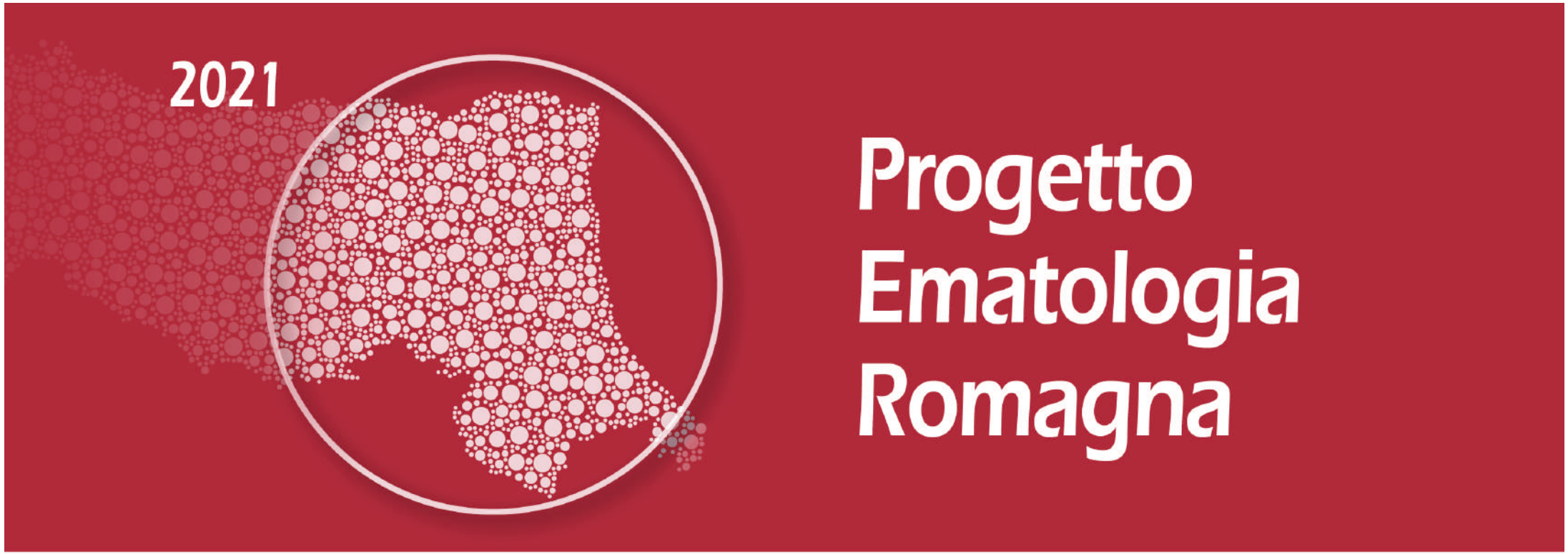

La Leucemia Acuta Promielocitica: Introduzione

Marco Vignetti

La Leucemia Acuta Promielocitica: Introduzione

Marco Vignetti

La storia della Leucemia Acuta Promielocitica è quasi miracolosa. Dopo pochi decenni la ricerca ha trasformato una malattia altamente letale in una delle forme più guaribili di leucemia

SISTEMA SANITARIO REGIONALE
AZIENDA OSPEDALIERA UNIVERSITARIA POLICLINICO UMBERTO I

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche.

Acta Medica Scandinavica. Vol. CLIX, fasc. III, 1957.

From the Medical Department A, Rikshospitalet, Oslo. Physician in chief: Professor P. A. Øwren.

Acute Promyelocytic Leukemia.

By

LEIF K. HILLESTAD.

(Submitted for publication August 13, 1957.)

This paper deals with three cases of a special type of acute myelogenous leukemia. One of the cases (case 1) has previously been described by Stormorken (1956). As far as can be seen from the literature, this type of leukemia has not been recognized as a distinct clinical entity before.

The most outstanding clinical feature is its very rapid downhill course. This is due to a severe bleeding tendency caused mainly by fibrinolysis (Astrup 1956, Macfarlane and Pilling 1946) and in part by the accompanying thrombocytopenia.

The white blood cell picture in the peripheral blood resembles that of the more chronic forms of leukemia, as it is dominated by promyelocytes and myelocytes with very few myeloblasts.

A logical name for this type of leukemia is *acute promyelocytic leukemia.*

Il primo articolo che la descrive è del 1957

Acta Medica Scandinavica. Vol. CLIX, fasc. III, 1957.

From the Medical Department A, Rikshospitalet, Oslo. Physician in chief: Professor P. A. Øwren.

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The white blood cell picture in the peripheral blood resembles that of the more chronic forms of leukemia, as it is dominated by promyelocytes and myelocytes with very few myeloblasts.

A logical name for this type of leukemia is *acute promyelocytic leukemia.*

Nell'articolo vengono descritti pazienti con gravi emorragie, fibrinolisi, rapido peggioramento delle condizioni cliniche e presenza di promielociti nel sangue periferico e midollo

L'inizio

«…Partimmo in tre, io, Ottaviani e Manai, ognuno con la propria macchina.

Viaggiammo tutta la notte e tutto il giorno, sull'Aurelia – l'autostrada ancora non esisteva – e arrivammo a Roma che era già tardi. Attraversammo tutta la città e, finalmente, fermai la mia macchina davanti al Policlinico Umberto I.»

