ASCO Clinical Evidence Review on the Ongoing Care of Adult Cancer Survivors: Cardiac and Pulmonary Late Effects—Review Summary

Context

In late 2005, ASCO convened an expert panel to develop a clinical practice guideline for assessing chemotherapy- and radiotherapy-induced cardiac and pulmonary late effects in asymptomatic cancer survivors (*J Clin Oncol* DOI: 10.1200/JCO.2007.10.9777). In June 2006, the ASCO Board of Directors rejected the guideline, citing that the current medical literature did not offer enough direct, high-quality evidence on the benefits and adverse effects associated with cardiopulmonary late effects and cancer survivorship. The ASCO Board then directed the panel to summarize the results of the systematic review of the literature with special attention to gaps in the literature and the provision of a detailed agenda for future research.

Methods

The Survivorship Expert Panel, a diverse group of clinical medicine and research experts, formed a special subcommittee to oversee the systematic review of clinical evidence regarding cardiopulmonary late effects. The literature review and analysis was conducted by searching MEDLINE, PreMEDLINE, and the Cochrane Collaboration Library through February 2006. Hand searching of selected reviews and personal files was completed to supplement and broaden the literature search results. Articles were analyzed for inclusion in the systematic review if they examined a screening intervention for cardiac or pulmonary disease; studied cancer survivors who had previously received chemotherapy, radiotherapy, or trastuzumab; and included primary outcomes of interest (ie, quality of life, overall survival, or morbidity) regarding screening and detection of cardiovascular or pulmonary disorders. Also included were articles reporting secondary outcomes such as disease-free survival, treatment risks, and cost-effectiveness.

Results

After review of 4,805 abstracts and full-text articles, the Cardiopulmonary Subcommittee found that although data on the incidence and prevalence of cardiac or pulmonary toxicity was presented in almost all of the studies, most of these studies were retrospectively designed with few prospective studies identified. In addition, while other studies reported on treating radiation- or chemotherapy-induced cardiopulmonary toxicity, few were designed for asymptomatic cancer survivors. Due to the heterogeneity of study results, a meta-analysis of the systematic review was not performed.

Discussion

Cardiac Disease in Adult Cancer Survivors Who Previously Received Anthracyclines or Platinum-Based Chemotherapy

Anthracyclines and platinum-based chemotherapy regimens have been shown to have a toxic effect on the hearts of long-term cancer survivors (ie, patients that live > 2 years after treatment completion). Evidence abounds on left ventricular abnormalities, cardiomyopathies, and congestive heart failures associated with anthracyclines and their derivatives. See Table 1 for a listing of anthracycline-associated risk factors for cardiomyopathy. Studies have shown that the cardiotoxic effects of many anthracyclines may be reduced, but not eliminated, with drugs (eg, dexrazoxane, epirubicin, and pegylated preparations) and/or changes in administration schedules. Direct and indirect effects of platinum- or cisplatin-based chemotherapy (PBCT) are also evidenced in the literature. Endothelial damage, which may lead to Raynaud-like symptoms and coronary artery disease, is a direct effect of PBCT. Indirect effects include an impact on traditional cardiac risk factors that may increase the survivors' risk of developing atherosclerosis. To further study these and anthracycline effects on survivor cardiovascular functioning, the Survivorship Expert Panel notes the need for quality research on routine noninvasive testing for cardiac dysfunction in asymptomatic cancer survivors. The panel also highlighted the need for more data on the role of treatments to prevent cardiac disease in this population.

Table 1. Anthracycline-Induced Cardiomyopathy Risk Factors

Characteristic
Patient
Young age (< 18 years) at treatment initiation
Age > 65 years at treatment initiation
Associated hypertension, pre-existing cardiac disease (coronary artery disease, left ventricular dysfunction)
Pregnant or contemplating pregnancy
Engaging in extreme/competitive athletics
Treatment
Higher cumulative dose equal to ≥ 300 mg/m ² of doxorubicin or ≥ 600 mg/m ² of epirubicin
Associated mediastinal radiation therapy
Combination chemotherapy (trastuzumab, cyclophosphamide, etoposide, melphalan, paclitaxel, mitoxantrone, idarubicin)
Longer duration of survival

Cardiac Disease Among Adult Cancer Survivors Previously Treated With Mediastinal, Chest, Mantle, or Left Breast Radiation

Pericardial damage is the most prevalent cardiac toxicity associated with radiation, though all heart structures are susceptible to radiation injury. Factors contributing to an increased risk of cardiovascular sequelae following mediastinal radiation are listed in Table 2. Data and information available through medical literature point to reductions in the incidence of cardiac toxicity when mediastinal radiation is delivered according to techniques developed after 1985. See Table 3 for a listing of these “modern techniques.” As with research limitations associated with chemotherapy-induced cardiotoxicity, radiation-cardiotoxicity studies are lacking for asymptomatic patients. In addition, there is almost no evidence on the true value of any treatments to alter the natural history of cardiac disease in cancer survivors.

