

Novel formulation of cytarabine and daunorubicin: A new hope in AML treatment

Lalit S. Raut

Abstract

Acute myeloid leukemia (AML) treatment has always been a challenge to the treating physician. Continuous efforts are being made to improve treatment outcomes in AML. CPX-351 is a pharmacologic advancement in this direction. It is a liposomal fixed drug combination of cytarabine and daunorubicin. Early studies indicate that it will play a big role in AML treatment. This is a short review about this drug.

Key words: CPX-351, cytarabine, daunorubicin, Acute myeloid leukemia, liposomes

Introduction

Treatment of acute myeloid leukemia (AML) continues to be a challenge. For more than three decades “7+3” chemotherapy with cytarabine and daunorubicin continues to be the standard induction chemotherapy. With this regimen, complete response (CR) is achieved in 60-80% of younger adults and cure rates are in the range of 5-60%. With intensive chemotherapies, CR rates are less in the elderly age group. Different modifications of “7+3” regimen like substitution of daunorubicin with mitoxantrone, use of double induction, and increasing the number of chemotherapy cycles were tried but without any advantage. Although some of the recent modifications like anthracycline dose intensification and addition of cladribine to the induction chemotherapy suggest improvement in the outcome of AML search for new ideas for improving the AML outcome continues and CPX-351 is one such modification destined to make a difference.

Some basics of combination chemotherapy

The “7+3” chemotherapy represents a cytogenetically rational approach to chemotherapy involving the combination of a non-cell cycle-active agent daunorubicin with a cycle-and phase-specific agent cytarabine. The ratio of individual agents in a combination determines the nature of action (synergism, antagonism, additive action, etc).^[1] But the variation in the uncoordinated pharmacokinetics of individual agent in free drug formulation alters the ratio and the nature of action *in vivo*.^[2] Hence, there is need to control the ratio of drugs after administration.

The ratiometric approach

The ratiometric approach aims at controlling drug ratios following systemic administration. Chemotherapeutic agents can be administered and maintained in a predetermined synergistic ratio by using nanoscale drug delivery vehicles. Cytarabine and daunorubicin can be combined in a desired ratio with formulation like a liposome. Liposomes are small artificial spherical vesicles created from cholesterol and natural nontoxic phospholipids. Liposomes retain the chemotherapeutic drugs in the synergistic ratio, minimize the first pass metabolism, and deliver drugs preferentially at the tumour site. They are promising systems of drug delivery opening new opportunities to enhance the effectiveness of existing and future treatment regimens.^[3]

What is CPX-351?

CPX-351 is a 100 nm bilamellar liposomal formulation of cytarabine and daunorubicin in a fixed 5:1 molar ratio. This ratio was chosen based on the study displaying the greatest degree of synergy and minimum antagonism *in vitro* and *in vivo*.^[4] In comparison with unencapsulated cytarabine plus daunorubicin combination it has enhanced activity. A total of one unit of CPX-351 is equal to 1.0 mg cytarabine plus 0.44 mg daunorubicin. CPX-351 is selectively ingested by leukemia cells providing enhanced efficacy and increased therapeutic index.^[5]

Pharmacology

CPX-351 exhibits first order elimination kinetics and prolonged elimination half-life. CPX-351 bioavailability is likely to be higher than conventional cytarabine/daunorubicin alone. Metabolism of drugs from the liposome in tissue is similar to that of the conventionally administered drug. The effective drug exposure of leukemic cells is extended by days beyond what is possible for conventionally delivered cytarabine and daunorubicin in addition to maintaining the desired 5:1 drug.^[6]

The same authors also suggested the maximally tolerated dose for CPX-351 of 101 U/m². The drug is administered on days 1, 3, and 5 by 90-min infusion for remission induction. Median half-life is 31.1 h (cytarabine) and 21.9 h (daunorubicin), with both drugs and their metabolites detectable more than 7 days after the last dose. The targeted 5:1 molar ratio is maintained at all dose levels for up to 24 h. The dose-limiting toxicities are hypertensive crisis, left ventricular dysfunction, and persistent cytopenias. The non-myelosuppressive adverse events, like rash, pruritus, stomatitis, nausea, vomiting, abdominal pain, decreased appetite, diarrhea, constipation, localized edema, cough, fatigue, headache, and insomnia, are qualitatively similar to 7+3 chemotherapy.^[7] A study testing different doses of the drug to see which dose is safer in children and adolescents is going on (<http://clinicaltrials.gov/ct2/show/NCT01943682>).