Era il ***27 dicembre 1957****.*

BLOOD *The Journal of Hematology*

AUGUST, 1957 VOL. XII, NO. 8

Variation in the Duration of Survival of Patients with Acute Leukemia

By BRIAN MACMAHON AND DONALD FORMAN

RESULTS

Variation by Cell Type

Percentage survival for various periods after diagnosis is shown for the total 623 patients in figure 1. Almost half the patients died before the end of the first month after diagnosis, and half again of the survivors to the first month died

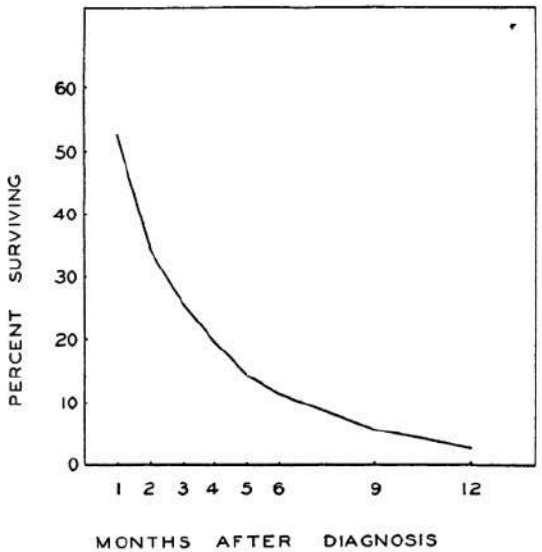
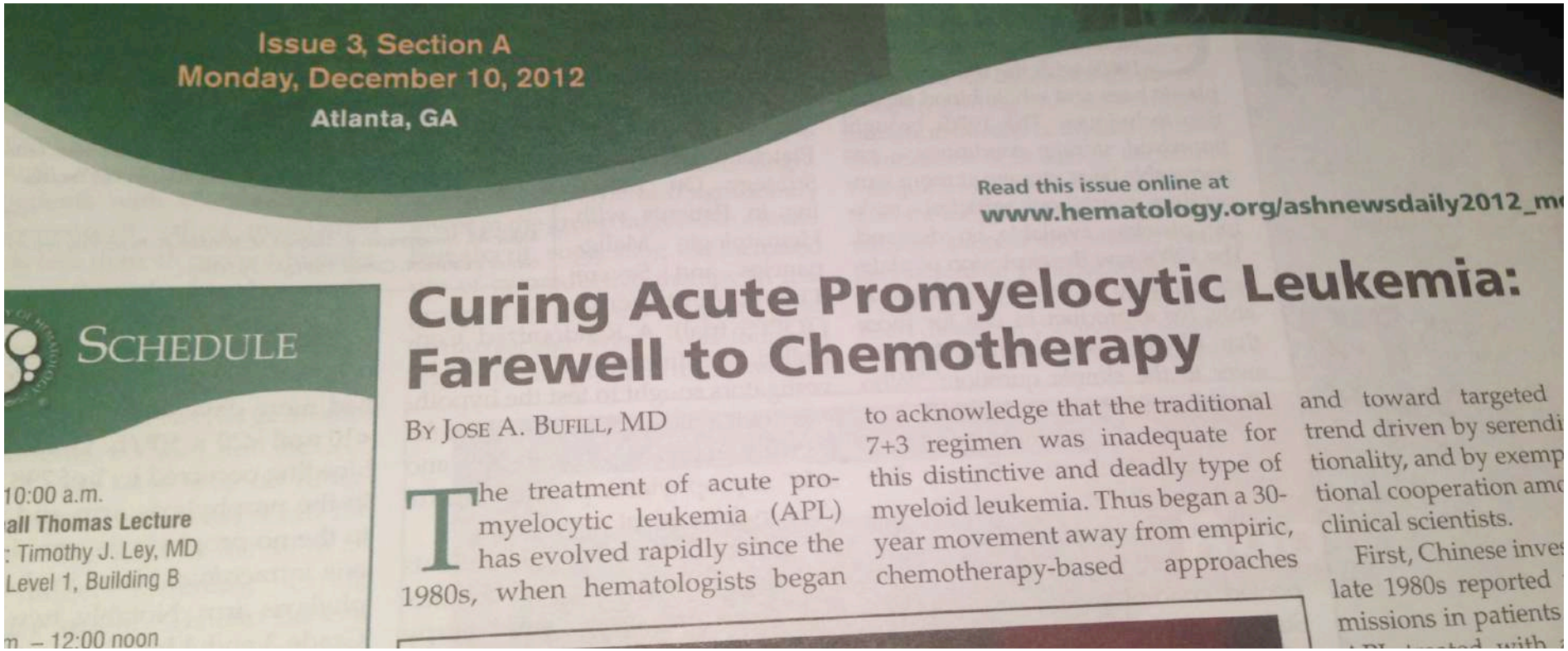


FIG. 1.—Percentage of patients with acute leukemia surviving for various periods after diagnosis, Brooklyn, 1943-52.

. . .chi non vorrebbe arrivare a un risultato così !



