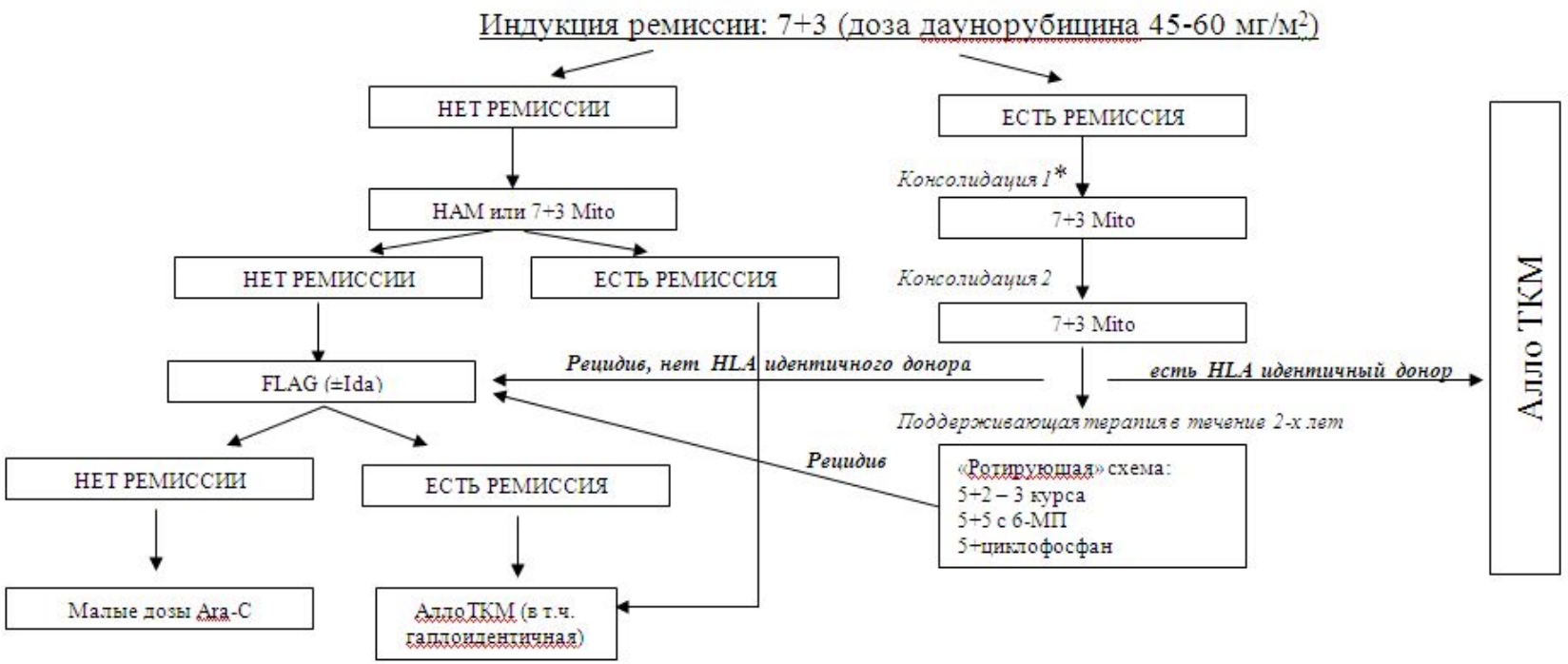
ОМЛ: пришло время для нового протокола?

Основные вопросы

- Нужна ли высокодозная консолидация в принципе (за исключением случаев с благоприятным прогнозом), какова доза цитозара, сколько курсов?
- Можно ли обойтись без поддерживающей терапии?
- Аутологичная трансплантация???

Протокол «Kz.AML.2010»

Протокол лечения острого миелобластного лейкоза у взрослых



* При благоприятном прогнозе (выявление при стандартном цитогенетическом исследовании t(8;21)(q22;q22), inv(16)/t(16;16) и/или генов CBFB/MYH11, AML1/ETO при молекулярно-генетическом исследовании) проводится высокодозная консолидация: один курс НАМ, три курса высоких доз цитозара (3 г/м² 2 раза в день 1, 3, 5, 7 дни курса)