In relapsed AML >65 years age

The results from the preclinical studies encouraged the investigators from the USA to test the efficacy of CPX-351 in the relapsed AML. In this phase 2b study, relapsed AML patients aged more than 65 years were randomized to receive either the study drug or intensive salvage treatment of investigators choice. The efficacy was demonstrated by the fact that in comparison with the control arm the secondary end points like the aplasia rate and CR + CRi were superior with CPX-351. Improved efficacy was observed in patients with unfavorable European Prognostic Index (EPI) scores and in those with no history of hemopoietic stem cell transplant (HSCT). The study described prolonged myelosuppression and increase grade 3-5 sepsis with CPX-351. The authors concluded based on the initial data that

Access this article online

Quick Response Code:



Website: www.sajc.org

DOI: 10.4103/2278-330X.149950

Department of Medicine, Leukemia/BMT Division, Vancouver General Hospital, Vancouver, British Columbia, Canada

Correspondence to: Dr. Lalit Raut, E-mail: lalitraut76@yahoo.co.in

CPX-351 has substantial clinical activity and is safe compared with salvage therapy.^[8]

Newly diagnosed AML (60-75 years)

In newly diagnosed AML in 60-75 years age group, a randomized phase 2 trial was conducted to demonstrate the efficacy and safety of CPX-351. A total of 57 patients completed the study drug compared with 28 who received 7+3 chemotherapy. CPX-351 achieved clearance of leukemia (CR or CRi) in 61.4% of treated patients compared with 50% in the 7+3 arm. The investigators also reported evidence of prolonged cytopenia, some additional grade 3 infectious adverse events, and a few cases of cardiac toxicity in an otherwise well-tolerated treatment. The 30-day mortality was almost same in both groups.^[9]

A separate analysis of the 51 patients with secondary AML demonstrated that the response rates (CR + CRi rate: 56% versus 32%), event-free survival (EFS), and overall survival (OS) with CPX-351 after 12 of 24 month follow-up were better than 7+3. Even though the recovery from neutropenia and thrombocytopenia was slower after CPX-351 resulting in more infection and bleeding events, there was no increase in death. Non-myelosuppressive adverse events were qualitatively similar to 7+3.^[10]

Relapsed AML (18-65 years): Study 205

In study 205, relapsed AML in 18-65-years age group with CR1 duration of more than a month were randomized to receive CPX-351 ($n = 81$) or conventional AML induction of investigators choice ($n = 44$). CR/CRi was achieved in 51% patients in CPX-351 arm versus 41% in the other arm. Response rates were higher in patients with intermediate and high EPI risk groups. The 90-day all cause mortality was lesser than the conventional approach of treating the relapsed AML. The study reported that the toxicity profile of CPX-351 was similar to standard therapy.^[11]

Induction failure with 7+3

In the study by J. Lancet *et al.*, patients who crossed over from the 7+3 arm to CPX-351 arm showed clearance of leukemia, suggesting that CPX-351 may be active in patients with primary induction failure.^[9] The subsequent analysis suggested the possibility to safely administer CPX-351 after 7+3 and that clearance of leukemia can be achieved in patients with induction failure with 7+3.^[12] In future, this will provide an option for inducing remission after 7+3 failure in patients who refuse CPX-351 as the primary induction therapy.

Consolidation

To establish the optimum consolidation schedule, Tardi *et al.*, compared three schedules, namely, day (1,3), day (1,5), and day (1,7) in a mouse model. Their key findings were as follows: Consolidation therapy improves antileukemic efficacy, marrow drug level is higher with the day (1,3) and day (1,5) schedule, and the marrow recovery is similar with all three schedules. As the drug elimination kinetics for mice are roughly 2-fold faster than in humans, the authors suggested that the day (1,5) schedule most closely resembles a day (1,3) schedule in humans. Based on this xenograft model, day (1,3) consolidation schedule is followed by most of the studies.^[13]

Another study established the feasibility of sequential therapy with CPX-351 followed by reduced-intensity conditioning stem

cell transplant (RIC SCT) as a strategy for refractory myeloid leukemia and MDS. However, there was longer period between CPX-351 and transplant resulting in more frequent disease progression and complications leading to aborting transplant plans. Pretransplant administration of CPX-351 did not affect the engraftment rate.^[14]