Issue 3, Section A
Monday, December 10, 2012
Atlanta, GA

Read this issue online at
www.hematology.org/ashnewsdaily2012_m

SCHEDULE

10:00 a.m.
all Thomas Lecture
: Timothy J. Ley, MD
Level 1, Building B

m – 12:00 noon

Curing Acute Promyelocytic Leukemia: Farewell to Chemotherapy

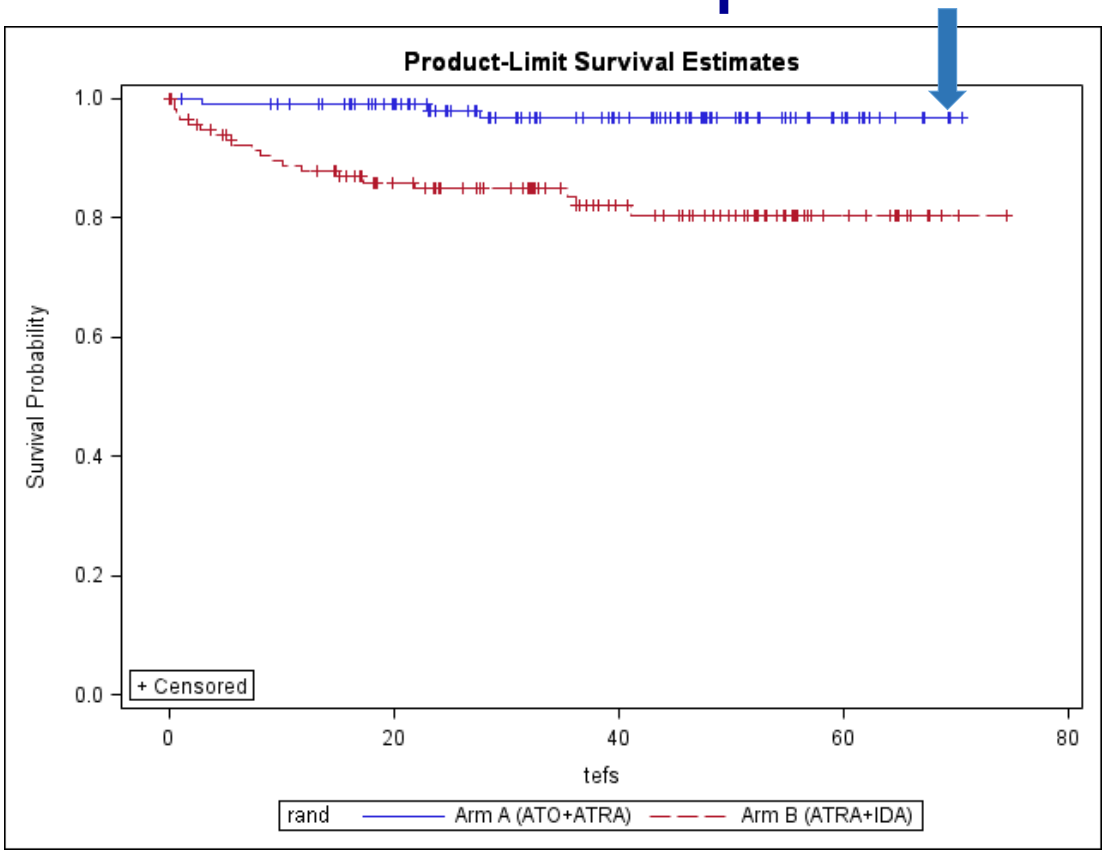
By Jose A. Bufill, MD

The treatment of acute promyelocytic leukemia (APL) has evolved rapidly since the 1980s, when hematologists began to acknowledge that the traditional 7+3 regimen was inadequate for this distinctive and deadly type of myeloid leukemia. Thus began a 30-year movement away from empiric, chemotherapy-based approaches and toward targeted
trend driven by serendi
tionality, and by exemp
tional cooperation amo
clinical scientists.

First, Chinese inves
late 1980s reported
missions in patients

Leucemia Acuta Promielocitica

30 anni dopo



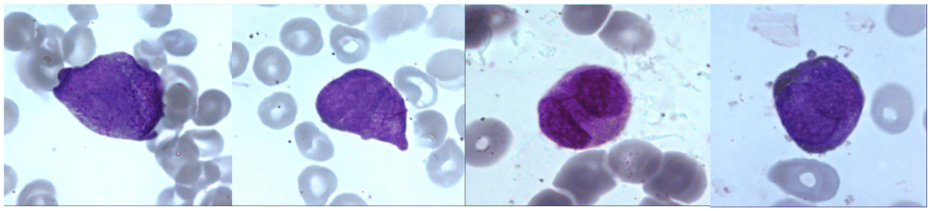
ACUTE PROMYELOCYTIC LEUKEMIA

Hypergranular or typical APL (M3)

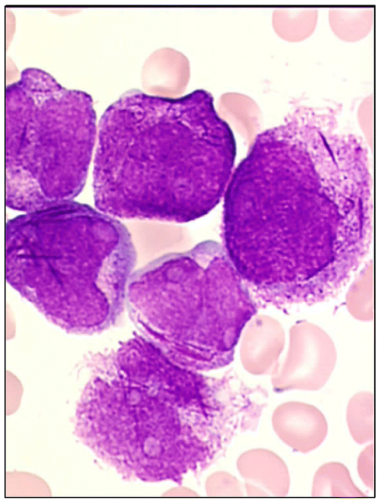
- 60% to 70% of cases.
- Low white blood cell count.
- Abnormal promyelocytes with numerous red to purple cytoplasmic granules that are typically darker and larger than normal neutrophil granules.
- Identifiable faggot/matchstick cells with numerous Auer rods.

