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Abstract

Session II of the Second International Colloquium on Cardio-Oncology (Kraków, May 2-4 2018), chaired by Drs. Breccia (Rome, Italy) and Jurczak (Krakòw, Poland), focussed on mechanisms and clinical course of cardiovascular toxicity of cancer treatment. Whereas the venerable anthracyclines keep challenging patients and clinicians with risk of left venticular dysfunction and heart failure, other newer drugs cause substantially different clinical phenotypes of cardiovascular toxicity. In particular, Session II focussed on arterial thrombosis and venous thromboembolism, but also hypertension or cardiomyopathy or atrial fibrillation induced by many otherwise life saving drugs. Dr. Breccia (Rome, Italy) reviewed incidence, mechanisms, risk factors and principles for prevention of cardiovascular events induced by tyrosine kinase inhibitors of hematologic interest, such as those used to treat chronic myeloid leukemia. Dr. Carver (Philadelphia, USA) reviewed the incidence, predisposing factors and principles for proactive management of cardiovascular events in patients treated by conventional chemotherapy or new drugs for treatment of multiple myeloma. Dr. Szmit (Warsaw, PL) discussed on how coagulation disorders should be classified according to patient- or drug-related factors and how they should be diagnosed and treated in patients with solid or hematologic tumors. Dr. Minotti (Rome. Italy) illustrated some potential pitfalls of accelerated drug development and approval and their possible impact on clinical incidence of cardiovascular events induced by tyrosine kinase inhibitors. Session II therefore offered a broad perspective of the risk-benefit ratio of new drugs that are plagued with concerns about cardiovascular events.

Keywords	Cancer, drugs, cardiovascular system, toxicity, cardio-oncology

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Giorgio Minotti

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Session Summary

Session II of the Second International Colloquium on Cardio-Oncology, co-chaired by Dr. Breccia (Rome, Italy) and Dr. Jurczak (Krakow, Poland), focused on mechanisms and clinical course of cardiovascular toxicity of cancer drugs. With an avalanche of new drugs now available to treat both solid and hematologic malignancies, clinical phenotypes of cardiovascular toxicity have changed substantially compared those seen in the past. In particular, arterial thrombosis and venous thromboembolism complicate clinical use of many otherwise life-saving drugs.

This session opened with Dr. Breccia reviewing the risk of cardiovascular events induced by tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukemia (CML). These drugs cause a dramatic effect on CML outcome but also show a potential for inducing a spectrum of events. Imatinib, prototypic inhibitor of CML molecular target, the Bcr-Abl kinase, was initially suspected to cause heart failure but such concern have been mitigated by many other studies. Vascular events represent the most feared untoward effect of CML TKIs, with second generation TKIs such as dasatinib and nilotinib causing significant higher rates of events as compared to imatinib[1]. Dasatinib can also cause an atypical course of pulmonary arterial hypertension, although this occurs in less than 1% of patients[2].

For nilotinib, 5-years follow up data from patients recruited to the ENESTnd trial showed that the rate of all arterial or venous thromboembolic events could be as high as 7.5% with 300 mg BID and 13.4% with 400 mg BID[3]. Peripheral occlusive arterial events (PAD) are typically associated with nilotinib, particularly for patients with one or more risk factors [4]. This denotes that vascular events build on pathobiologic interactions between nilotinib and pre-existing disease. Such interactions became a recurrent motif for all CML TKI. A prospective analysis showed that pathological ankle brachial index (ABI) was more frequently observed in patients treated with nilotinib, particularly in older patients with cardiovascular risk factors or developing diabetes or dyslipidaemia in response to nilotinib. Canonical risk factors such as older age, previous positive

cardiac history and metabolic disorders were likewise associated with vascular events by bosutinib, whether given frontline or second line to CML patients.[5]

The unique interplay between risk factors and comorbidities became exceptionally evident for the third generation and most potent TKI, ponatinib. This was tested as third or fourth line treatment for patients intolerant or resistant to other TKIs in the prospective phase II trial, PACE. After 5 years of follow-up as many as 31% of chronic phase CML patients experienced PADs, almost equally represented by cardiovascular (16%), peripheral (14%), or cerebrovascular (13%) events[6]. Patients with 2 or more risk factors had an increased probability to develop events, and the number of previous TKIs also emerged as a predisposing risk factor.

