The Interaction of the Cardioprotective Agent ICRF-187 ((+)-1, 2bis(3,5-dioxopiperazinyl-1-yl)propane); Its Hydrolysis Product (ICRF-198); and Other Chelating Agents With the Fe(III) and CU(II) Complexes of Adriamycin." Agents and Actions. 26(3/4):380-385, 1989.
5. Herman, E.H., Ferrans, V.J., Myers, C.E., Van Fleet, J.F. "Comparison of the Effectiveness of (+)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane (ICRF-187) and N-acetylcysteine in Preventing Chronic Doxorubicin Cardiotoxicity in Beagles." *Cancer* Res. 45(1):276-281, 1985.
6. Saltiel, E., McGuire, W. "Doxorubicin (Adriamycin) Cardiomyopathy." *Western J. Med.* 139(3):332-341, 1983.
7. Legha, S.S., Wang, Y-M, Mackay, B., Ewer, M., Hortobagyi, G.N., Benjamin, R.S., Ali, M.K. "Clinical and Pharmacologic Investigation of the Effects of *a*-tocopherol on Adriamycin Cardiotoxicity." *Ann. NY Acad. Sci.* 393:411-418, 1982.
8. Paterna, S., Furitano, G., Scaffidi, L., et. al. "Effects of L-carnitine on Adriamycin-Induced Cardiomyopathy in Rabbits." *Int. J. Tissue React.* 6:91-95, 1984.
9. Herman, E.H., El-Hage, A., Ferrans, V.J. "Protective Effect of ICRF-187 on Doxorubicin-Induced Cardiac and Renal Toxicity in Spontaneously Hypertensive (SHR) and Normotensive (WKY) Rats." *Toxicol. Appl. Pharmacol.* 92(1):42-53, 1988.
10. Herman, E.H., Ferrans, V.J., Young, R.S.K., Hamlin, R.L. "Effect of Pretreatment With ICRF-187 on the Total Cumulative Dose of Doxorubicin Tolerated by Beagle Dogs." *Cancer Res.* 48(23):6918-69925, 1988.
11. Filppi, J., Imondi, A.R., Wolgemuth, R.L. "Characterization of the Cardioprotective Effect of (S) (+)-4,4'-propylene-2,6-piperazinedione (ICRF-187) on Anthracycline Cardiotoxicity." In Hacker, M., Lazo, J.S., and Tritton, T.R. (eds): *Organ Directed Toxicities of Anticancer Drugs.* Boston: Martinus Nijhoff Publishing, p. 225, 1987.
12. Herman, E.H., Ferrans, V.J. "Pretreatment With ICRF-187 Provides Long-Lasting Protection Against Chronic Daunorubicin Cardiotoxicity in Rabbits." *Cancer* Chemother. Pharmacol. 16(2):102-106, 1986.
13. Herman, E.H., Ferrans, V.J. "Influence of Vitamin E and ICRF-187 on Chronic Doxorubicin Cardiotoxicity in Miniature Swine." *Lab. Invest.* 49(1):69-77, 1983.
14. Herman, E.H., Ardalan, B., Bier, C., Waravdekar, V. "Reduction of Daunorubicin Lethality and Myocardial Cellular Alterations by Pretreatment with ICRF-187 in Syrian Golden Hamsters." *Cancer Treat. Rep.* 63(1)89-92, 1979.
15. Speyer, J.L., Green, M.D., Kramer, E., et. al. "Protective Effect of the Bispiperazinedione ICRF-187 Against Doxorubicin-Induced Cardiac Toxicity in Women With Advanced Breast Cancer." *N. Engl. J. Med.* 319:745-752, 1988.
16. Myers, C.E. "Role of Iron in Anthracycline Action." In Hacker, M.P., Lazo, J.S., Tritton, T.R. (eds): *Organ Directed Toxicities of Anticancer Drugs.* Boston: Martinus Nijhoff Publishers, p. 17-30, 1987.
