EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2024
EMA/CHMP/322756/2024
Committee for Human Medicinal Products (CHMP)

Concept paper on the need for a Reflection Paper on assessment of cardiovascular safety of oncology medicinal products

Agreed by the Cardiovascular Working Party	6 June 2024
Agreed by the Oncology Working Party	23 May 2024
Adopted by CHMP for release for consultation	25 July 2024
Start of public consultation	1 August 2025
End of consultation (deadline for comments)	31 October 2024

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Keywords	Cardiovascular safety, oncology, anti-cancer drugs

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1. Introduction

In 2016, the Cardiovascular Working Party (CVSWP) published a *Reflection Paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)* focused on medicinal products for vascular and metabolic diseases [CHMP, 2016]. Although it states that same principles of data generation and assessment may apply to other therapeutic areas, the document does not take into consideration the existence of important differences with other therapeutic areas that may make it necessary to prepare a more specific document for medicinal products in a different clinical setting.

The purpose of the proposed reflection paper is to provide recommendations for the planning, collection of data and evaluation of cardiovascular (CV) safety of oncology medicinal products taking into account specific issues that apply to the oncology setting with respect to type of medicinal products applied, patients and trials designs.

2. Problem statement

Data from real-life registries show that about 1 in every 3 patients develops CV toxicity due to oncological treatments [Lopez-Sendon et al, 2021]. With the expected 23.6 million new cancer cases worldwide each year by 2030, the rapidly growing number of patients surviving cancer and the increasing number of patients aged over 65 who need chronic cancer therapy, there will be a significant increase in subjects experiencing CV toxicity of these treatments in the upcoming years, which is a matter of concern [Lancelotti et al, 2019].

Cardio-oncology is a discipline aimed at reducing the burden of CV disease in oncology patients allowing them to receive the best antitumor therapy (chemotherapy, targeted molecular therapies, hormone therapy, immunotherapy or radiotherapy) [Lancellotti et al, 2019]. The European Society of Cardiology created the Council of Cardio-Oncology (ESC-CCO) in August 2018 as a multidisciplinary constituent body which encourages the prevention, early diagnosis and management of cancer therapy-related CV diseases [ESC, 2023].

Many studies have assessed CV toxicities in patients undergoing various types of cancer therapies. However, direct comparisons in terms of assessment of CV safety between clinical trials in oncology field have proven difficult due to lack of uniformity in CV toxicity endpoints and assessment [Rao et al, 2021; Oren et al, 2021]. There are also inconsistencies in addressing toxicities in the "Common Terminology Criteria for Adverse Events" (CTCAE) guidelines [Herrmann et al, 2022]. Therefore, there is a need for improvement of reporting and assessing CV safety outcomes in registration-track oncology trials. Similarly, in clinical practice, there can be substantial differences in the understanding of what constitutes CV toxicity, which can lead to significant variation in patient management and outcomes [Lyon et al, 2022].

The aim of the reflection paper is to outline how to address the CV safety concerns in drug development in oncology in order to support the safety evaluation. It is anticipated that the new systematic approach to collection and assessment of CV toxicity in oncology trials that is to be proposed in the reflection paper will be beneficial for patients as it will permit to balance the risk of cancer - treatment related cardiovascular toxicity (CTR-CVT) against the absolute benefit of the cancer treatment before and during treatment as well as make the comparison between treatment approaches easier.

3. Discussion (on the problem statement)

In the evaluation of contemporary oncology medicinal products, more than 1 in 4 have required a cardiotoxic effects safety warning, including more than 40% targeted and immune-based drugs [Bonsu et al, 2021]. In post-marketing experience, there may be a delay in the identification and diagnosis of cardiotoxic effects, which is concerning, particularly given the rapid emergence of many targeted and immune-based cancer therapies, and the potentially devastating consequences of CV toxicity events [Bonsu et al, 2021].

An important characteristic of drug development in cancer, due to the generally bad prognosis of the disease when there are no curative treatments, is that cardiac safety signals are not normally stopper signals impeding development of effective drugs, and an early identification of CV safety signals during drug development should be balanced with the potential benefit [Seltzer et al, 2021]. Some challenges of assessing CV safety in oncology trials are related to the relatively small sample sizes used and the lack of control group in many cases, the differential follow-up between the experimental and control arms when the trials are comparative, the strict inclusion/exclusion criteria with a poor representation of patients at the highest risk of developing CV toxicity and the presence of previous exposure to other therapies that may be also associated with CV toxicity [Seltzer et al. 2021]. In addition, while some CV events may be easily identifiable, as they occur in the short term [Lyon et al, 2022; Goldman et al, 2021; Fradley et al, 2021], in other cases they become evident only after the heart has been exposed to a drug/metabolite over a prolonged period, or they are so rare that a safety signal requires thousands of patients exposed. In such cases, it is difficult to delineate the CV safety profile of the new compound before authorization, and these uncertainties should be managed under the Risk Management Plan (RMP) [EMA, 2018].

