UniversityHospital Heidelberg

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

Characteristics and Outcome of Therapy-Related Acute Promyelocytic Leukemia After Different Front-line Therapies

Sabine Kayser,* Julia Krzykalla, Michelle A. Elliott, Kelly Norsworthy, Patrick Gonzales, Robert K. Hills, Maria R. Baer, Zdeněk Ráčil, Jiri Mayer, Jan Novak, Pavel Žák, Tomas Szotkowski, David Grimwade, Nigel H. Russell, Roland B. Walter, Elihu H. Estey, Jörg Westermann, Martin Görner, Axel Benner, Alwin Krämer, B. Douglas Smith, Alan K. Burnett, Christian Thiede, Christoph Röllig, Anthony D. Ho, Gerhard Ehninger, Martin Tallman, Mark J. Levis, Uwe Platzbecker

***Department of Internal Medicine V**
University Hospital of Heidelberg
and German Cancer Research Center (DKFZ) Heidelberg
Germany

7th International Symposium on Acute Promyelocytic Leukemia

Background

- Information on the true incidence of t-APL is scarce[1]
- However, increasing incidence has been suggested, based on growing reports of patients with t-APL in recent years [2]
- The chemotherapy-free regimen with ATO/ATRA has been shown to be very effective in *de novo* low- to intermediate- risk APL[3]
- So far, this regimen has not been evaluated in a large cohort of t-APL patients

ATO, arsenic trioxide; ATRA, all-trans retinoic acid;
t-APL, therapy-related acute promyelocytic leukemia.

1. Sanz MA, et al. Blood. 2009;113:1875-91.
2. Ravandi F. Haematologica. 2011;96:493-495.
3. Lo-Coco F, et al. N Engl J Med. 2013;369:111-21.

Objectives

To evaluate:

- Biological and clinical characteristics of t-APL
- Outcome according to different treatment strategies

Patients and Treatment

- Cohort:
  - N = 103 (international cooperation)
  - Treated between 1991 and 2015
  - 11 study groups/institutions in the USA and Europe
- Median age:
  - 59 years (range 18–80)
- Treatment:
  - CTX/ATRA n = 53[a]
  - ATO/ATRA n = 24[b]
  - CTX/ATO/ATRA n = 19[3]
  - ATRA only n = 7

[a] Idarubicin + ATRA or daunorubicin + ATRA as induction; different CTXs + ATRA as consolidation.
[b] n = 21, according to Lo-Coco et al.[1] and n = 3, according to Burnett et al.[2]

CTX, chemotherapy.

1. Lo-Coco F. et al. N Engl J Med. 2013;369:111-21.
2. Burnett AK, et al. Lancet Oncol. 2015;16:129.
3. Gore SD, et al. J Clin Oncol. 2010;28:1047-1053.

Primary Diseases

		N	%
Solid cancer		**87**	**84**
	Breast	38	
	Prostate	14	
	Head and neck	9	
	Gastrointestinal	9	
	Other	14	
Hematologic malignancy		**8**	**8**
	Non-Hodgkin lymphoma	5	
	Hodgkin lymphoma	3	
Autoimmune		**8**	**8**

Median latency period from prior malignancy/non-malignant disorder to the onset of t-APL: 3.5 years (range 0.4–26.2)

Baseline Characteristics

	CTX/ ATRA	ATO/ ATRA	CTX/ ATO/ATRA	ATRA only	P-value
Median age, years	57.0	60.0	56.0	69.6	0.002
Cytogenetics (%)					
t(15;17) sole	77	57	87	75	0.20
t(15;17) & abn	23	43	13	25	
Risk categorization[a] (%)					
Low/Intermediate	80	87	79	71	0.63
High	20	13	21	29	
***FLT3*-ITD (%)**					
Mutated	74	57	29	33	0.10
Unmutated	26	43	71	67	
M3 (%)	94	87	100	86	0.23
M3v (%)	6	13	–	14	

No difference in: gender; hemoglobin level; LDH; PB and BM blasts; WBC count

[a] Prognostic score of APL (Sanz Score):[1] WBC < 10.0 g/L (low- to intermediate-risk) vs WBC ≥ 10.0 g/L (high-risk)[1].

abn, abnormality; BM, bone marrow; FAB, French–American–British; *FLT3*-ITD, internal tandem duplication of the FMS-like tyrosine kinase 3 gene; M3, M3, APL subtype according to the (FAB) classification of acute myeloid leukemia; M3v, microgranular variant; LDH, lactate dehydrogenase; PB, peripheral blood; WBC, white blood cell.