Ann Hematol (2012) 91:825–835
DOI 10.1007/s00277-012-1436-z

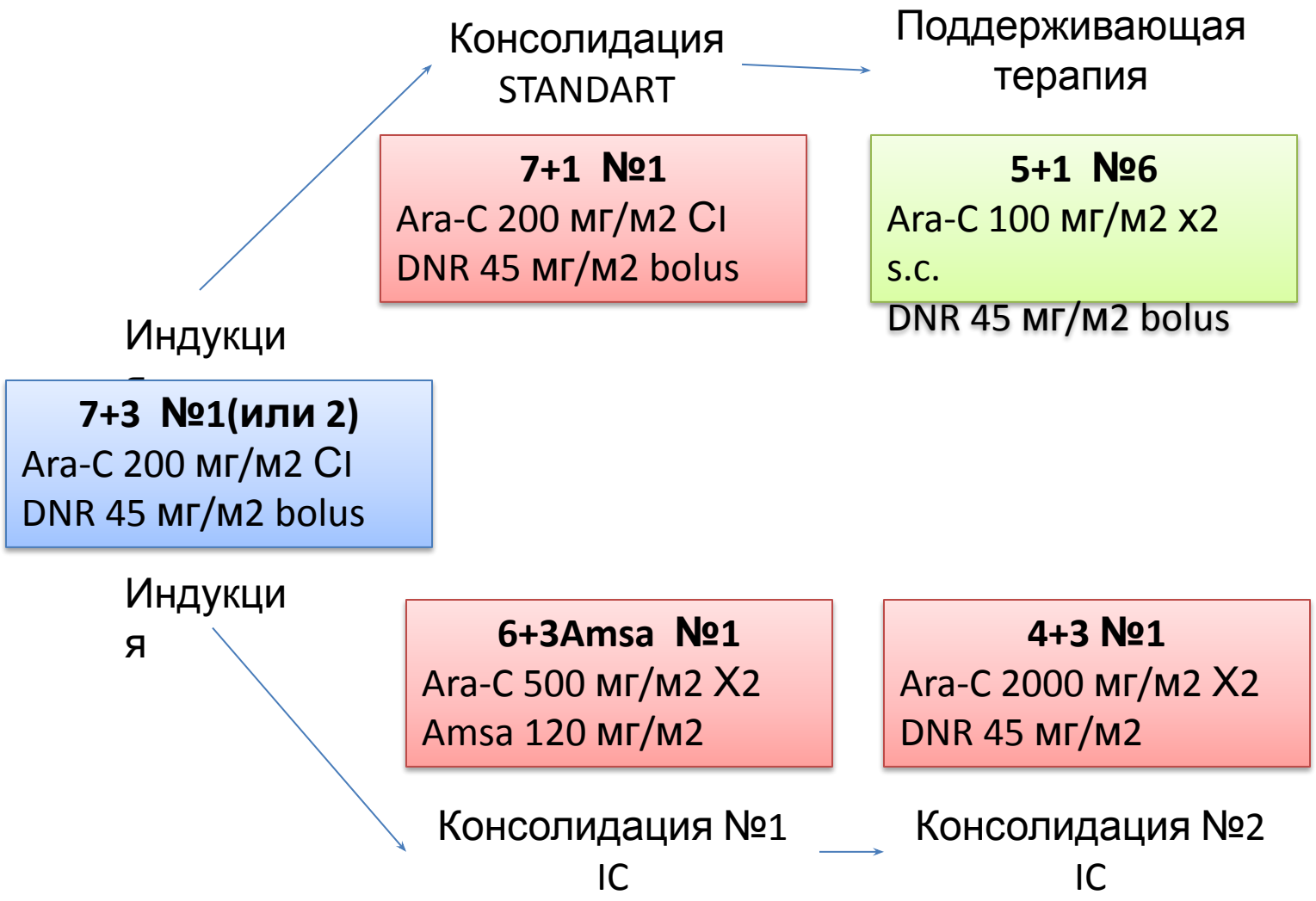
ORIGINAL ARTICLE

Intensive consolidation therapy compared with standard consolidation and maintenance therapy for adults with acute myeloid leukaemia aged between 46 and 60 years: final results of the randomized phase III study (AML 8B) of the European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups

Marysia Hengeveld · Stefan Suciu · Matthias Karrasch · Giorgina Specchia · Jean-Pierre Marie · Petra Muus · Maria C. Petti · Bruno Rotoli · Sergio Amadori · Guiseppe Fioritoni · Pietro Leoni · Enrica Morra · Joseph Thaler · Luigi Resegotti · Paola Fazi · Marco Vignetti · Franco Mandelli · Robert Zittoun · Theo de Witte

Received: 12 November 2011 / Accepted: 19 February 2012 / Published online: 31 March 2012
© The Author(s) 2012. This article is published with open access at Springerlink.com

