

Selected Summary

Risk-adapted Treatment of Acute Promyelocytic Leukemia with all-trans-retinoic Acid and Anthracycline Mono Chemotherapy : A Multicenter Study by the PETHEMA Group

Miguel A Sanz, Guillermo Martin, Marcos Gonzalez, Angel Leon, Chelo Rayon, Concha Rivas, Dolores Colomer, Elena Amutio, Francisco J Capote, Gustavo A Milone, Javier de la Serna, Jose Roman, Eva Barragan, Juan Bergua, Lourdes Escoda, Ricardo Parody, Silvia Negri, Maria J Calasanz and Pascual Boulfer

BLOOD 2004;103:1237-1243

SUMMARY

Prognosis of patients with acute promyelocytic leukemia (AML-M3) have improved significantly in the past decade. Currently, all transretinoic acid (ATRA) & anthracycline based chemotherapy is considered standard for remission induction. Following achievement of complete remission (CR) patients receive anthracycline based consolidation chemotherapy followed by maintenance using ATRA and oral low dose chemotherapy.

Present study explored use of ATRA with anthracycline in consolidation therapy. Patients were stratified according to risk group approach. In this multi-centric, prospective study 437 patients with de-novo AML-M3 with t(15:17) or PML-RAR α were enrolled in this multicentric, prospective study. The study was conducted between Nov, 1996 & Aug, 2002 and patients were divided into 2 groups : LPA-96 (Nov 1996-Oct 1999) & LPA 99 (Nov,99 –Aug, 02); 426 patients were evaluable for induction therapy.

For induction patients received oral ATRA - 45 mg/m²/d divided into 2 daily doses which was maintained until CR was achieved or for a maximum of 90 days and Idarubicin (12mg/m²/d) given as an intravenous bolus dose on day 2,4,6 and 8. For patients of 20 years of age or younger, the ATRA dose was adjusted to 25mg m²/d.

From Nov, 1999 the dose of idarubicin on day 8 was omitted for patients older than 70 years of age. In the LPA - 96 Group, all patients attaining complete remission received 3 cycles of consolidation therapy; the first course consisted of Idarubicin 5mg/m²/d on Day1 through 4. The second course consisted of mitoxantrone 10mg/m²/d by IV bolus daily on day1 through 5. The third course consisted of Idarubicin 12mg/m² on day 1.

In the LPA- 99 Group, patients with intermediate and high risk group received ATRA combined with reinforced consolidation chemotherapy. ATRA 45mg/m²/d was given on day1 to day 15 in combination with Idarubicin in the first course and of administering Idarubicin for 2 consecutive days instead of one in the third course.

The maintenance phase which was given to all PML/RAR α negative patients and consisted of 6MP (50mg/m²/d), methotrexate (15mg/m²/wk) and oral ATRA (45mg/m²/d) for 15 days every 3 months.

Of the 426 (LPA-96,n=175, LPA-99,n=251) evaluable patients, 384 achieved CR (90%, 95% CI 87 - 92%). Both the group had similar results for induction outcome. The only statistical significant result was in the cases which were >70 years of age ; CR- LPA-96 : CR -60% , LPA-99 –CR 75%. At the end of induction, molecular analysis was carried out in 355 patients; 173

(48.7%) tested positive. 382 patients who achieved CR received consolidation therapy. In the LPA-96 study 5/157 & in the LPA-99 group 2 of 227 patients had persistent molecular disease. 32 of 384 patients relapsed; 22/157 in LPA96, & 10/227 in LPA99). The 3 year cumulative incidence of relapse (CIR) was 20.15 in LPA -96 and 8.75 in LPA-99. For low risk patients from both studies, the 6 year cumulative incidence of relapse was 6.4%. The 3 year disease-free survival rates were 81% +/- 6% in LPA-96 and 90% +/- 5% in the LPA-99. The overall survival after 3 year was 78% ± 6% in LPA- 96 and 85% ± 5% in LPA-99 group.

COMMENTS

The simultaneous use of ATRA and Anthracyclines have significantly reduced the incidence of ATRA syndrome during induction of APML¹⁻² and its use during maintenance is associated with reduced risk of relapse.³⁻⁵

However, its role during consolidation is unclear. Present study have explored the use of ATRA during consolidation; with reinforcement of anthracyclines in consolidation therapy according to risk groups. The induction results of LPA96 and LPA-99 studies have confirmed virtual absence of leukemia resistance using ATRA and Idarubicin treatment alone. There was no significant risk of ATRA syndrome and haemorrhage associated mortality. Molecular monitoring of minimal residual disease had little outcome on overall relapse rates in low and intermediate risk patients. The significant improvement of the antileukemic efficacy in LPA- 99 study compared with LPA-96 was certainly caused by modified consolidation therapy (although it is not clear whether it is a result of ATRA or

chemotherapy or both). However, there were few limitations of this study; first this a non randomized control study, secondly follow up period for LPA-99 is relatively shorter compared to LPA-96 (21 vs 48 months). Positive points were - this study was multicentric and was without selection bias and eligibility criteria were unchanged throughout the study.

Thus, the benefit of ATRA and reinforced chemotherapy in consolidation therapy should be studied in all risk categories and should be settled by randomised control trial (s) and with longer follow up.

REFERENCES :

1. Tallman MS, Nabhan C, Fausnar JH. Acute promyelocytic leukemia; evolving therapeutic strategies. *Blood* 2002;99:759-767.
2. S de Botton, S Chevret, V Coiteux. Early onset of chemotherapy can reduce the incidence of ATRA syndrome in newly diagnosed acute promyelocytic leukemia with low white blood cell counts: results from APL 93 trial. *Leukemia* 2003;17:339-342.
3. Tallman MS, Andersen JW, Schiffer CA. All transretinoic acid in acute promyelocytic leukemia. *NEJM* 1997;337:1021-1028.
4. Ohno R, Asou K, Ohnishi K. Treatment of acute promyelocytic leukemia: strategy toward further increase of cure rate. *Leukemia* 2003;17:1454-1463.
5. Fenaux P, Claude C, Sylvie C. A Randomized comparison of ATRA followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. *Blood* 1999;94:1192-1200.
6. Sanz MA, Martin G, Rayon C. A modified AIDA protocol with anthracycline based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RAR α positive acute promyelocytic leukemia. *Blood* 1999;94:3015-3021.

Ravi Sekhar Patnaik

Department of Medical Oncology
Institute Rotary Cancer Hospital, AIIMS,
New Delhi