Predictors of response to CPX-351

Multivariate analysis has identified three factors that each impact OS, EFS, and 60-day mortality: One related to AML biology (adverse cytogenetics), one to patient fitness (hypoalbuminemia), and a final factor related to stage of disease at start of treatment (treatment of newly diagnosed AML with frontline therapy).^[15] Patients with unfavourable EPI score have survival advantage.^[16] Another study suggested that prior therapy with hypomethylating agents is likely to have minimal impact on response to CPX-351.^[17] Prior SCT probably has a adverse effect on the response to CPX-351 and needs to be studied in further trials.^[18]

Phase 3 trial

A phase 3 trial to confirm the efficacy of CPX-351 compared with 7+3 as first line therapy in elderly patients (60-75 years) with high risk (secondary) AML is currently being carried out. The primary efficacy endpoint of this trial will be OS.^[19]

Other diseases

Apart from AML, CPX-351 is suggested as a potent antileukemic agent for a wide diversity of leukemia diagnoses.^[20]

Summary

Ratiometric dosing of anticancer drug combinations can profoundly influence therapeutic outcomes. With the evolving technologies like liposomes, it is possible to achieve this and CPX-351 is a good example. Early data suggest CPX-351 use in relapsed as well as newly diagnosed AML. It can be used as primary remission induction therapy, in induction failure patients and for consolidation with or without SCT. Though the EFS and OS data are emerging in favor of CPX-351, it is too early to predict anything on the basis of this short term follow-up data. Till then, let us be optimistic about the future of this drug.

References

1. Chou TC, Talalay P. Quantitative analysis of dose-effect relationships: The combined effects of multiple drugs or enzyme inhibitors. *Adv Enzyme Regul* 1984;22:27-55.
2. Mayer LD, Janoff AS. Optimizing combination chemotherapy by controlling drug ratios. *Mol Interv* 2007;7:216-23.
3. Mayer LD, Harasym TO, Tardi PG, Harasym NL, Shew CR, Johnstone SA, *et al.* Ratiometric dosing of anticancer drug combinations: Controlling drug ratios after systemic administration regulates therapeutic activity in tumor-bearing mice. *Mol Cancer Ther* 2006;5:1854-63.
4. Tardi P, Johnstone S, Harasym N, Xie S, Harasym T, Zisman N, *et al.* *In vivo* maintenance of synergistic cytarabine: Daunorubicin ratios greatly enhances therapeutic efficacy. *Leuk Res* 2009;33:129-39.
5. Harasym T, Lim W, Tardi P, Xie S, Fan M, Huang R, *et al.* Leukemia Cell-Selective Uptake of Cytarabine (Cyt) and Daunorubicin (Daun) Mediated by CPX-351 Liposome Injection in the Bone Marrow Compartment [abstract]. Presented at the 14th Congress of the European Hematology Association; 2009 June 4-7; Berlin, Germany. *Haematologica* 2009;94:1-694.
6. Feldman E, Lancet J, Kolitz JE, Trang JM, Mayer L, Louie A. Pharmacology of CPX-351: A Nano-scale Liposomal Fixed Molar Ratio Cytarabine-Daunorubicin for Patients with Advanced Leukemia. Presented at the 14th Congress of the European Hematology Association; 2009 June 4-7; Berlin, Germany. *Haematologica* 2009;94:1-694.