Mechanisms for TKI related vascular events have been explored with only partial success. For nilotinib, alterations of glucose metabolism, reduced adiponectin levels, hypercholesterolemia and expression of adhesion molecules are very likely to play a role[7]. Less is known for ponatinib. Ponatinib inhibits the survival and growth of umbilical vein endothelial cells in vitro but whether endothelial toxicity occurred in vivo and contributed to vascular events remains uncertain. Clinical relevance of ponatinib inhibiting the tyrosine kinase domain of vascular endothelial growth factor receptor 2 also remains uncertain at this point in time. This having been said, one cannot avoid emphasizing the dramatic improvement TKI offered in CML settings. TKI are so effective that the life expectancy of individuals diagnosed with CML in 2013 will not differ too much from that observed for the general population[8] (**Figure 1**). This should be the starting point for any further consideration, and this should prompt clinicians to devise preventive strategies that mitigate risk and allows TKI to deliver optimum curative effects.

An Italian consensus panel suggested that primary prophylaxis with antiplatelet agents, such as low dose aspirin or the thienopyridine, clopidogrel, might be considered for chronic phase CML patients candidate to ponatinib, even if cardiovascular risk was deemed to be low by conventional scoring charts[9]. Other approaches, largely inspired by common sense and risk awareness, have also been reported[10]. Clearly, these are position or consensus-like papers that do not approach the level of evidence-based recommendations or guidelines. Much remains to be done to provide clinicians and CML to improve the risk-benefit ratio of CML TKI in everyday life.

The session continued with Dr. Carver focussing on cardiovascular complications of treatment for multiple myeloma (MM), which represents 10% of all hematologic malignancies. MM shows a highly variable course with periods of smouldering disease, not requiring treatment, and periods of aggressive, relapsing or refractory disease that require interventions. Treatment goals are to produce increase remission duration while also preventing organ damage and maintaining quality of life (QoL) for the affected patients.

MM treatment has evolved from “conventional” chemotherapy with 5 year survival of 29% to incorporation of combinations of new classes of drugs at all stages of disease[11]. This has increased survival duration and QoL significantly with prospects for ultimate cure Immunomodulatory drugs and proteosome inhibitors (PI) have significantly increased survival but also introduced new phenotypes of on and off target cardiovascular toxicity. Moreover, since MM is more often a disease of the elderly (mean age of diagnosis is 65 years), MM impose their toxicity in presence of cardiovascular risk factors or pre-existing cardiovascular disease. It follows that in assessing cardiovascular toxicity and understanding the literature, both patient and disease factors need to be considered, similar to what Dr. Breccia discussed for CML patients.

Major cardiovascular adverse events of the MM drug armamentarium include de novo and accelerated hypertension, cardiomyopathy and congestive heart failure, arrhythmias and conduction disease, ischemic heart disease and coronary syndromes, arterial and venous thrombosis[12]. Drug treatment consists of mono or combination therapy of classes of medications with different cardiovascular toxicities (**Table 1**). Carfilzomib has consistently shown the highest rates of cardiac toxicity with all-grade cardiac toxicity of 18%[13]. The incidence for bortezomib is less clear and based on numerous single patient case reports describing cardiovascular events. However, meta-analysis of thousands of patients in clinical trials reveals no statistically significant increase in cardiovascular events with bortezomib, although there is an increase compared to no treatment[14]. In head to head comparisons, it is clear that carfilzomib shows a higher incidence of all defined cardiovascular toxicities. To date there is one case report of cardiomyopathy associated with ixazomib, suggesting that this might be a class effect[15].

