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Liposomal doxorubicin: emergent data in lymphoproliferative disease

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Doxorubicin is classified as an anthracycline antibiotic. Doxorubicin is an effective antineoplastic agent and is widely used as one of the components in multiple-drug chemotherapy in the treatment of Hodgkin's lymphoma, aggressive non Hodgkin's lymphomas, acute lymphoblastic leukaemia, metastatic breast carcinoma, ovarian carcinoma, lung carcinoma and sarcoma. However, the clinical utility of the drug is limited by irreversible cardiomiopathy. Doxorubicin-associated myocardial damage is cumulative, dose-related, progressive and may lead to congestive heart failure (CHF).[1] The incidence of CHF varies as the results of differences in study populations, treatment regimens, and the duration of follow-up. Von Hoff and coworkers[2] reported 3%, 7% and 18% of patients developed clinical congestive heart failure while receiving cumulative doses of 400, 550, and 700 mg/m^2 of doxorubicin respectively. In a retrospective analysis of three phase III trials in which patients received doxorubicin in combination with other chemotherapy agents[3,4] the estimated cumulative proportion of patients developing CHF was 5% at a cumulative doxorubicin dose of 400 mg/m^2, 26% at 550 mg/m^2, and 48% a 700 mg/m^2. A cumulative dose of 450 to 500 mg/m^2 generally is considered as a dangerous dose for inducing cardiotoxicity. However, considerable variation exists in an individual's susceptibility to developing chronic cardiomyopathy and CHF, and discontinuation of doxorubicin therapy prematurely using simply empiric maximal dose limits may defer those patients who may actually benefit from this powerful antineoplastic agent at highr dose. Acute or subacute cardiotoxicity immediately after infusion is rare and usually is transient. The chronic cardiomyopathy induced from anthracycline can be progressive and irreversible in some patients despite maximal medical therapy, whereas other patients may present with permanent reduction in left ventricular ejection fraction (LVEF) and persistent symptoms of CHF, or other experience gradual improvement in symptoms and LVEF after congestive heart failure therapy.

Cardiotoxicity occurs when metabolic free radicals cause lipid peroxidation.[5] Initially, damage to the heart is subclinical; however, continued treatment will lead to progressive myocyte damage. The resulting cumulative cardiac dysfunction may become evident during therapy, or in the months or years after the final doxorubicin dose. Several factors increase, or are thought to increase, a patients risk of developing anthracycline-induced cardiotoxicity.[6]

These include:
- higher cumulative anthracycline dose
- an increased rate of drug administration
- advanced or younger age
- mediastinal radiation
- being female
- pre-existing heart disease
- hypertension.

Liposomal doxorubicin

Liposomal encapsulation of anthracyclines has been investigated with a view to decreasing the cardiotoxicity and, therefore, improving the therapeutic index of the drugs.[7] The rationale used as a basis for the design of liposomal doxorubicin is that intravenously injected liposomes cannot exit the circulation through the tight capillary junctins found in healthy tissues such as the heart, but can exit through leaky tumor-associated vessels.[8]

Pharmacodynamic and pharmacokinetic properties

In preclinical studies of liposomal doxorubicin in dogs the peak distribution of doxorubicin to the heart and gastrointestinal mucosa was reduced compared with conventional doxorubicin. Liposomal doxorubicin was less cardiotoxic than conventional doxorubicin in two studies in dogs.[9]. In terms of drug distribution, radiolabeled liposomal doxorubicin was associated with lower levels of radioactivity in the

myocardium and gastrointestinal tissues of dogs, but higher levels in the liver, spleen, and bone marrow, compared with radiolabeled conventional doxorubicin. The pharmacokinetic properties of intravenous liposomal doxorubicin have been assessed in two single-dose studies. One was a substudy of a large, randomized, multicenter trial, in which 20 women with metastatic breast cancer received either liposomal or conventional doxorubicin 60 mg/m^2 (both in combination with cyclophosphamide 600 mg/m^2).[10] In the other study, 17 evaluable patients with solid tumors received liposomal doxorubicin 75 mg/m^2.[11] Metabolism and elimination of doxorubicin occur primarily by the hepatobiliary route: therefore dosage adjustment of liposomal doxorubicin may be necessary in patients with impaired hepatic function.

Tolerability

This issue was evaluated considering data from three well designed trials of liposomal doxorubicin in women with metastatic breast cancer.[12,13,14] There were no between-group differences in the incidence of hematologic or non-hematologic toxicities. The incidence of cardiotoxicity was significantly lower with liposomal doxorubicin, compared with conventional doxorubicin. More than twice as many conventional doxorubicin monotherapy recipient versus liposomal doxorubicin monotherapy recipients developed CHF or an asymptomatic reduction in LVEF (29% vs 13% p=0.0001) and the incidence of cardiotoxicity in conventional doxorubicin plus cyclophosphamide recipients was more than three times that in liposomal doxorubicin plus cyclophosphamide recipients (21% vs 6% p=0.0001).[12, 13] There was no significant between-group difference in the proportion of patients with cardiotoxicity when liposomal doxorubicin was compared with epirubicin (no patients experienced CHF). All or almost all, of the patients in any treatment group who experienced cardiotoxicity received a cumulative dose of doxorubicin of ≥300 mg/m^2 (the cumulative dose included doxorubicin received prior to trial entry). The estimated median cumulative dose of doxorubicin at the first occurrence of cardiac toxicity for liposomal vs conventional doxorubicin was > 2220 vs 480 mg/m^2 in one trial and 785 vs 570 mg/m^2 in another trial.

