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IM - COMMENTARY

Bringing new players into the field: onco-pharmacovigilance in the era of cardio-oncology

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The world is growing older, not only in terms of a time-line but also in terms of population demographics: the elderly are becoming an increasingly large segment of the population in the vast majority of western countries. This is due to numerous factors: low birth rates, fewer deaths due to infectious diseases, and an increasing ability of medicine to cope with the chronic degenerative pathologies: cardiovascular disease and cancer.

Clinically the reality is changing, in that we are often seeing more patients with both cardiovascular and oncologic disease. The cardiologic complications of anti-neoplastic therapy are moving into the limelight as cancer patient survival increases [1]. This has drawn the attention of internal medicine, as indicated in the article by Raschi and De Ponti [2] in this issue of IAEM. Originally, the cardiotoxicity associated with classic chemotherapies was just one of the numerous severe complications to these approaches, and survival of oncologic patients was low, so that cardiac complications were not a major concern. The advent of targeted therapies in cancer, together with classic approaches, has increased survival of cancer patients, but has also broadened the problems of cardiotoxicity. What was considered to be a "normal" cardiovascular (CV) event must now be seen in a different light, with greater concern, as this may be the critical problem that the patient, and physician, whether internist, cardiologist or oncologist, must overcome in a complementary and integrated way. The therapeutic combination where cardiotoxicity gained clinical recognition was that of the HER2 targeted agent, trastuzumab, in combination with anthracylines in therapy of breast cancer patients, where a synergy between concurrent use of these two drugs, highly effective in breast cancer but also highly cardiotoxic, led to progressive dismissal of this regimen for sequential schedules. One could envision use of less cardiotoxic HER2 inhibitors, such as lapatinib, in patients at risk [3], although lapatinib is associated with other toxicities.

There is a basic problem: clinical oncologists and cardiologists "speak" rather different "languages", the two disciplines are both quite complex per se, thus there is a gap in communication that requires the attention of internists as a bridge between these two disciplines. The cardiotoxicity of oncology therapy has given rise to a field now known as cardio-oncology. However this field, rather than presuming the existence of one specialist with global knowledge, usually refers to teamwork, where the oncologist must be aware of the risk for CV events, ask for a CV evaluation

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before therapy and CV monitoring during treatment. We must also keep in mind that drug-induced events such as hypertension and thromboembolism are part of the cardio-oncologic spectrum, and care and prevention of these conditions are areas where the internist plays a critical role [4].

The cardiotoxicity problem often arises late in the game, when the drug is already on the market or about to be approved. One problem is the reporting of adverse events, it has been suggested that nearly 40% of serious adverse events in pivotal oncology trials are not reported, and almost 50%, not described in the initial drug labels [5]. Oncologists tend to under evaluate adverse events that are not strictly related to progression of the oncologic disease. In particular, adverse CV events need to be paid more attention. In trials of drugs for therapy of diabetes, CV events are very closely monitored, as it would be expected with a high-risk group that has a reasonable life expectancy. Now that the survival of cancer patients is increasing, we need to consider the oncology patient as a high-risk group, although some are clearly at much higher risk than others. Current recommendations ask for monitoring of Q–T intervals, however this has been very controversial for assessing cancer chemotherapy-associated cardiotoxicity. Unlike in diabetes [6], Q–T interval changes do not correlate well with, nor predict, most severe CV events in the oncology patient in therapy [1]. The choice of Q–T monitoring may also be due in part to the associated low cost, but analysis of troponins [7], also relatively inexpensive and not invasive, as well as echography, can provide key clinical information [1]. Routine echographic analysis should become an integral part of cardio-oncologic examination prior to and during therapy, including serial left ventricular ejection fraction (LVEF) analyses.

We are lacking a full range of markers for determining onset and extension of adverse CV events. Troponin evaluates cardiomyocyte death, but as pointed out above, this is one of many mechanisms involved in cardio-oncologic complications. Brain natriuretic peptide (BNP) is a sensitive marker, but not specific, as it is often elevated in renal function impairment (another complication in cancer therapy), and in other pathologies. Development of biomarkers must become a priority [7].

In this issue of IAEM, Raschi and De Ponti [2] call into action the role of pharmacovigilance oriented to oncologic drugs to promote awareness among physicians, supporting oncologists and cardiologists towards optimizing patient outcome. They point out that a key is the prompt reporting of unusual adverse reactions, in particular during the pre-marketing phase of drug development. Oncologists must learn a new series of adverse events, many associated with cardiotoxicity, for evaluation of new therapeutics and their potential risks. This brings into the game not only oncologists and cardiologists, but also the clinical pharmacologist in an ever more interactive teamwork approach. We would also suggest the involvement of internists with expertise in thrombosis to assist in management of these complications. Just as computer networking has changed our ways of interacting socially, this philosophy may very well be useful in creating cardio-oncologic pharmacovigilance teams involving also internal medicine. Raschi and De Ponti [2] provide a detailed view of the cardiotoxicity of targeted agents, and suggest a series of management approaches for the key sectors associated with the cardiotoxicity of targeted agents: hypertension, left ventricular dysfunction/heart failure, and thrombo-embolic complications [2]. One point we are missing is the approach of intervention to reverse or prevent cardio-oncologic complications. For example, use of ACE inhibitors and beta blockers has been used as an early intervention to prevent clinical manifestations [8] when initial damage is revealed. The final goal will be to maintain efficacious cancer therapy while preventing or reversing CV damage. New approaches to prevention and treatment of cardio-oncologic complications need to be envisioned and enter into trials.

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