Proposed mechanisms for proteasome inhibitor-associated cardiovascular events include oxidative stress on cardiac myocytes, endothelial effects as a result of proteasome inhibition leading to hypertension and vascular dysfunction, and an increase in coronary vascular tone and reactivity.[16] Monoclonal antibodies (daratumumab, elotuzumab) to date have not been implicated with an increase in cardiovascular events when used as monotherapy.

Because of multiple possible competing causes of cardiovascular events (primary disease, baseline cardiac risk factors and pre-existing cardiac disease, heavily pre-treated myeloma) it is difficult to ascribe causality to the drugs used to treat this disease. Management suggestions therefore include thorough baseline cardiovascular assessment to identify and proactively manage pre-treatment co-morbidity coupled with vigilant monitoring of patients after treatment initiation and unwavering aggressive management of cardiac risk factors and cardiovascular complications. These suggestions are based and intuitively include the close cooperation between cardiologists and oncologists.[17]

Dr. Szmit furthered the discussions from Professors Breccia's and Carver's lectures to provide a thoughtful analysis of how coagulation disorders should be classified, diagnosed and treated in oncology or haematology settings. Szmit emphasized that in recent years Common Terminology Criteria for Adverse Events have been changed significantly. Among other events, arterial thromboembolic events were taken into account and the severity of pulmonary embolism was detailed. The immediate reason for, and consequence of such awareness is the increasing incidence of these two different pathophysiological types of vascular complications in cancer patients. As anticipated by Carver for MM, such an increased awareness leads to identifying at least 3 groups of risk factors for thrombosis in oncology: cancer-related, patients-related and treatment-related. The last group includes major surgery, hospitalization, chemotherapy (particularly with cisplatin, hormonal therapy, antiangiogenic agents, immunomodulatory drugs, erythropoiesis-stimulating agents), transfusions, central venous catheters. For each predisposing iatrogenic factor, appropriate biomarkers should be considered[18] (**TABLE 2**).

A major issue to address concerns how to protect cancer patients against the occurrence of arterial or venous thrombosis. Anticoagulant therapy in oncology currently based on low molecular

weight heparins does not seem to be fully effective because recurrence of venous thromboembolic disease in cancer patients is still frequently observed, even up to 16% within 12 months of follow-up[19]. Recurrent venous thromboembolism can be observed in patients with cancer diagnosed during active anticoagulation and the risk can persist for many years[20]. The long-term risk of chronic thromboembolic pulmonary hypertension is also real. In oncology the guideline endorsed treatment with heparins compared to vitamin K antagonist does not decrease the mortality at any time point as well as bleeding in every degree.

An important question for the future therefore addresses a therapeutic place for oral anticoagulants and an optimal duration of antithrombotic prophylaxis, both primary and secondary. Detailed evaluation strategies seem to be necessary for both arterial and venous thromboembolic events in modern oncology. There is a need to protect against all possible vascular complications by using anticoagulation preferably with oral administration and suitable profile for arterial and venous system. Likewise, secondary thromboembolic prophylaxis should be redefined regarding duration time and indications for new anticoagulants, and in fact, the available data confirm that treatment of venous thromboembolism should be longer than 6 months[20]. However, patients may not accept long-term management with the use of subcutaneous injections with heparins. When examined in this context non-Vitamin K antagonist oral anticoagulants should be considered for efficacy but also for analogue-related potential interactions with other drugs and sensitivity to renal or hepatic dysfunction, which can determine efficacy and safety of concomitant anticancer therapy. Ongoing studies, like The Cancer-associated thrOmboSIs - patient-reported outcoMes with rivarOxaban (COSIMO study) will hopefully provide real-world information on treatment satisfaction in patients with active cancer who switch from low molecular weight heparin or vitamin K antagonists to rivaroxaban for the treatment of acute venous thromboembolism or to prevent its recurrence[21]. Similarly undefined prophylaxis remains in cancer patients with atrial fibrillation especially in subgroups with high risk of bleeding. Thanks to the safety profile, apixaban seems promising[22] but convincing results from randomized studies are mandatory.