Дизайн исследования



Безрецидивная выживаемость

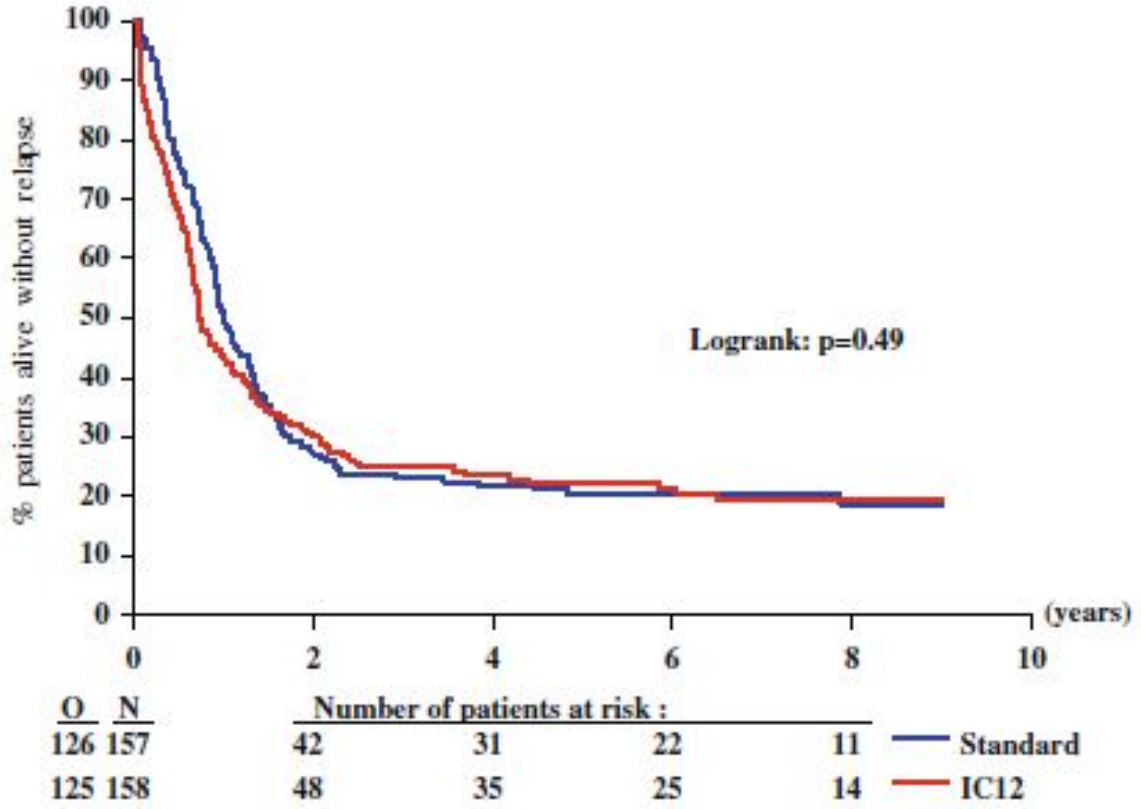


Fig. 2 Kaplan–Meier plot of relapse-free survival according to the randomized arm. *N* number of patients, *O* observed number of events (relapse or death in first complete remission), *Standard* standard consolidation and maintenance therapy, *IC12* intensive consolidation therapy