Cardiac Disease Among Adult Cancer Survivors Who Previously Received Trastuzumab for the Treatment of Breast Cancer

Research has shown that trastuzumab-related cardiac dysfunction rarely contributes to patient mortality, and unlike anthracycline-induced myocardial damage, it is not dose-related. Also, in most cases, cardiovascular dysfunction is reversible when trastuzumab is discontinued and/or the patient is treated with cardiac medications. Evidence has shown a dangerous and unacceptable risk of developing congestive heart failure when trastuzumab is taken concurrently with doxorubicin. Patient age and decreasing left ventricular ejection fraction are the only prospectively defined risk factors evidenced in the literature for trastuzumab-related cardiac dysfunction. Although there continues to be an increased understanding of the short-term cardiac toxicity of

Table 2. Factors Increasing the Risk of Cardiac Sequelae After Mediastinal Radiation Therapy

Risk Factor
Patient
Associated anthracycline chemotherapy
Location of tumor close to heart border*
Age < 18 years
Associated cardiac risk factors
Baseline cardiac disease*
> 10-year postradiation therapy
Radiation
Orthovoltage radiation (rarely used since the 1970s)
Volume of irradiated heart*
Total dose to the heart > 30 Gy
Daily dose fraction > 2 Gy/day
Absence of subcarinal blocking

* These factors are consensus-based and not individually validated.

Table 3. Modern Techniques for Radiation Therapy

Technique
Three-dimensional treatment planning
Intensity-modulated radiation therapy in selected cases
Positron emission tomography, computed tomography fusion planning in selected cases
Reducing total dose (being tested in randomized trials)*
Reducing treatment field size (ongoing trials testing further reducing involved-field radiation therapy to involved-node radiation therapy using conformal techniques)*
Daily fraction size ≤ 2 Gy

* Pertains to the lymphoma patient population in which mediastinal radiation is often employed.

trastuzumab, there are currently no data about the long-term effects of this medication on cardiac function.

Pulmonary Disease Among Adult Cancer Survivors Who Previously Received Chemotherapy or Radiotherapy

Knowledge of the incidence and spectrum of cardiac toxicity of chemotherapy and mediastinal radiation are clinically important because there are evidence-based effective treatments available even for asymptomatic patients. Studies of pulmonary function testing in long-term cancer survivors who received chemotherapy and/or radiation therapy have been reported. See Table 4 for specific chemotherapeutic agents associated with pulmonary toxicity. No study has demonstrated that identification of abnormal pulmonary function testing in the asymptomatic adult cancer survivor leads to an improved clinical outcome.

Table 4. Chemotherapy Agents Associated With Pulmonary Toxicity

Agent
Bleomycin
Busulfan
Carmustine
Chlorambucil
Cyclophosphamide
Cytosine arabinoside
Docetaxel
Etoposide
Fludarabine
Gemcitabine
Methotrexate
Mitomycin
Paclitaxel
Procarbazine
Vinca alkaloids

It is important to realize that many management questions have not been comprehensively addressed in randomized trials, and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results.

Accordingly, ASCO considers adherence to this guideline to be voluntary, with ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

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ASCO Survivorship Clinical Practice Guidelines

Given the broad range of topics to address in a cancer survivorship guideline, the Survivorship Expert Panel decided to develop a series of practice guidelines in addition to the clinical evidence review. The series will include topics on hormone deficiencies, second malignancies, and psychological and neurological function.

Additional Resources

The full-text version of the review was published online June 18, 2007 (<http://www.jco.org>). Additional resources including a summary slide set can be accessed at <http://www.asco.org/guidelines/review>. Patient-friendly information on survivorship is available on the *People Living With Cancer* Web site at <http://www.plwc.org/survivorship>.

The ASCO Clinical Evidence Review on the Ongoing Care of Adult Cancer Survivors: Cardiopulmonary Late Effects was developed and written by Joseph R. Carver, Charles L. Shapiro, Andrea Ng, Linda Jacobs, Cindy Schwartz, Katherine S. Virgo, Karen L. Hagerty, Mark R. Somerfield, and David J. Vaughn.

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