The heterogeneous nature of cancer patients with different histological and molecular tumors of different localization, having various co-morbidities and bleeding risk, receiving various

anticancer treatment, will certainly result in a special need for tailored individualization of the anticoagulation.

The session ended with some considerations by Dr. Minotti on the potential pitfalls of drug development and approval and their possible impact on clinical incidence of cardiovascular events. Minotti considered that the new drugs, and especially the TKI, are much less specific than usually reported and can target kinases other than those expressed in tumors, thus paving the rod to off target effects in the cardiovascular system. Because of their prospective life saving effects, the new drugs usually proceed through premarket phase I-II studies that do not always adopt a reasonably long follow up. These studies build on maximum tolerated doses that may or may not be appropriate for targeting the desired tumor kinases while sparing those expressed in the cardiovascular system. A paradigmatic example of how these pifalls can jeopardize the safety of new drugs is offered by the pankinase inhibitor, ponatinib. As outlined by Breccia in his presentation, ponatinib was approved to treat patients affected by acute lymphoblastic leukemia or CML and showing resistance or intolerance to other anti Bcr-Abl TKI. The ponatinib case, illustrated by the disturbing incidence of arterial thrombotic events in patients recruited in the pivotal PACE trial, broke when the drug was already in the market. The Food and Drug Administration (FDA) could only react by withdrawing the drug from the market. The accelerated development and fast track approval of ponatinib was harshly commented on by key opinionists.[23]

This having been said, one cannot escape the fact that the surge of cardiovascular events was anything but unprecedented. The FDA clinical pharmacology review document had judiciosly noted that the recommended dosage of 45 mg/day probably was too high.[24] Moreover, pharmacokinetic data available at the time of approval clearly showed that 45 mg of ponatinib/day produced plasma peaks that exceed the 40 nM level needed to inhibit kinases and to suppress the outgrowth of mutant clones. Careful consideration of ponatinib life saving effects, especially for patients carrying the otherwise uncurable T315I Bcr-Abl mutant, led the FDA to reintroduce ponatinib in the market, but needless to say, the drug was marred by the ignominous fame of being the most toxic TKI ever developed. Patience and pharmacologic insight could help mitigate the scenario. The summary of product characteristics now reads that the dose can be safely reduced

from 45 to 15 mg/day once a major molecular response has been obtained. Retrospective analyses show that dose reduction will significantly reduce the risk of vascular events associated with ponatinib.[25] And the everyday clinical practice now shows that ponatinib saves life with a resonably good safety profile.

The clinical pharmacology review the FDA provides for each drug under evaluation is something to be valued. It often questions the dose regimen proposed by the applicants. Based on pharmacokinetic and pharmacodynamic considerations the agency cautions that the proposed dosages may be unnecessarily high. The new drugs are in fact approved, as the may save countless lives worldwide; however, the need for post approval studies that evaluate the efficacy and safety of lower doses is judiciously communicated by the FDA to the applicants. Is this recommendation taken by the applicants and translated into new clinical studies? The answer is negative as post-approval studies are invariably designed to explore new indications and to move a drug from e.g., second or third line line treatment to frontline indication. This means that the new drugs enter the market with a relatively limited information about safety, and cardiovascular events may surface in survivors of pre-approval studies at the same time when the new drugs become popular in the general population or enter studies of new indications, leaving the modalities of prevention and treatment to the common sense of clinicians. Similar concerns might apply to the Bruton tyrosine kinase inhibitor, ibrutinib, which offers important opportunities for treatment of chronic lymphocytic leukaemia, mantle cell lymphoma, and Waldenström macroglobulinemia. Pharmacokinetic considerations suggest that currently approved dosages produce plasma peaks that are nearly one log higher than the IC-50 of ibrutinib in vitro. On a different note, currently approved dosages exceed those needed for >90% occupation of the target kinase in circulating cells.[26] These facts should be kept in mind when considering that ibrutinib may cause atrial fibrillation. Patients candidate for ponatinib are already exposed to an age-related risk of atrial fibrillation[27]. It goes without saying that any unneeded milligram of ibrutinib would accelerate the spontaneous development of atrial fibrillation in predisposed patients.