Hypogranular or microgranular APL (M3v)

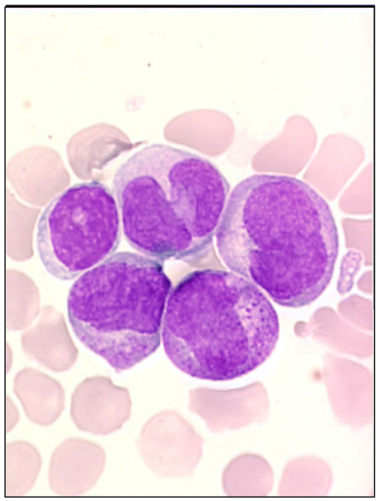
- Leukocytosis.
- Numerous abnormal promyelocytes readily identified on a peripheral blood smear.
- Irregular nucleus and granulations sparser and finer compared with the hypergranular form.
- Faggot cells with multiple Auer rods less commonly seen.



AML-3

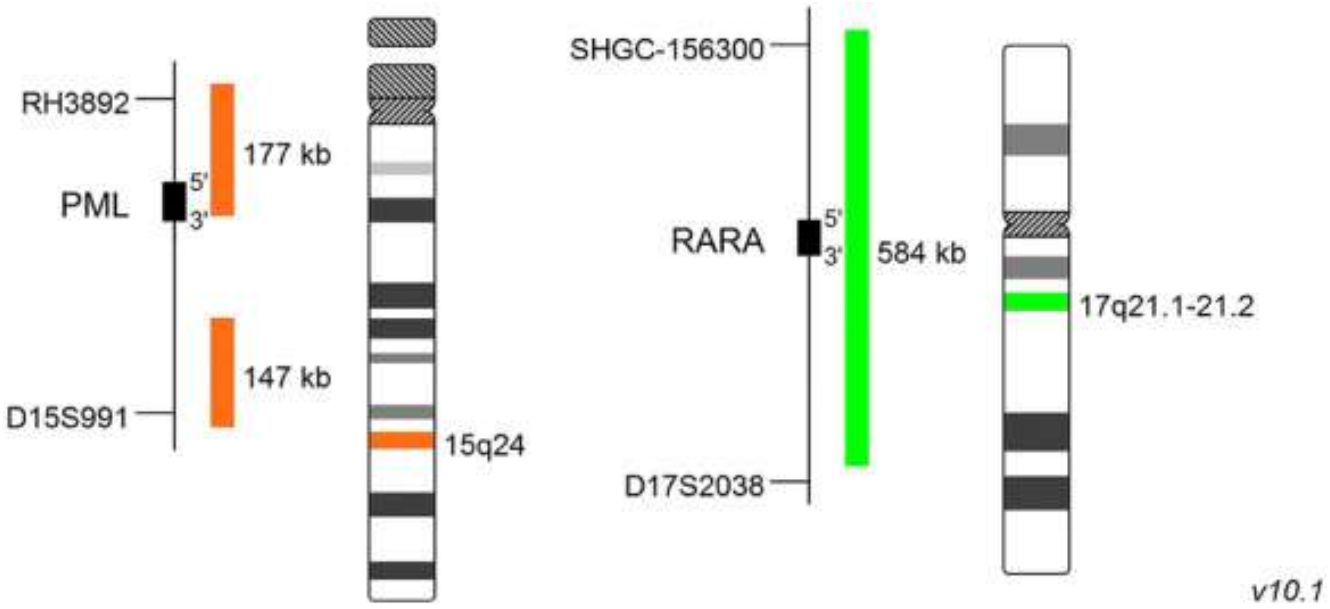


AML-3v



https://link.springer.com/article/10.1007/s40487-018-0091-5

La malattia è un raro sottotipo di leucemia acuta mieloide (<10%) con una incidenza stimata in 0.1/100.000 nei paesi occidentali.



La APL è caratterizzata a livello molecolare da una traslocazione cromosomica che unisce il gene PML presente sul cromosoma 15 con quello del recettore Alpha dell'acido retinoico (RARa) sul cromosoma 17

Data on large published series of APL patients treated with combinations of cytotoxic agents during the pre-ATRA era

Reference	Period	No. of patients	Induction regimen	CR (%)	Median DFS
Marty et al. [25]	1972–1982	60	DNR	70	17 months
		18	DNR + AraC	72	48 months (maintenance)
Cordonnier et al. [37]	1972–1982	57	DNR + AraC ± other	53	11 months
Kantarjian et al. [38]	1973–1984	60	Amsa or DNR + AraC	53	15 months
			Adr + AraC ± other		NA (maintenance)
Goldberg et al. [39]	1974–1985	34	DNR or Adr + AraC	74	24 months
Hoyle et al. [40]	1976–1986	115	DNR + AraC + TG	60	13 months
Sanz et al. [41]	1976–1986	34	DNR	68	24 months
Cunningham et al. [42]	1974–1983	53	DNR or Amsa + AraC + TG	72	15 months
Rodeghiero et al. [31]	1984–1987	131	DNR	67	NA
		137	DNR or Adr + AraC ± other	58	NA
Thomas et al. [43]	1974–1989	67	DNR + AraC ± other	64	16 months
Fenaux et al. [29]	1974–1988	70	DNR	80	17 months
			DNR + AraC		NA (maintenance)
			Amsa or RBZ + AraC		

Adr adriamycin, *Amsa* amsacrine, *AraC* cytarabine, *CR* complete remission, *DFS* disease-free survival, *DNR* daunorubicin, *NA* not available, *RBZ* rubidazone, *TG* thioguanine

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7360001/

1977

Acta Haematologica

Acute Promyelocytic Leukemia: Results of Therapy and Analysis of 13 Cases

Ruggero D. · Baccarani M. · Guarini A. · Gugliotta L. · Gobbi M. · Ricci P. · Zaccaria A. · Lauria F. · Tomasini I. · Fiacchini M. · Santucci M.A. · Tura S.

