

Clinical activity and cardiac tolerability of non-pegylated liposomal doxorubicin in breast cancer: a synthetic review

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Background

Anthracycline-containing regimens have demonstrated significant disease-free and overall survival benefits in the adjuvant setting and also provide palliative benefit in metastatic disease¹. Over the past two decades, an increasing proportion of patients have been exposed to adjuvant anthracyclines with concomitant reduction in their use for palliation, as a result of concerns regarding efficacy and cumulative anthracycline-associated cardiotoxicity, as well as the availability of other systemic chemotherapeutic options.

This report reflects the consensus view of a meeting of oncologists, pharmacologists and cardiologists held in Florence, Italy, on April 30, 2010. The objectives of the meeting were to review the role and limits of conventional anthracyclines in the treatment of breast cancer, to provide recommendations for the use of novel anthracycline formulations, such as non-pegylated liposomal doxorubicin (NPLD), and to identify potential future indications for NPLD that warrant further research.

Cardiotoxicity of conventional anthracyclines: how important is the problem today?

The occurrence of cardiac failure (2% of cases) and acute myeloid leukemia (0.5%) related to the use of conventional anthracyclines is largely compensated by their observed clinical benefit and has not prevented the widespread use of this class of drugs for many years. With the introduction of trastuzumab into anthracycline-based adjuvant treatment of patients with HER2-positive breast cancer, cardiac toxicity immediately appeared as the key safety issue, with the observation of clinically evident congestive heart failure in nearly 4% of patients enrolled in clinical trials¹. Moreover, data presented at the last ASCO Meeting 2010 indicated that the cardiotoxic potential of

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anthracyclines and trastuzumab may be further increased by the sequential administration of bevacizumab, which is being increasingly used in breast cancer².

NPLD

NPLD is a liposomal formulation of doxorubicin that has been developed with the aim of improving the therapeutic index of anthracyclines by reducing their toxicity while maintaining antitumor efficacy. The molecule allows to take full advantage of anthracycline efficacy since it is at least as effective as conventional anthracyclines (in anthracycline naïve and pretreated patients), with a trend towards improvement in several parameters. NPLD gives a significantly higher objective response rate than doxorubicin (and a reduced risk of cardiotoxicity) in anthracycline-pretreated patients, probably due to the high concentration of doxorubicin released at tumor sites and to the higher median cumulative dose (>1260 mg/m²) that can be safely administered.

Overall, NPLD is well tolerated, with no new or unexpected toxicity and no increase in the incidence or severity of known doxorubicin toxicity. Moreover, no hand-foot syndrome has been recorded during clinical trials.

The comparable efficacy and better safety profile shown in phase III trials in metastatic breast cancer have sparked research interest in other breast cancer settings (such as neoadjuvant therapy) or in new combinations with many chemotherapeutic agents (e.g. taxanes), including potentially cardiotoxic agents such as trastuzumab. Moreover, in non-Hodgkin lymphoma, the activity of NPLD was shown to be independent of MDR-1 status. This was possibly due to the ability of NPLD to overcome excessive drug efflux due to P-gp (MDR-1) overexpression³.

Identification of patient-related risk factors for the development of anthracycline-induced cardiotoxicity

The panelists agreed that cardiac safety of conventional anthracyclines is a long-term issue. This assumption is based on the post mortem evidence that doxorubicinol was found in the cardiac muscle of asymptomatic patients many years after doxorubicin administration (long-lived toxic reservoir).

An adequate classification or taxonomy of risk factors for anthracycline-induced cardiac damage is lacking.

In this perspective, the panel agrees that the following risk factors should be taken into account: 1) pre-existing co-morbidities – hypertension, overt diabetes, obesity, dislipidemia, family history of cardiac and metabolic disorders; 2) life-style factors – active cigarette smoking,

inactivity; 3) age >60-65 years; 4) patients with LVEF <45% at baseline; 5) radiotherapy to the left chest wall in patients with left tumors; it still has to be included among risk factors as we do not have adequate follow-up for new radiotherapy techniques.

Active cardiac prevention through the administration of drugs such as beta blockers or ACE inhibitors might be feasible, even though prospective studies have not yet been performed. However, the panelists argued that this strategy might result in an over-medicalization of healthy women with early breast cancer, except for those patients pretreated with adjuvant anthracyclines, with at least one risk factor and candidate to rechallenge with anthracyclines as first-line chemotherapy.

Apart from LVEF determination (either MUGA-scan or with ultrasound), at the present time no other diagnostic tool may be recommended during follow-up for cardiac monitoring.

Predictive factors of anthracycline sensitivity

The expert panel acknowledged that HER2-positive patients are the most likely to achieve a response to anthracycline administration. However, HER2 cannot be considered the true molecular target of anthracyclines. HER2 status should remain a biomolecular marker for trastuzumab and other anti-HER2 agents use, but not for anthracycline delivery.

The assessment of topo 2 alpha isomerase status, the true anthracycline molecular target, cannot be recommended as well, since the assay is not yet standardized and scientific data are inconsistent.

Triple-negative breast cancer is a heterogeneous disease, and the use of anthracyclines cannot be discarded, especially in those patients with a high proliferation index. In clinical practice, anthracyclines should be administered in association with taxanes in the adjuvant setting.

The panelists agreed that at present there is no biological factor that can be evaluated in clinical practice to assess individual anthracycline responsiveness.

Clinical recommendations

Rechallenge with anthracyclines remains an option for metastatic breast cancer patients, provided relapse-free survival is >1 year after the end of adjuvant anthracycline-containing chemotherapy. This approach may be appropriate in symptomatic patients, requiring a rapid response, and is supported by published data indicating that re-treatment with anthracyclines in the metastatic setting is active also in anthracycline-pretreated patients^{4,5}, but discouraged by the risk of cardiotoxicity associated with high cumulative doses⁶. In this perspective, NPLD is associated with a significantly

reduced risk of cardiotoxicity compared with conventional doxorubicin, even in patients with prior anthracycline exposure⁷.

As a consequence NPLD:

- 1) can be safely administered up to high cumulative doses and may represent an attractive drug for patients requiring anthracycline rechallenge;
- 2) can be considered an option in the adjuvant setting for patients at increased cardiologic risk; although data supporting this are lacking, the panel consider this option feasible on a patient-tailored basis;
- 3) is not recommended in the routine administration plus trastuzumab in the neoadjuvant setting, but available data indicate that this is a feasible combination⁸ that may be used in HER2-positive patients with inflammatory breast cancer or locally advanced disease⁹;
- 4) may be used in HER2-negative patients in combination with taxanes, as this is a viable option in clinical practice;
- 5) in combination with cyclophosphamide may be used as a first-line metastatic option due to the low cardiotoxic potential, which allows higher cumulative anthracycline dosages;
- 6) can be also considered in anthracycline-pretreated patients in subsequent lines of treatment if sequential monochemotherapy is the preferred choice.

Conclusions

In conclusion, the panelists agreed that NPLD is a viable option in breast cancer and that its use should be preferred to conventional anthracyclines, especially in those patients at risk of developing cardiotoxicity. Patients candidate to rechallenge with anthracyclines after adjuvant administration could be suitable for NPLD due to the possibility of a more prolonged treatment, not limited by cumulative dosages. In light of the cardiotox-

ic potential of new target-directed agents, such as trastuzumab and bevacizumab, their combinations with NPLD should be investigated in the adjuvant/neoadjuvant setting.

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