17. Rajagopalan, S., Politi, P.M., Sinha, B.K., Myers, C.E. "Adriamycin-Induced Free Radical Formation in the Perfused Rat Heart; Implications for Cardiotoxicity." Cancer Res. 48(17):4766-4769, 1988.
18. Gianni, L., Vigano, L., Lanzi, C., Niggeler, M., Malatesta, V. "Role of Daunosamine and Hydroxyacetyl Side Chain in Reaction With Iron and Lipid Peroxidation by Anthracyclines." *J. Natl. Cancer Inst.* 80:1104-1111, 1988.
19. Bertazzoli, C., Bellini, O., Magrini, U., Tosama, M.G. "Quantitative Experimental Evaluation of Adriamycin Cardiotoxicity in the Mouse." *Cancer Treat. Rep.* 63(11/12):1877-1883, 1979.
20. Herman, E.H., Ferrans, V.J. "ICRF-187 Exerts Cardioprotection When Administered Simultaneously With, Or Two Hours After, Doxorubicin in Beagle Dogs." *Proc. Am. Assoc. Cancer Res.* 31:442, 1990.
21. Verhoef, V., Bell, V., Colborn, D., Filppi, J. "Protective Effect of ADR-529 (ICRF-187) on the Development of Delayed Doxorubicin Cardiotoxicity in the Mouse." *Proc. Am. Assoc. Cancer Res.* 30:542, 1989.
22. Creighton, A.M., Hellmann, K., Whitecross, S. "Antitumor Activity in a Series of Bisdiketopiperazines." *Nature.* 222:384-385, 1969.
23. Herman, E.H., Witiak, D., Hellmann, K., Waravdekar, V.S. "Biological Properties of ICRF-159 and Related Bis(dioxopiperazine) Compounds." *Adv. Pharmacol. Chemother.* 19:249-290, 1982.
24. Wadler, S., Green, M.D., Muggia, F.M. "Synergistic Activity of Doxorubicin and the Bisdioxopiperazine [(+)-1,2-bis(3,5-dioxopiperazinyl-1-yl)propane] (ICRF-187) Against the Murine Sarcoma S180 Cell Line." *Cancer Res.* 46(3):1176-1181, 1986.
25. Verhoef, V., Bell, V., Filppi, J. "Effect of the Cardioprotective Agent ADR-529 (ICRF-187) on the Antitumor Activity of Doxorubicin." *Proc. Am. Assoc. Cancer Res.* 29:273, 1988.
26. Baldwin, J.R., Uhrig, B., Imondi, A.R., Narang, P.K. "Disposition of Cardioprotective Agent ADR-529 in Rats." *Pharmaceut. Res.* 5:S-186, 1988.
27. Narang, P.K., Baldwin, J.R., Benjamin, E.J., Bianchine, J.R. "ADR-529: Disposition of a Cardioprotective Agent in Mice." *Pharmaceut. Res.* 5:S-189, 1988.
28. Belt, R.J. "Prevention of Adriamycin-Induced Cardiotoxicity by ICRF-187(NSC-169780)." *Proc. Am. Soc. Clin. Oncol.* 3:27, 1984.

Asia Pacific Cancer Conference Scheduled

The International Union Against Cancer has scheduled a major scientific conference on Early Detection, Prevention and Clinical Management in Cancer Control. The 10th Asia Pacific Cancer Conference will be held on August 20-27, 1991, in Beijing, China.

Topics to be discussed within the conference's overall theme include cancer epidemiology, chemoprevention, risk assessment, mutagenesis, tumor virology, and many other areas of concern.

Registration information is available from the Secretariat of 10th APCC, c/o Ms. FANG Jin, CICCST, P.O. Box 300, Beijing 100086, China. Telephone: 861/831-3335; Telex: 222337 ICCST CN; Telefax: 861/831-6091 or 89-8116.