Author affiliations

Keywords: Acute promyelocytic leukemia · Acute myeloid leukemia · Daunomycin · Platelet transfusion

Acta Haematol 1977;58:108–119

https://doi.org/10.1159/000207816

https://doi.org/10.1159/000207816

1984

ELSEVIER

Leukemia Research
Volume 8, Issue 4, 1984, Pages 729-735

Sequential combination of high dose ARA-C (HiDAC) and asparaginase (ASP) for the treatment of advanced acute leukemia and lymphoma ☆

Sergio Amadori, Giuseppe Papa, Giuseppe Avvisati, Susanna Fenu, Bruno Monarca, Maria Concetta Petti, Alessandro Pulsoni, Franco Mandelli

https://doi.org/10.1016/0145-2126(84)90021-3

1988

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY
British Society for Haematology

Acquired alpha-2-antiplasmin deficiency in acute promyelocytic leukaemia

Giuseppe Avvisati, Jan W. Ten Cate, Augueste Sturk, Roy Lamping, Maria C. Petti, Franco Mandelli

First published: September 1988 | https://doi.org/10.1111/j.1365-2141.1988.tb02432.x | Citations: 73

1989

THE LANCET
Volume 334, Issue 8655, 15 July 1989, Pages 122-124

TRANEXAMIC ACID FOR CONTROL OF HAEMORRHAGE IN ACUTE PROMYELOCYTIC LEUKAEMIA

Giuseppe Avvisati [a], HarryR. Büller [b], JanWouterTen Cate [b], Franco Mandelli [a]

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Abstract

In a double-blind study, 12 consecutive patients with acute promyelocytic leukaemia were randomised either to tranexamic acid (TA group) or to placebo (control group) for 6 days to see whether inhibition of fibrinolysis would reduce haemorrhage and transfusion requirements. The total study period was 14 days. In the TA group, there were fewer haemorrhagic episodes, as determined by a scoring system. Packed red cell transfusion requirements decreased; and fewer additional platelet concentrate transfusions were needed. These beneficial effects were more pronounced in the second week. There were no thromboembolic complications.

https://doi.org/10.1016/S0140-6736(89)90181-5

Hematological ONCOLOGY

Article

Terminal transferase positive acute myeloid leukemia: Immunophenotypic characterization and response to induction therapy

Dr. Francesco Lo Coco, Manuela Lopez, Daniela Pasqualetti, Enrico Montefusco, Arturo Cafolla, Bruno Monarca, Cecilia Sgadari, Giulio De Rossi

First published: March/April 1989 | https://doi.org/10.1002/hon.2900070208 | Citations: 12

https://doi.org/10.1002/hon.2900070208

European Journal of Haematology

Idarubicin in combination with intermediate-dose cytarabine in the treatment of refractory or relapsed acute leukemias*

Angelo M. Carella, Ester Pungolino, Gabriella Piatti, Eugenia Gaozza, Sandro Nati, Mauro Spriano, Domenico Giordano, Tiziana D'Amico, Eugenio Damasio

First published: October 1989 | https://doi.org/10.1111/j.1600-0609.1989.tb00304.x | Citations: 3

* Supported by Associazione Italiana Ricerca sul Cancro (AIRC) 1989.

https://doi.org/10.1111/j.1600-0609.1989.tb00304.x

1990

Idarubicin (4-demethoxydaunorubicin) as single agent for remission induction of previously untreated acute promyelocytic leukemia: A pilot study of the Italian cooperative group GIMEMA

G. Avvisati, F. Mandelli, M. C. Petti, M. L. Vegna, A. Spadea, V. Liso, G. Specchia, C. Bernasconi, E. P. Alessandrino, C. Piatti, A. M. Carella

First published: April 1990 | https://doi.org/10.1111/j.1600-0609.1990.tb00389.x | Citations: 47

https://doi.org/10.1111/j.1600-0609.1990.tb00389.x

Immunological definition of acute promyelocyte leukemia (FAB M3): A study of 39 cases

G. De Rossi, G. Avvisati, S. Coluzzi, S. Fenu, F. LoCoco, M. Lopez, M. Nanni, D. Pasqualetti, F. Mandelli

First published: September 1990 | https://doi.org/10.1111/j.1600-0609.1990.tb00446.x | Citations: 35

This work was partially supported by Grant 60% MPI Facolta

https://doi.org/10.1111/j.1600-0609.1990.tb00446.x

MULTICENTER STUDY | JUNE 1, 1990

Early deaths and anti-hemorrhagic treatments in acute promyelocytic leukemia. A GIMEMA retrospective study in 268 consecutive patients [see comments]

F Rodeghiero, G Avvisati, G Castaman, T Barbui, F Mandelli

Blood (1990) 75 (11): 2112–2117.