7. Feldman EJ, Lancet JE, Kolitz JE, Ritchie EK, Roboz GJ, List AF, *et al.* First-in-man study of CPX-351: A liposomal carrier containing cytarabine and daunorubicin in a fixed 5:1 molar ratio for the treatment of relapsed and refractory acute myeloid leukemia. *J Clin Oncol* 2011;29:979-85.
8. Cortes JE, Feldman EJ, Goldberg SL, Rizzieri DA, Paulsen KH, Louie AC, *et al.* CPX-351: A Randomized Phase 2b Study of CPX-351 v. Intensive Salvage Therapy in 65 Yo First Relapse AML Patients: Initial Efficacy and Safety Report. Presented at the ASH 2011 Annual Meeting; 2011 December 9-13; San Diego, CA. *Blood*; 2011:118.
9. Lancet J, Feldman E, Cortes J, Hogge D, Kovacsovics T, Tallman M *et al.* Phase II b Randomized Study of CPX-351 vs. Conventional Cytarabine+Daunorubicin in Newly Diagnosed AML Patients Aged 60-75: Safety Report [abstract]. Presented at the ASH 2009 Annual Meeting; 2009 December 9-13; New Orleans, LA. *Blood* 2009;114.
10. Lancet J, Cortes J, Kovacsovics T, Hogge D, Kolitz JE, Tallman MS, *et al.* CPX-351 versus cytarabine (CYT) and daunorubicin (DNR) therapy in newly diagnosed AML patients age 60-75: Safety and efficacy in secondary AML (sAML) [abstract]. Presented at ASCO 2011 Annual Meeting; 2011 June 3-7; Chicago, IL, USA. *J Clin Oncol* 2011;29.
11. Cortes JE, Feldman EJ, Goldberg SL, Rizzieri DA, Louie AC, Paulsen KH, *et al.* Phase II B, multicenter, randomised, open-label trial of CPX-351 (cytarabine: daunorubicin) liposome injection versus intensive salvage therapy in adult patients \geq 65 years old with aml in first relapse following an initial CR>1 month duration (study 205). Available from: http://www.celatorpharma.com/new/files/poster_2011_Cortes%20et%20al%20205%20ASH%202011.pdf [Last accessed on 2014 Feb 10].
12. Lancet J, Feldman E, Cortes J, Hogge D, Kovacsovics T, Tallman M *et al.* CPX-351 Can Induce Remission in AML Immediately After Failed Induction with Cytarabine and Daunorubicin [abstract]. Presented at ASCO 2010 Annual Meeting; 2010 Jun 4-8; Chicago, IL, USA. *J Clin Oncol*; 2010;28.
13. Tardi P, Harasym T, Dos Santos N, Lim W-S, Xie S, Ciofani T, *et al.* CPX-351, a liposome formulation containing a synergistic 5:1 molar ratio of cytarabine (Cyt) and daunorubicin (Daun), exhibits improved efficacy against human leukemia xenografts when administered at intermediate frequency in consolidation treatment [abstract]. Presented at the AACR 2009 Annual Meeting; 2009 April 18-22; Denver, CO: AACR; 2009.
14. Gergis, Usama, Roboz, Gail J, Ritchie, Ellen, *et al.* A novel sequential treatment utilizing cpx-351 as salvage chemotherapy followed by a reduced intensity conditioning allogeneic stem-cell transplantation for patients with refractory leukemia. Presented at the ASH 2011 Annual Meeting; 2011 December 9-13; San Diego, CA. *Blood*; 2011:118.
15. Feldman E, Lancet J, Kolitz JE, Hogge D, Tallman MS, Goldberg S, *et al.* Multivariate analysis of factors affecting overall survival, event free survival, and 60-day mortality among AML patients treated with CPX-351 or intensive chemotherapy [abstract]. Presented at the ASCO 2013 Annual Meeting; 2013 May 31-June 4; Chicago. *J Clin Oncol* 2013;31:15.
16. Goldberg S, Cortes J, Feldman EJ, Rizzieri DA, Kantarjian HM, Limor S, *et al.* Initial salvage therapy in first relapse AML: A phase IIb study of CPX-351 versus investigator's choice: A subset analysis by prognostic group [abstract]. Presented at the ASCO 2012 Annual Meeting; 2012 June 1-5; Chicago, IL, USA. *J Clin Oncol* 2012;30:15.
17. Lancet JE, Cortes JE, Kovacsovics T, Hogge D, Kolitz JE, Tallman MS, *et al.* The Impact of Prior Hypomethylating Agent Treatment among Secondary AML Patients Treated with CPX-351 or 7+3 Chemotherapy [abstract]. Presented at the 16th Congress of the EHA; 2011 June 9-12; London. *Haematologica* 2011;96:1-773.
18. Cortes JE, Feldman EJ, Goldberg SL, Rizzieri DA, Louie AC, Kolitz JE. Significance of Prior HSCT on the Outcome of Salvage Therapy with CPX-351 or Conventional Chemotherapy among First Relapse AML patients [abstract]. Presented at the ASH 2011 Annual Meeting; 2011 December 9-13; San Diego, CA. *Blood* 2011:118.
19. Phase III Study of CPX-351 Versus 7+3 in Patients 60-75 Years Old With Untreated High Risk (Secondary) Acute Myeloid Leukemia. Available from: <http://clinicaltrials.gov/ct2/show/results/NCT01696084> [Last accessed on 2014 Feb 10].
20. Tyner JW, Mayer L, Tardi P, Fletcher LB, Spurgeon SE, Kovacsovics T, *et al.* Evaluation of cpx-351 anti-leukemic activity against primary patient leukemia cells [abstract]. Presented at the ASH 2010 Annual Meeting; 2010 December 4-7; Orlando, FL. *Blood* 2010:116.

How to cite this article: Raut LS. Novel formulation of cytarabine and daunorubicin: A new hope in AML treatment. *South Asian J Cancer* 2015;4:38-40.

Source of Support: Nil. **Conflict of Interest:** None declared.