Кумулятивная инцедентность смерти в первой полной ремиссии

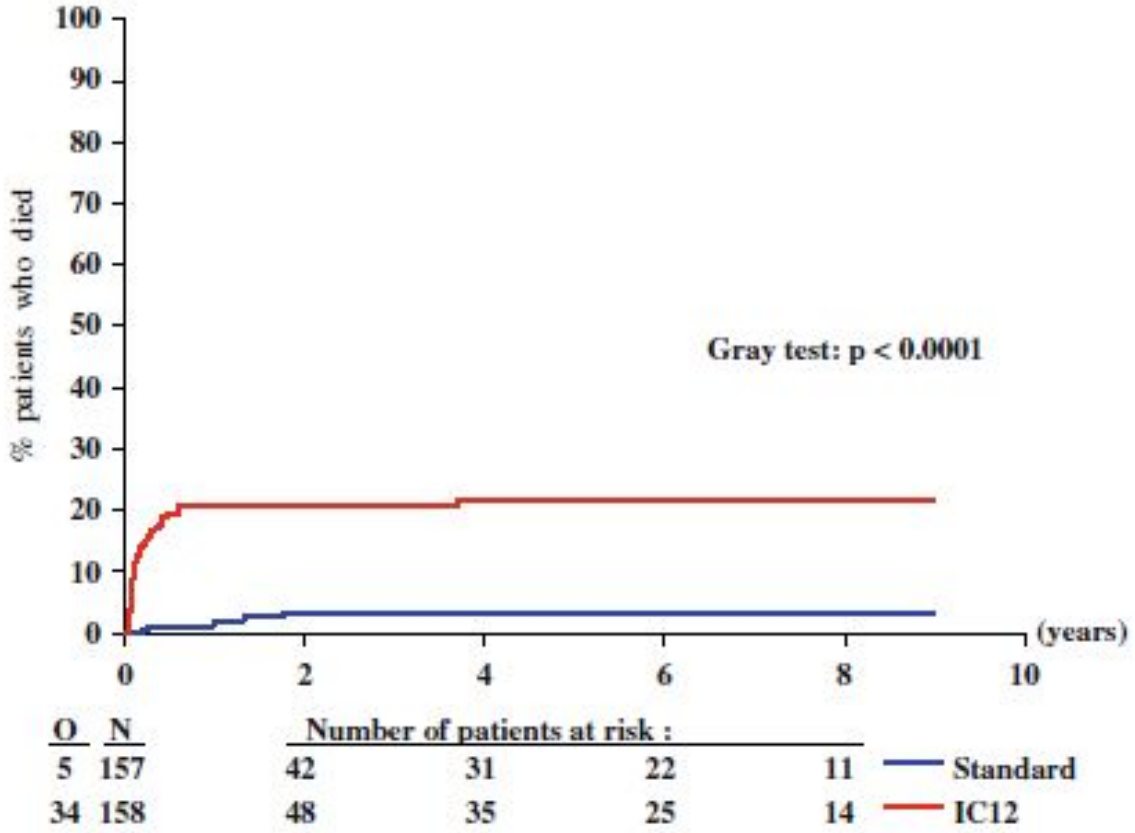


Fig. 4 Cumulative incidence of death in first complete remission according to randomized arm. *N* number of patients; *O* observed number of events (death in first complete remission), considering relapse as a competing risk; *Standard* standard consolidation and maintenance therapy; *IC12* intensive consolidation therapy

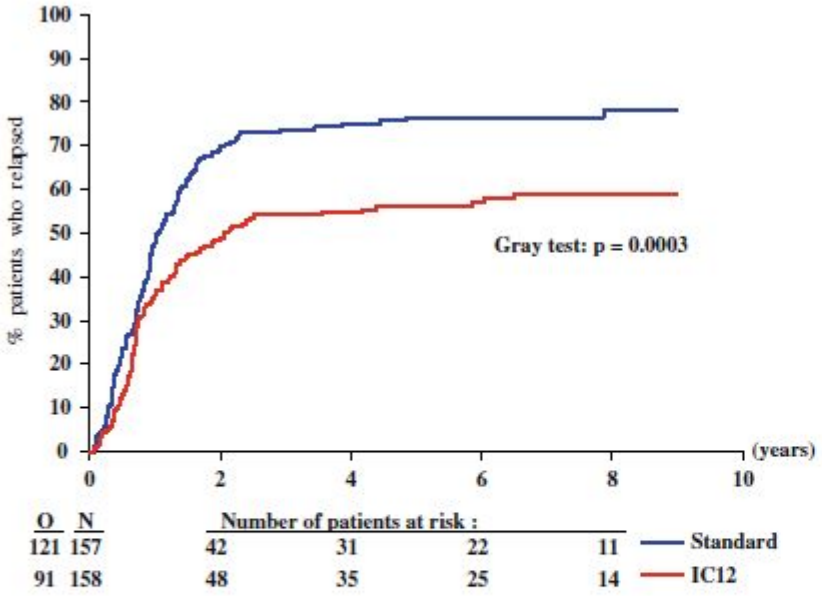


Fig. 3 Cumulative incidence of relapse according to randomized arm. *N* number of patients; *O* observed number of events (relapse), considering death in first complete remission as a competing risk; *Standard* standard consolidation and maintenance therapy; *IC12* intensive consolidation therapy

