'Retarded Pharmaceuticals' Assuming a Clinical Role

Doxorubicin has played a major role in the treatment of breast cancer since the pioneering studies of Gianni Bonadonna and co-workers in the early 1970s [1], and this role was further refined as it was applied to adjuvant therapy. Unfortunately, acute toxicity as well as the threat of cardiomyopathy on repeated exposure rendered its palliative role particularly problematic [2]. Accordingly, its role in metastatic breast cancer has gradually lessened as its use in adjuvant regimens has become widely adopted. Such evolution has taken place in spite of many concerted efforts by pharmaceutical companies to find less toxic analogues [3] or to introduce protectors against specific toxicities [4].

'Passive targeting' relying on enhanced permeability and retention (EPR) of molecules in the tumor microenvironment has been demonstrated experimentally with polymer-linked compounds and with long-circulating liposomes as might be achieved through pegylation [5]. Comparisons of free doxorubicin versus pegylated liposomal doxorubicin (such as Caelyx®, Essex Pharma, Munich, Germany or Doxil®, Tibotech Therapeutics, Division of Ortho Biotech, Bridgewater, NJ, USA) in animals bearing human tumor xenografts consistently revealed a therapeutic advantage for the liposomes both in enhancing tolerance as well as its antitumor effect [6]. It is timely to review whether the expectation of such benefit has been fulfilled through this 'retarded pharmaceutical'.

Favorable clinical experience with pegylated liposomal doxorubicin was first reported in Kaposi's sarcoma and in ovarian cancer [7]. Trials in Kaposi's sarcoma confirmed remarkable accumulations of drug in the tumor, as well as equivalence of antitumor effects with lesser toxicity in comparison to doxorubicin or doxorubicin-containing regimens. In ovarian cancer, the activity of pegylated liposomal doxorubicin (Caelyx/Doxil) was demonstrated in several phase II and phase III trials and found to be similar to the activity of other second-line drugs such as topotecan [8]. A direct comparison with doxorubi-

cicin was not deemed necessary since this drug was dropped as being too toxic and insufficiently active for this palliative setting. However, nagging questions persist as to whether therapeutic advantages over the free drug have indeed been proven.

In the treatment of breast cancer, phase II and phase III trials with pegylated liposomal doxorubicin (Caelyx/Doxil) have extended these observations and allowed comparisons with the free drug, doxorubicin. In this disease, the therapeutic effects appear quite similar, although the toxicity spectrum as might be expected is radically different. In my view, one cannot extrapolate this equivalence to ovarian cancer (where the liposomal doxorubicin may be superior) or to other cancers such as sarcomas and lymphomas (where free doxorubicin has the established role). However, comparative clinical trials should continue to be encouraged in most disease sites where doxorubicin plays a role. Such clinical trials should not be confined to head-to-head comparisons in induction but also test the role of Caelyx as maintenance and in combinations.

As clinical experience with pegylated liposomal doxorubicin accumulates, several potential advantages emerge in the use of this drug over the parent compound. Starting with a purely practical issue, extravasation skin necrosis is not apparent with this formulation. We have stressed the safety of maintenance treatment provided every 4 to 6 weeks in patients with gynecologic cancer, and have also provided retrospective data from pooled clinical studies that no significant effects on left ventricular ejection fraction occurred in 34 patients not previously exposed to cardiotoxic drugs and who had received 500 mg/m² or more of the liposomal formulation [9, 10]. Finally, a role for pegylated liposomal doxorubicin in combination with other agents may emerge. In ovarian cancer, we have focused on two combinations: with carboplatin in platinum-sensitive recurrences [11], and with topotecan in platinum-resistant disease [12]. The latter agent is notoriously difficult to combine

with other myelosuppressive drugs, but an active and safe regimen was developed with Doxil/Caelyx and topotecan by 14-day infusion. In breast cancer, a combination of the liposomal compound with trastuzumab is proving safe, and impressive responses have been observed when the drug was combined with docetaxel alone or in combination with trastuzumab [13–15]. Moreover, as the experience of Mlineritsch et al. [16] indicates, one can safely consider such treatment even in patients previously exposed to anthracyclines.

In conclusion, clinical results are fulfilling some of the experimental premises that have led to the introduction and widespread use of formulations such as pegylated liposomal doxorubicin. As trials are launched to expand their clinical role, it is important to recognize the major differences that a retarded pharmaceutical such as Caelyx imparts on the pharmacology of doxorubicin, and how one might optimize its clinical use. Maintenance and combination chemotherapy are two major aspects to address in its future clinical development.

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