In summary, the new drugs are good drugs but the dose may be wrong. For such new drugs, the role of cardiologists and oncologists, and probably of pharmacologists above them all,

should be to interact with regulatory bodies before the approval process is concluded or the post-approval development deviates from searching the lowest active dose.

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Table 1

Cardiovascular toxicities associated with multiple myeloma drugs

Class	Drugs	Cardiovascular toxicities
Alkylating agents have	Cyclophosphamide, melphalan, bendamustine	No consistent CV toxicity.
Immunomodulary agents	Thalidomide, lenalidomide, pomalidomide	Consistent increase of the risk of venous thrombosis with only scattered case reports of arrhythmias, dyspnoea and cardiomyopathy of low incidence.
Proteasome inhibitors	Bortezomib, carfilzomib, ixazomib	Consistent increase of all cardiovascular events recorded for alkylating and immunomodulatory agents

Table 2

Iatrogenic risk factors for cancer-associated thrombosis

Treatment-related factors	Candidate biomarkers
Major surgery	Platelet count ≥ 350 000/mm^3
Hospitalization	Leukocyte count > 11 000/mm^3
Chemotherapy (particularly cisplatin)	Hemoglobin < 10 g/dL
Hormonal therapy	Elevated tissue factor
Anti-angiogenic agents (bevacizumab, sunitunib, sorafenib)	Elevated D-dimer
Immunomodulatory drugs (thalidomide, lenalidomide)	Elevated soluble P-selectin
Erythropoiesis-stimulating agents	Elevated C-reactive protein
Transfusions (platelets and red blood cells)	Thrombin generation potential
Central venous catheters	

Modified from reference [18].