https://doi.org/10.1182/blood.V75.11.2112.2112

1990

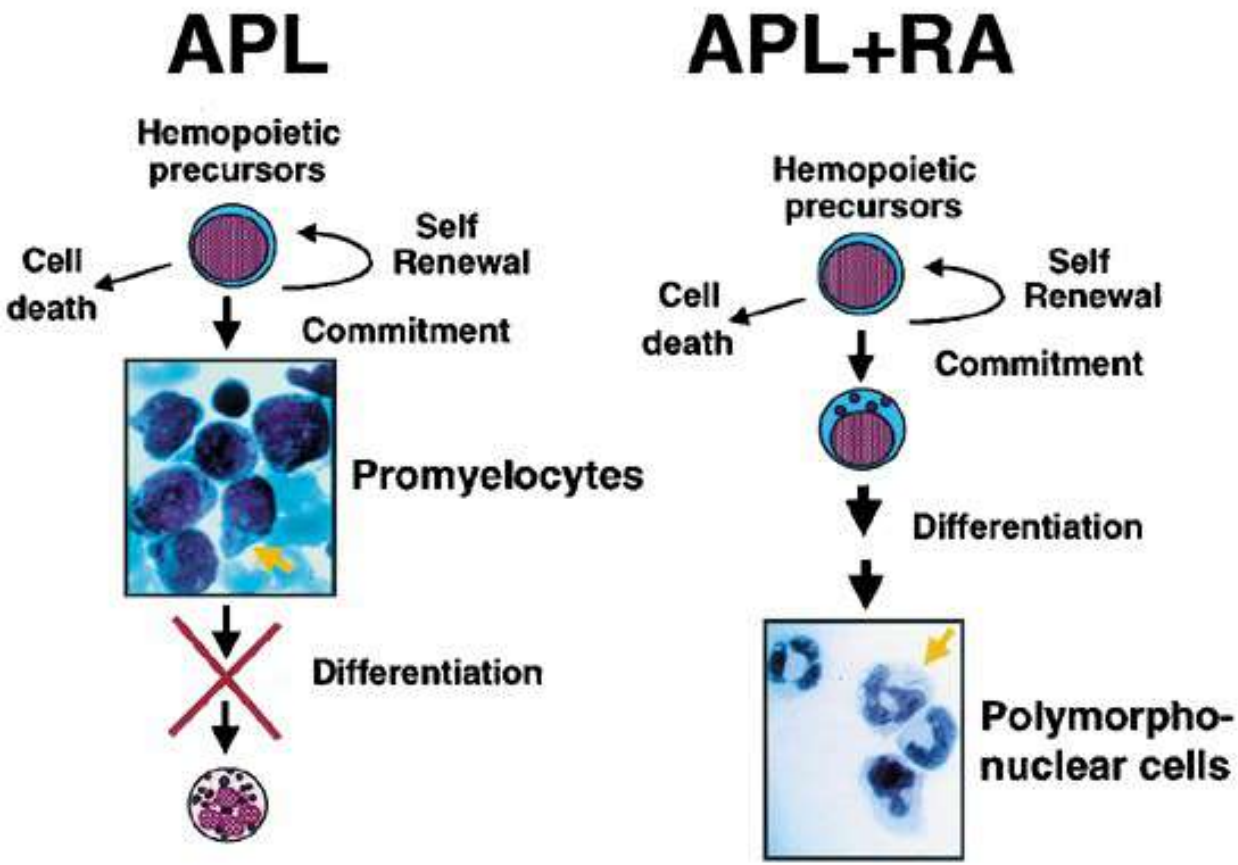
Early Deaths and Anti-Hemorrhagic Treatments in Acute Promyelocytic Leukemia. A GIMEMA Retrospective Study in 268 Consecutive Patients

By Francesco Rodeghiero, Giuseppe Avvisati, Giancarlo Castaman, Tiziano Barbui, and Franco Mandelli

The records of 268 consecutive patients with acute hypergranular promyelocytic leukemia, treated at 29 Italian centers between January 1984 and December 1987, have been reviewed to assess the incidence of early hemorrhagic deaths and the effectiveness of various anti-hemorrhagic treatments. Three separate groups were considered: 94 patients were treated with heparin, 67 with anti-fibrinolytics (tranexamic acid, ϵ-aminocaproic acid, or aprotinin), and 107 with supportive therapy alone. The overall incidence of early hemorrhagic death (within the first 10 days of treatment) was 9.4%, with no significant differences between the various groups. Similarly, there were no differences in complete remission rates or duration of survival. The consumption of packed red blood cells and platelet concentrates was similar for two of the groups, and there was a significantly greater use of platelet concentrates for heparin-treated patients. High blast cell counts on the day of admission were significantly associated with hemorrhagic death within the first 10 days. These counts, plus high blast cell counts and low platelet counts, were associated with death within 24 hours.