1. Sanz MA, et al. Blood. 2009;113:1875-91.

Response to Induction Therapy[a]

% (N)	CTX/ ATRA	ATO/ ATRA	CTX/ATO/ ATRA	ATRA only
CR	**78** (40)	**100** (23)	**95** (18)	**57** (4)
PR	**10** (5)[b]	–	–	–
ED	**12** (6)	–	**5** (1)	**43** (3)

[a] Response data were available in n = 100/103 (97%) patients; (missing data: CTX/ATRA, n = 2; ATO/ATRA, n = 1).
[b] All patients went on to consolidation and achieved CR thereafter.

CR, complete remission; ED, early death; PR, partial remission.

Competing Events in Remission

Numbers	CTX/ ATRA	ATO/ ATRA	CTX/ATO/ ATRA	ATRA only
Relapse of the prior malignancy	2	1	1	3
Infections	2	1	-	-
t-AML	2[a]	-	-	-
Relapse of t-APL	3[b]	-	-	-
Other[c]	2	1	-	-

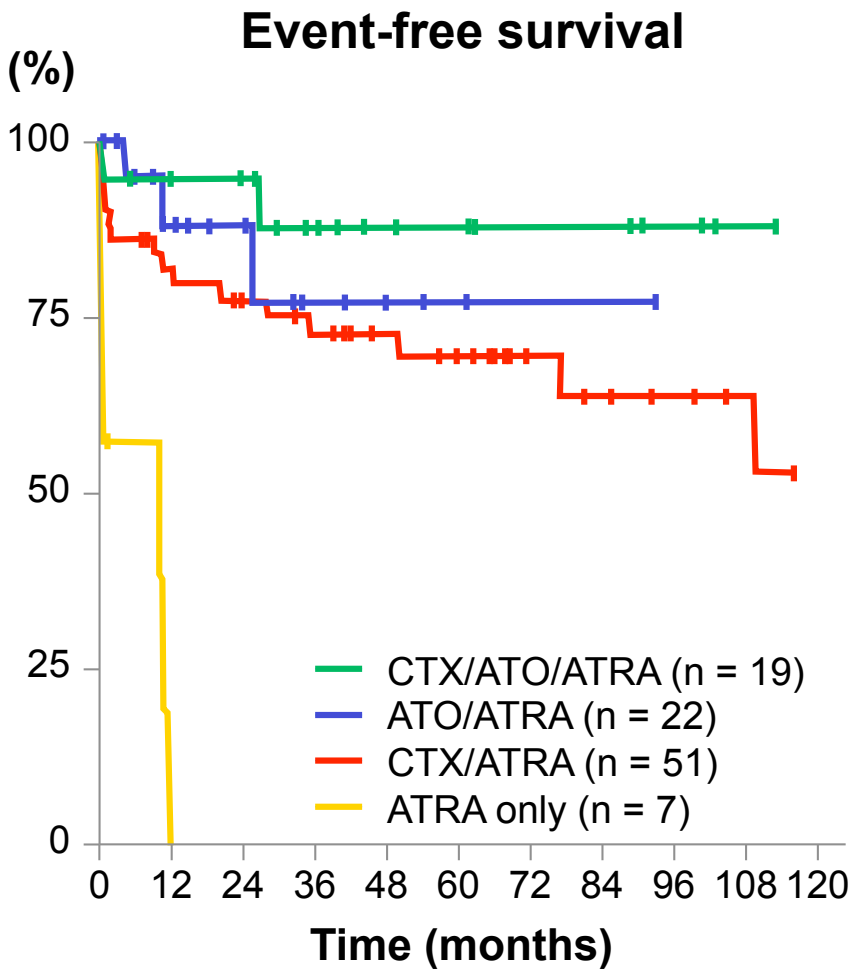
[a] Both patients were refractory to salvage CTX and died shortly thereafter.