The ESC organized a Cardiovascular Roundtable (CRT) Workshop on "The cancer patient and cardiology", in 2019. The aim of this workshop was to review main cardio-oncology issues from preclinical, clinical and regulatory issues.

The International Cardio-Oncology Society (ICOS) [Herrmann et al, 2022], published a document addressing these issues and provided consensus definitions for the most commonly reported CV toxicities. There are five focus areas of CV toxicities covered in the IC-OS document, which include: a) cardiac dysfunction/heart failure; b) myocarditis; c) arrhythmias/QT prolongation [; d) hypertension; and e) vascular toxicity, including myocardial infarction, stroke, transient ischemic attack, venous thromboembolic event, arterial thromboembolism, peripheral ischemia, vasculitis, vascular disorder and venous injury. This consensus effort aims to provide a structure for definitions of CV toxicity in the clinic and for future research.

The first ESC clinical practice guideline on cardio-oncology, published in 2022, was developed by the task force on cardio-oncology of the European Society of Cardiology (ESC) in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) [Lyon et al, 2022]. The ESC guideline on cardio-oncology adopted the ICOS consensus statement for defining CV toxicities [Herrmann et al, 2022].

Current approach to CV toxicity of oncology drugs in clinical practice is based on: a) the assessment of baseline CV toxicity risk, including clinical assessment and complementary tests [; b) A close follow-up for early detection of the CV toxicity and reassessment of CV toxicity risk; and c) the implementation of appropriate treatment according to the type of CV toxicity detected [Lyon et al, 2022]. These recommendations regarding the assessment of CV toxicity risk, the use of validated methods and standardized definitions for an early detection and qualification of the different CV toxicity events and a proper management of these events may serve as a starting point to plan and assess CV toxicity also

during clinical trials with the newer oncology treatments and to protect patients from the potential consequences that these CV events may have in their prognoses.

In summary, a reflection paper on assessment of cardiovascular safety of oncology medicinal products is foreseen due to the reasons outlined above, including, among others, the lack of uniformity in CV toxicity endpoints, characterization of the baseline CV risk, monitoring, assessment and follow-up in oncology studies to date.

The proposed reflection paper is planned to cover the following aspects, which will be tailored to the different potential scenarios:

- Selection of populations: inclusion/exclusion criteria, collection of CV risk factors.
- Study design, duration.
- Prospective definition of CV endpoints and analysis.
- CV safety monitoring during registration trials.
- Reporting of CV outcomes.
- Labelling implications.
- RMP implications.

4. Recommendation

The Cardiovascular Working Party (CVSWP) at the EMA recommends the preparation, in collaboration with the Oncology Working Party (ONCWP), of a reflection paper on cardiovascular safety of oncology medicinal products taking into account the issues identified above.

5. Proposed timetable

The Concept Paper is released for 3-month public consultation. The draft reflection paper will be discussed within the CVSWP and with the ONCWP and will be released within 12 months after adoption of the Concept Paper by the CHMP for 6 months of external consultation and, following the receipt of comments, it will be discussed again within the CVSWP and with the ONCWP and finalised within approximately 12 months.

6. Resource requirements for preparation

The drafting process will involve the cooperation between the CVSWP and the ONCWP at the EMA.

7. Impact assessment (anticipated)

It is anticipated that the proposed reflection paper will help to standardize the prospective planning and reporting of cardiovascular safety endpoints in oncology trials.

8. Interested parties

The following interested groups may provide additional valuable input:

- Disease specific patient representatives: ESC Patient Forum (idrossart@escardio.org), European Cancer Patient Coalition (ECPC) (info@ecpc.org).
- Learned societies: European Society of Cardiology (ESC) & ESC Council of Cardio-Oncology, European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO), and the International Cardio-Oncology Society (IC-OS).

- Pharmaceutical industry representatives: European Federation of Pharmaceutical Industry Associations (EFPIA).

9. References to literature, guidelines, etc.

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