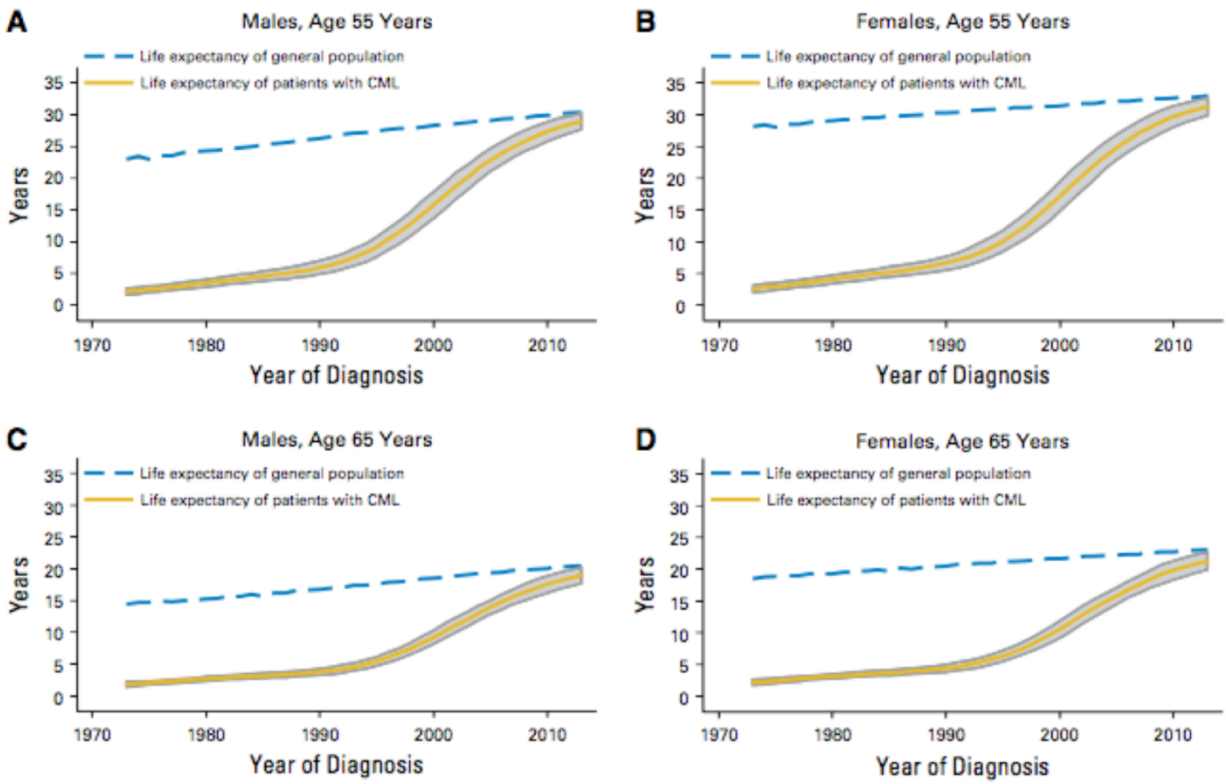

FIGURE 1

Gender and age-adjusted effects of TKI on improving the life expectancy of CML patients.

(From reference 10).

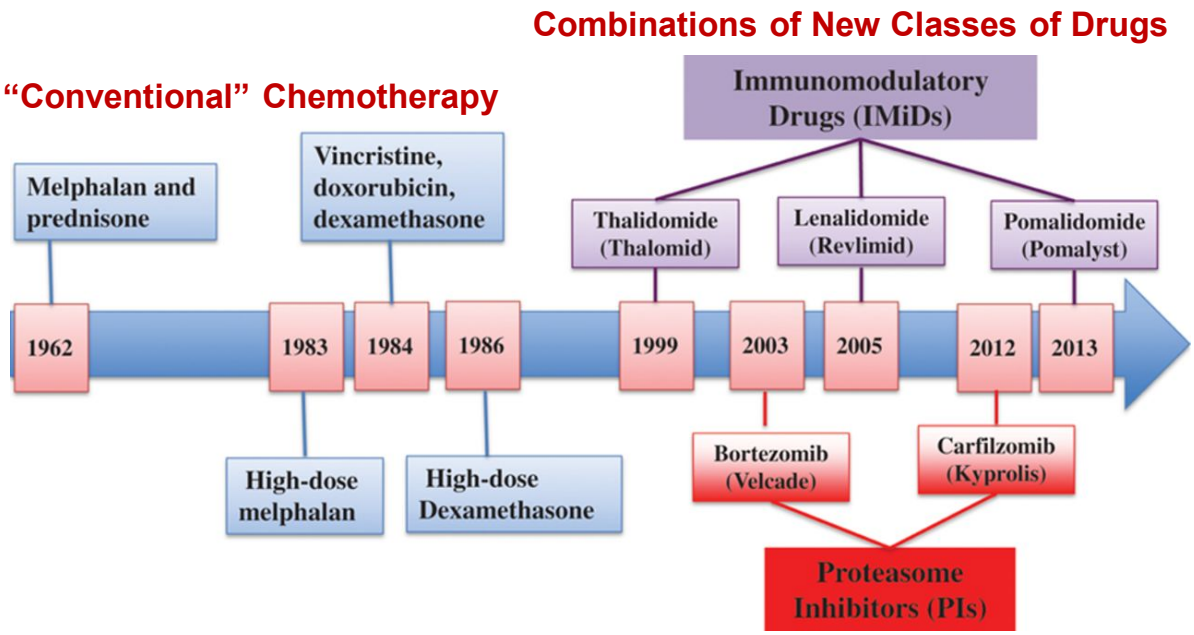

Figure 2

Pharmacologic evolution of multiple myeloma treatment (from reference 11).