https://doi.org/10.1182/blood.V75.11.2112.2112

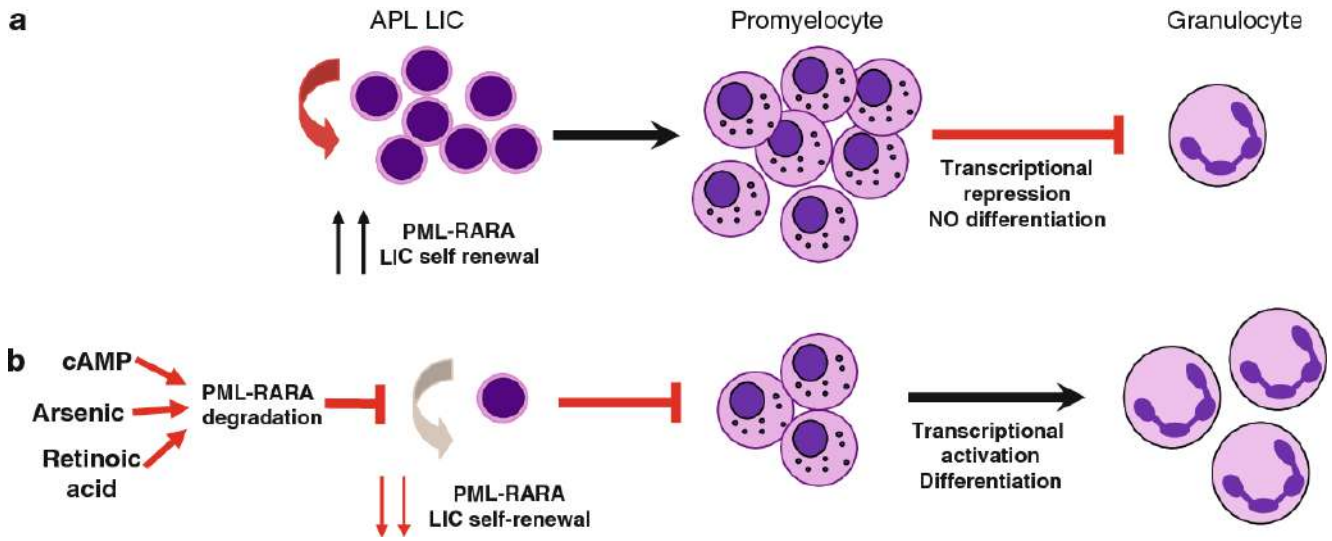

Ematologo
Radiologo
Radioterapista
Nutrizionista
LAB
Laboratori
Scuola
in ospedale
Chirurgo
Pediatra
Anestesista
Cardiologo
PAZIENTE
Psicologo
Ecografista
Infettivologo
Odontoiatra



1999

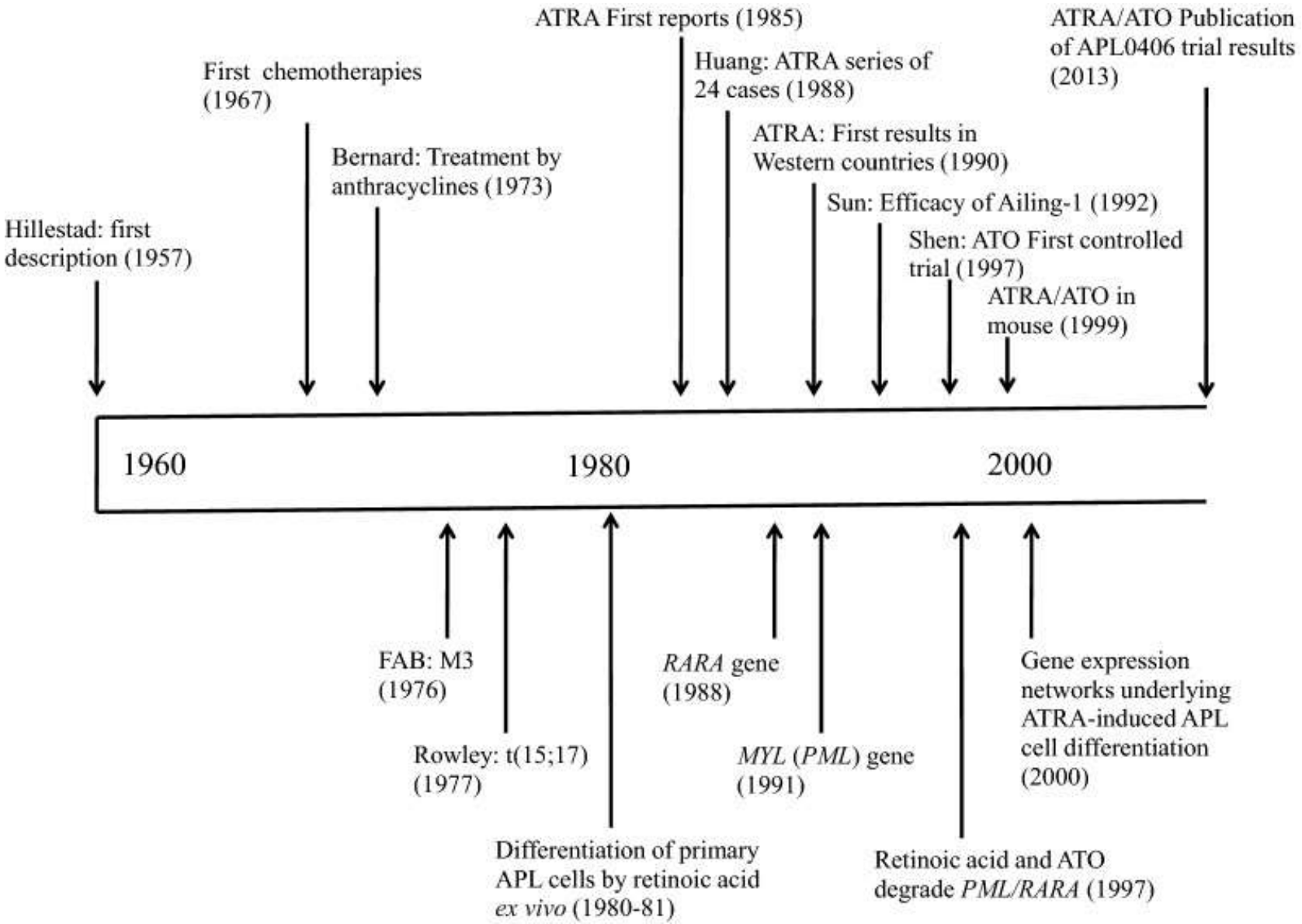
Differentiation therapy in APL. APL is characterized by the clonal expansion of malignant myeloid cells blocked at the promyelocytic stage of hemopoietic differentiation. All-trans retinoic acid (RA) induces the malignant promyelocytes to terminally differentiate towards mature granulocytes. Occasionally, Auer rods (indicated by the yellow arrows), pathognomonic structures found in the cytoplasm of APL malignant promyelocytes, are still observed in the mature granulocytes upon RA treatment demonstrating that these mature cells originated from the neoplastic clone