Therapeutic efficacy in non Hodgkin's lymphomas

The potential of liposomal doxorubicin as a replacement for conventional doxorubicin in the CHOP regimen has been assessed in two phase I/II trials in patients with newly diagnosed AIDS-related lymphoma,[15] or intermediate and high-grade lymphoma [16] and additionally in a phase II trial in elderly patients with diagnosis of advanced diffuse large B-cell lymphoma.[17] The overall objective response rate was 88% in AIDS-related NHL, 83% in the second study and 92% in elderly patients. The median duration of complete remission was in all studies ≥16 months.

Personal experience

From june 2003 we replaced the conventional doxorubicin with liposomal doxorubicin (Myocet 50 mg/m^2 in COMP and 25 mg/m^2 in MBVD) for the treatment of 29 patients. The patients were negatively selected according to factors that are thought to increase patients risk of developing anthracycline-induced cardiotoxicity: advaced age, high cumulative anthracyclines dose, pre-existing heart disease, hypertension. Twenty-four patients with NHL were treated with R-COMP and 5 Hodgkin's lymphoma with MBVD. The median age was 68 years (range 54-76). Three pts were stage I, 9 stage II, 7 stage III and 10 stage IV. According to histology: 20 were DLBL, 3 mantle cell lymphoma and one marginal zone lymphoma. According to IPI score, for NHL only, 8 pts were low risk, 8 low-intermediate, 7 intermediate-high and 1 high risk. Seven were pre-treated with doxorubicin (490 mg median cumulative dose), 15 pts showed impaired cardiac function (5 ischemic, 8 hypertensive and 2 hypokinetic). The median left ventricular ejection fraction (LVEF) at diagnosis was 59% (range 45%-70%). We performed cardiac evaluation at diagnosis, after three cycles and at the end of therapy. All pts but one had no change in LVEF, one patient (4%) presented a myocardial disfunction resolved with medical therapy. The average dose of liposomal doxorubicin for patients who concluded therapy was 465 mg (range 80-600 mg). At the moment 23 out 29 patients are evaluable for response: 17 pts obtained a complete remission (74%) three a partial remission with an overall response of 86%, one patient stopped therapy due to myocardial disfunction and two patients died one for a stroke and the other for gastrointestinal bleeding. After 143 cycles we have observed one toxic event and two concomitant complications. No significant hematological toxicity was recorded. Three pts died of disease and after a median observation period of 12 months (range 1-32) the overall survival was 80%.

We conclude that liposomal doxorubicin allows to treat patients with factors that are thought to increase a patients risk of developing anthracycline-induced cardiotoxicity which could limit the use of conventional anthracycline. Myocet is feasible and effective in a subset of patients with very negative characteristics at diagnosis. It reduces cardiotoxicity risk without reducing chemotherapeutic efficacy.

References

1. Marty M. Breast 2001; 10 Suppl. 2: 28-33.
2. Von Hoff DD, Layard MW, Basa P, et al. Ann Intern Med 1979; 91: 710-7.
3. Swain SM, Whaley FS, Ewer MS. Cancer 2003; 97: 2869-79.
4. Safra T. Oncologist 2003; 8 Suppl. 2: 17-24.
5. Batist G, Barton J, Chaikin P, et al. Expert Opin Pharmacother 2002; 3: 1739-51.
6. Pai VB, Nahata MC. Drug Saf 2000; 22: 263-302.
7. Rivera E. Oncologist 2003; 8 Suppl 2: 3-9.
8. Batist G. Breast 2001; 10 Suppl. 2: 16-21.
9. Swenson CE, Perkins WR, Roberts P, et al. Breast 2001; 10 Suppl. 2 : 1-7.
10. Swenson CE, Bolcsak LE, Batist G, et al. Anticancer Drugs 2003; 14: 239-46.
11. Mross K, Niemann B, Massing U, et al. Cancer Chemother Pharmacol 2004; 54: 514-24.
12. Batist G, Ramakrishnan G, Rao CS, et al. J Clin Oncol 2001; 19: 1444-54.
13. Chan S, Davidson N, Juozaityte E, et al. Ann Oncol 2004; 15: 1527-34.
14. Harris L, Batist G, Belt R, et al. Cancer 2002; 94: 25-36
15. Levine AM, Tulpule A, Espina B, et al. J Clin Oncol 2004; 22: 2662-70.
16. Tulpule A, Espina BM, Berman N, et al. Eur J Cancer 2001; 37 Suppl 6 S91.
17. Federico M, Dyer MJS, Caballero MD, et al. Blood 2004; 104 (11 Pt 2): 230b.