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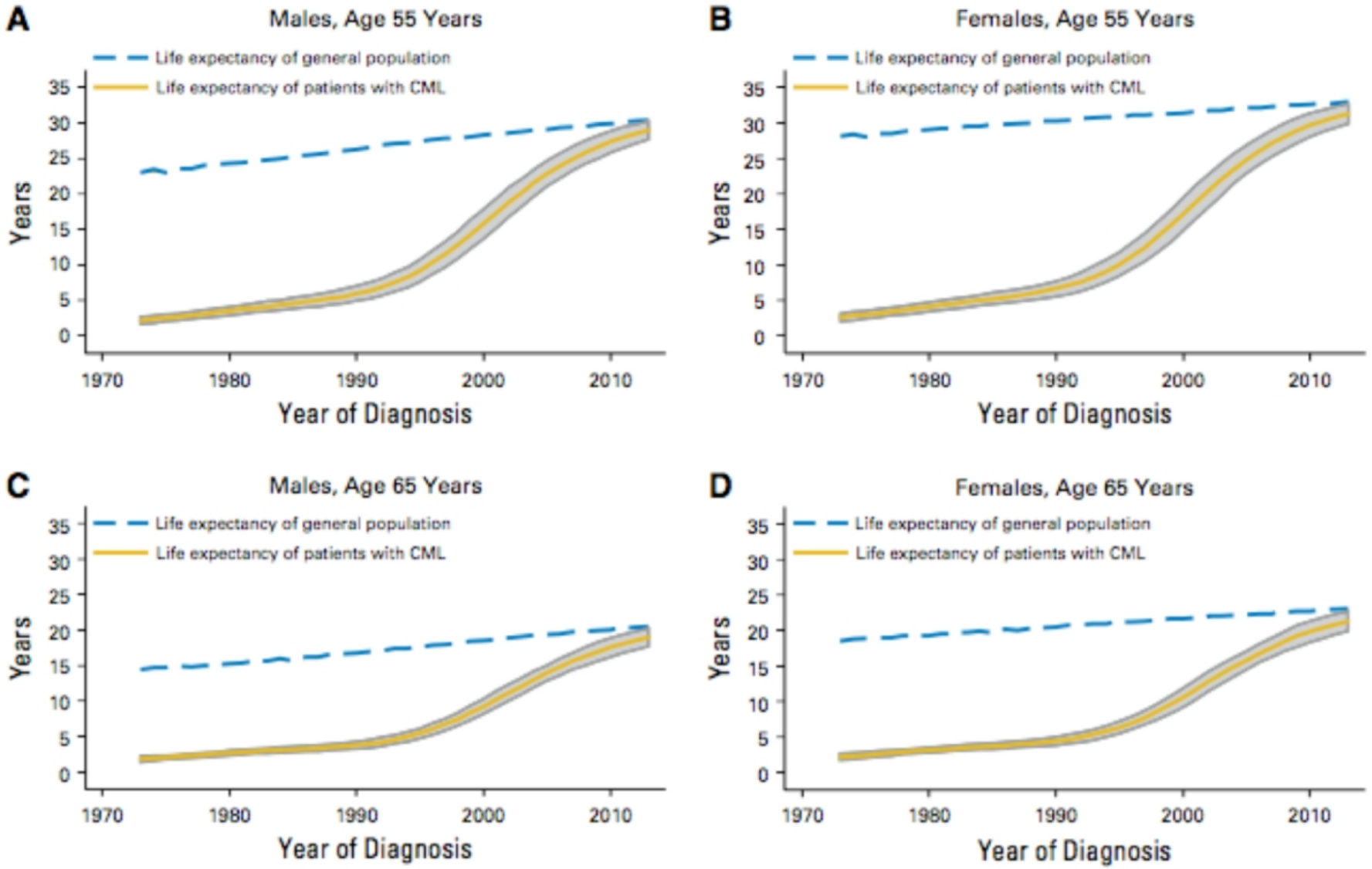
A
Males, Age 55 Years
Life expectancy of general population
Life expectancy of patients with CML
Years
0
5
10
15
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1970
1980
1990
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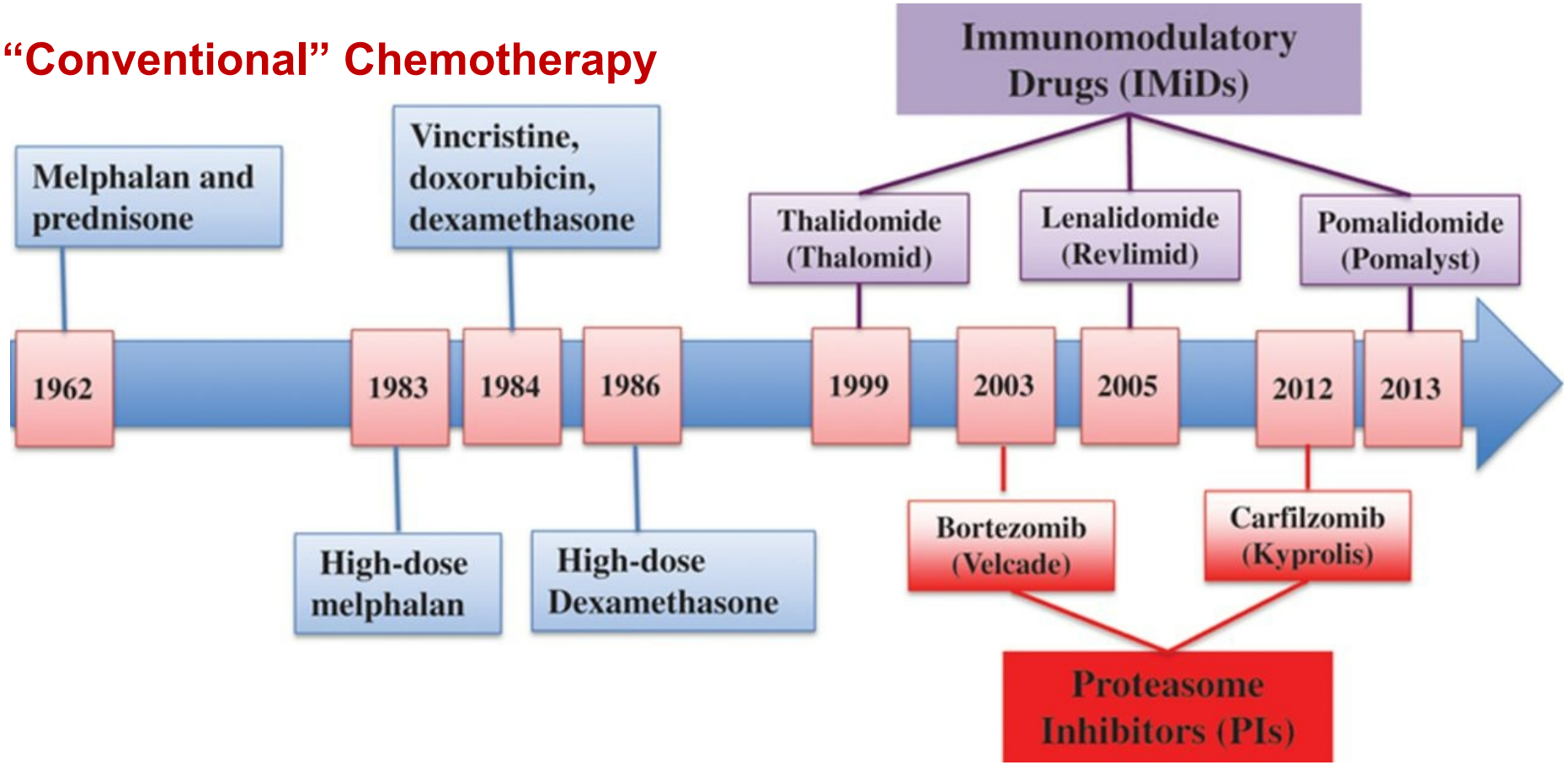
2010
Year of Diagnosis
B
Females, Age 55 Years
Life expectancy of general population
Life expectancy of patients with CML
Years
Year of Diagnosis
C
Males, Age 65 Years
Life expectancy of general population
Life expectancy of patients with CML
Years
Year of Diagnosis
D
Females, Age 65 Years
Life expectancy of general population
Life expectancy of patients with CML
Years
Year of Diagnosis

Combinations of New Classes of Drugs

"Conventional" Chemotherapy



No conflict of interest to declare