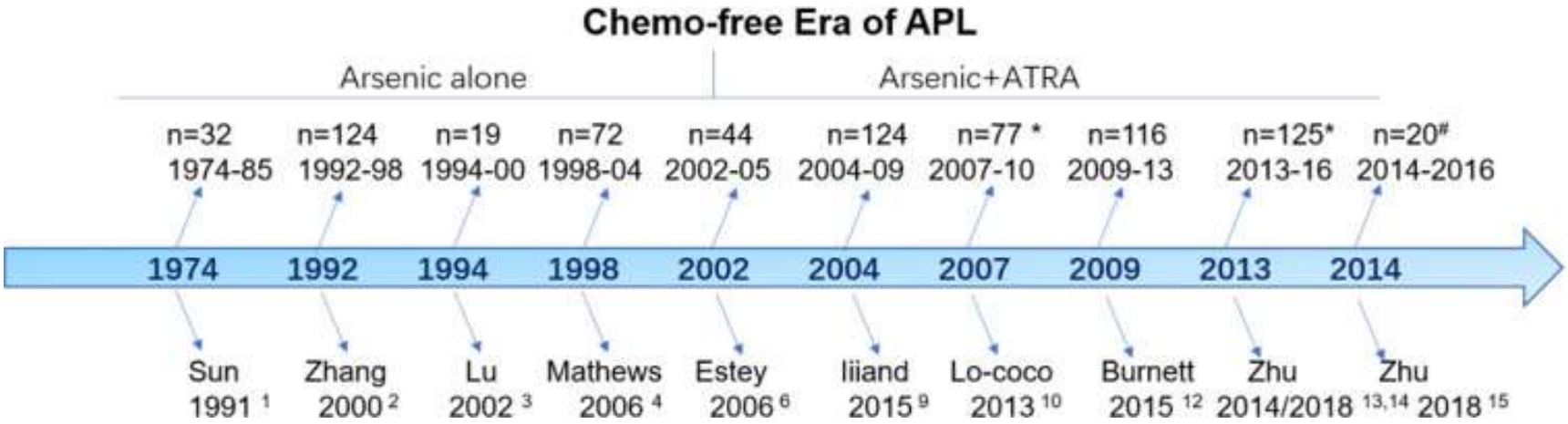
https://www.nature.com/articles/1203088



2010
APL pathogenesis and mechanisms of action of retinoic acid, arsenic and cAMP. a Expression of PML/RARA confers self-renewal properties to APL leukemic cells and blocks their differentiation at the promyelocytic stage. b RA, As and cAMP trigger PML/RARA degradation that is mainly responsible for the eradication of APL leukemic stem cells and correlates to the cure from APL. These drugs also induce PML/RARA transcriptional activation that leads to the differentiation of promyelocytes

https://www.semanticscholar.org/paper/Eradication-of-acute-promyelocytic-cells-by-Nasr-Th%C3%A9/0ac91d22ed40a0f69b18e794de8c6c45af48dde3


ATRA First reports (1985)
ATRA/ATO Publication of APL0406 trial results (2013)
First chemotherapies (1967)
Huang: ATRA series of 24 cases (1988)
Bernard: Treatment by anthracyclines (1973)
ATRA: First results in Western countries (1990)
Hillestad: first description (1957)
Sun: Efficacy of Ailing-1 (1992)
Shen: ATO First controlled trial (1997)
ATRA/ATO in mouse (1999)
1960
1980
2000
FAB: M3 (1976)
RARA gene (1988)
Gene expression networks underlying ATRA-induced APL cell differentiation (2000)
Rowley: t(15;17) (1977)
MYL (PML) gene (1991)
Differentiation of primary APL cells by retinoic acid ex vivo (1980-81)
Retinoic acid and ATO degrade PML/RARA (1997)


Chemo-free Era of APL
Arsenic alone
Arsenic+ATRA
n=32 1974-85
n=124 1992-98
n=19 1994-00
n=72 1998-04
n=44 2002-05
n=124 2004-09
n=77 * 2007-10
n=116 2009-13
n=125* 2013-16
n=20# 2014-2016
1974
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Sun 1991 [1]
Zhang 2000 [2]
Lu 2002 [3]
Mathews 2006 [4]
Estey 2006 [6]
Iiiand 2015 [9]
Lo-coco 2013 [10]
Burnett 2015 [12]
Zhu 2014/2018 [13,14]
Zhu 2018 [15]

Durata 3:30

“Il valore di una persona **risiede in ciò che è capace di dare** e non in ciò che è capace di prendere.”

Albert Einstein