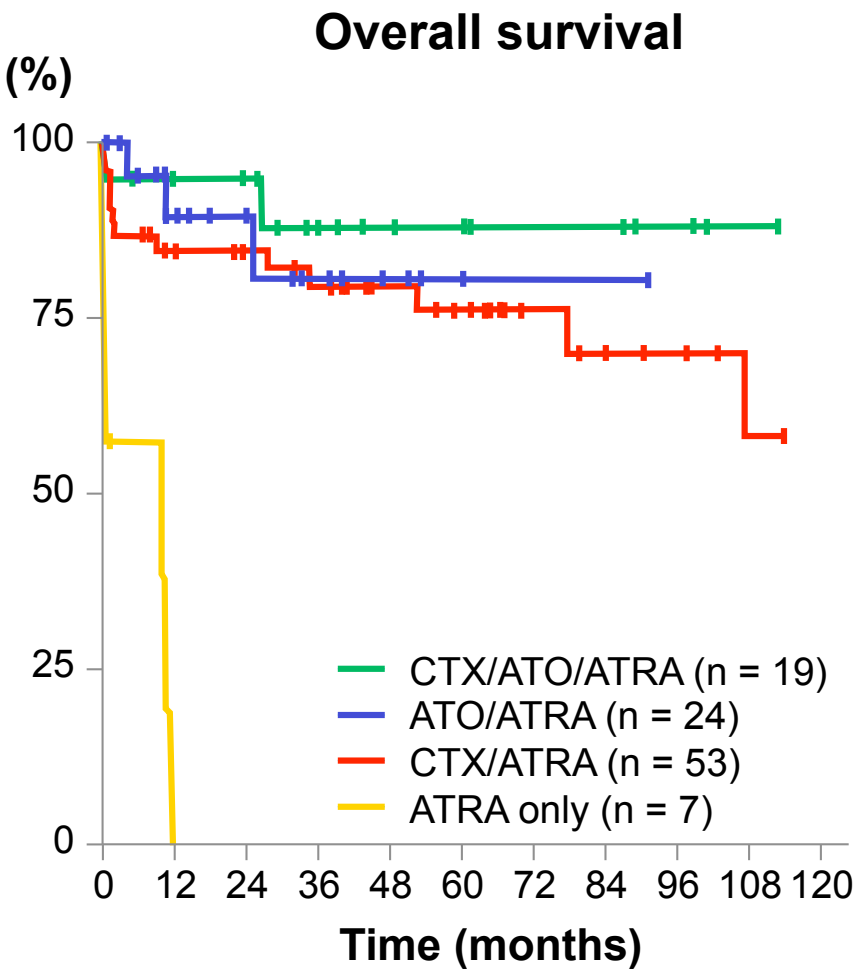
[b] Patients were successfully salvaged with ATO/ATRA +/- CTX and went on to autologous (n = 1) or allogeneic transplant (n = 2).

[c] Development of DLBCL (CTX/ATRA, n=1); unknown cause (CTX/ATRA, n=1); cardiopulmonary arrest during therapy (ATO/ATRA, n = 1).

DLBCL, diffuse large B-cell lymphoma; t-AML, therapy-related acute myeloid leukemia.

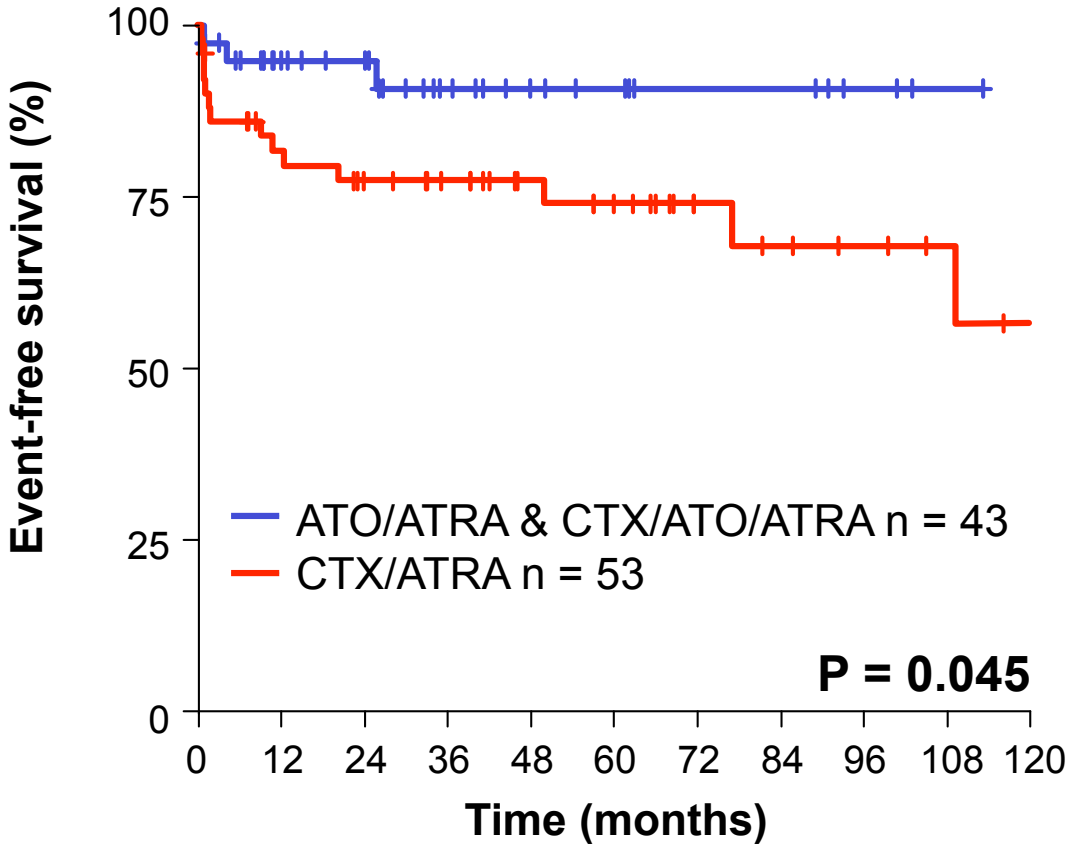
Survival according to Treatment Groups



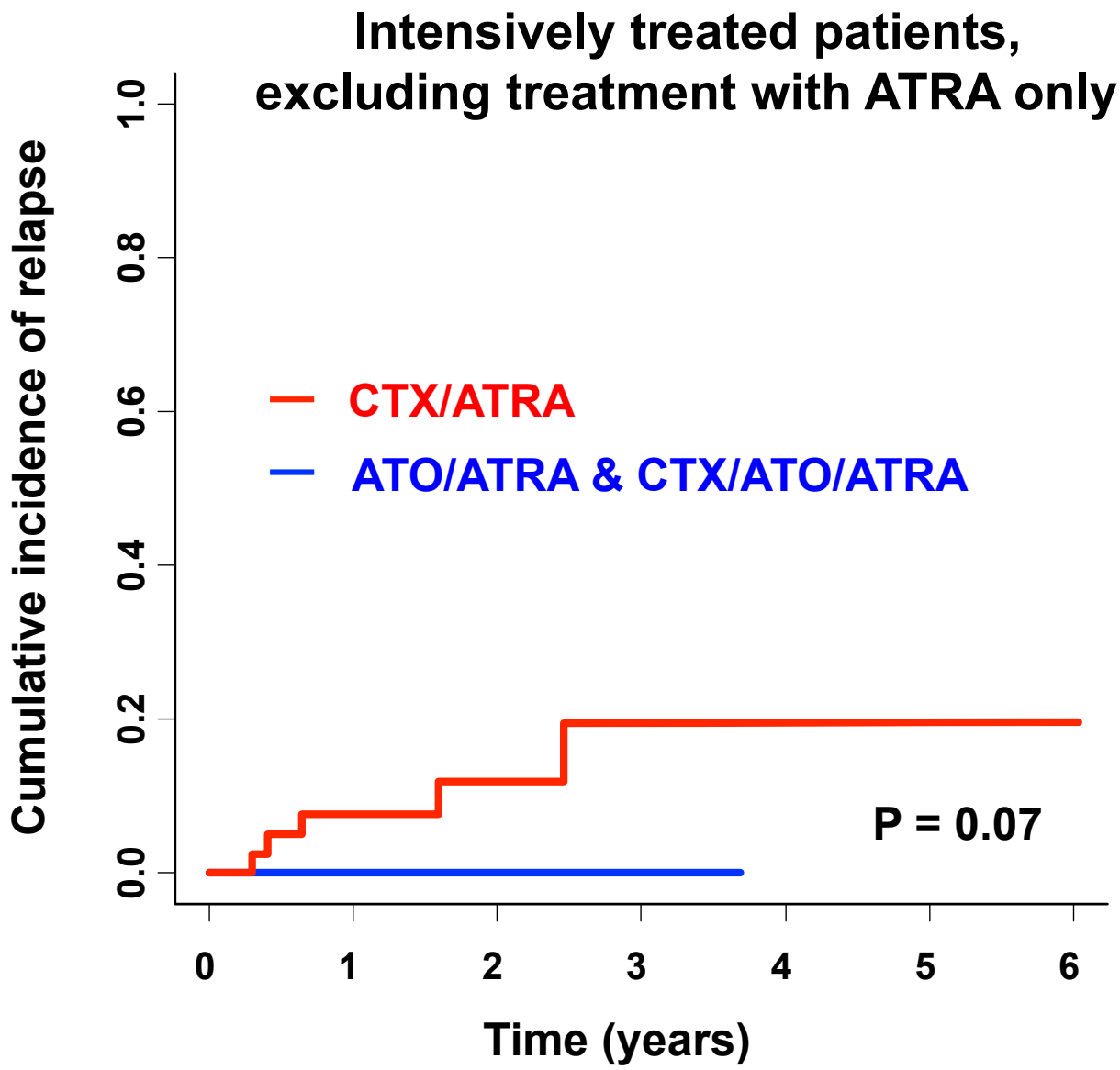


Event-Free Survival Excluding Death due to Primary Malignancy

Intensively treated patients, excluding treatment with ATRA only



Cumulative Incidence of Relapse according to Treatment Groups



Conclusions

- Distribution of clinical and biological characteristics in t-APL is comparable with what has been described in *de novo* APL
- Excellent and sustained response, as well as favorable survival, following ATO-based regimens for first-line treatment
- ATO, when added to ATRA or CTX/ATRA, is a feasible treatment and leads to better outcomes compared with CTX/ATRA

Mark Levis
Kelly Norsworthy
B. Douglas Smith
Johns Hopkins University

David Grimwade
King's College London
deceased

Robert K. Hills
Cardiff University
School of Medicine

Alan K. Burnett
Nigel H. Russell
Nottingham University Hospitals NHS Trust

Zdeněk Ráčil, Jiri Mayer,
Jan Novak, Pavel Žák,
Tomas Szotkowski
The Czech Leukemia Study Group for Life

Martin Tallman
Patrick Gonzales
Memorial Sloan Kettering Cancer Center

Roland B. Walter
Elihu H. Estey
Fred Hutchinson Cancer Research Center

Christoph Röllig
Christian Thiede
Uwe Platzbecker
Gerhard Ehninger
University of Dresden
Study Alliance Leukemia

Maria R. Baer
University of Maryland School of Medicine

Michelle A. Elliott
Mayo Clinic Rochester

Jörg Westermann
Charité Berlin

Martin Görner
Klinikum Bielefeld Mitte

Axel Benner
Julia Krzykalla
German Cancer Research Center Heidelberg

Sabine Kayser
Anthony D. Ho
Alwin Krämer
University Heidelberg