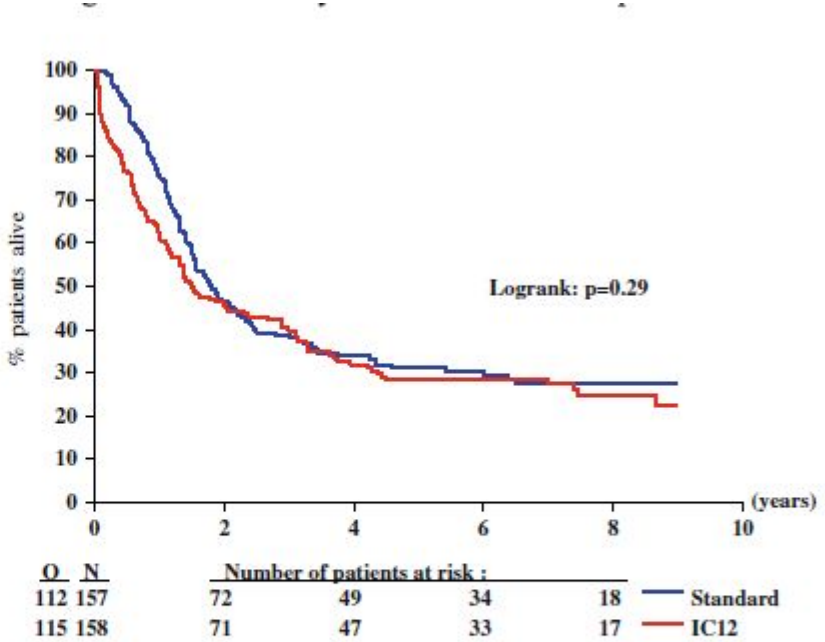


Fig. 5 Kaplan–Meier plot of survival according to the randomized arm. *N* number of patients, *O* observed number of deaths, *Standard* standard consolidation and maintenance therapy, *IC12* intensive consolidation therapy

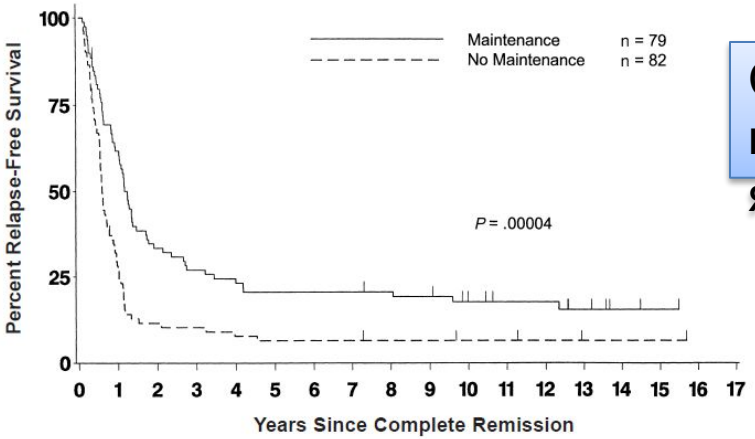
При высокодозной консолидации в первую очередь вероятность смерти выше у пациентов с высокой вероятностью рецидива

Acute Myeloid Leukemia in Adults: Is Postconsolidation Maintenance Therapy Necessary?

Thomas Büchner,[a,*] Wolfgang Hiddemann,[b] Bernhard Wörmann,[c] Helmut Löffler,[d] Wolf-Dieter Ludwig,[e] Claudia Schoch,[b] Torsten Haferlach,[b] Georg Maschmeyer,[e] Peter Staib,[f] Carlo Aul,[g] Axel Heyll,[h] Andreas Grüneisen,[i] Herbert Rasche,[j] Hartmut Eimermacher,[k] Leopold Balleisen,[l] Hermann-Josef Pielken,[m] Hans Edgar Reis,[n] Frank Griesinger,[o] Albrecht Reichle,[p] Maria-Cristina Sauerland,[q] Achim Heinecke[q], for the German AMLCG

[a]Department of Hematology/Oncology, University of Münster, Germany; [b]Department of Hematology/Oncology, University of Munich, Germany; [c]Department of Internal Medicine, Municipal Hospital Braunschweig, Germany; [d]Department of Hematology/Oncology, University of Kiel, Germany; [e]Department of Hematology/Oncology, Robert-Rössle Medical Center, Humboldt University Berlin, Germany; [f]Department of Hematology/Oncology, University of Cologne, Germany; [g]Department of Internal Medicine, St. Johannes-Hospital, Duisburg, Germany; [h]Department of Hematology/Oncology, University of Düsseldorf, Germany; [i]Department of Hematology/Oncology, Krankenhaus Neukölln Berlin, Germany; [j]Department of Hematology/Oncology, Zentralkrankenhaus St. Jürgen-Strasse Bremen, Germany; [k]Department of Internal Medicine, Katholisches Krankenhaus Hagen, Germany; [l]Department of Hematology/Oncology, Evangelisches Krankenhaus Hamm, Germany; [m]Department of Hematology/Oncology, St. Johannes-Hospital Dortmund, Germany; [n]Department of Internal Medicine, Maria-Hilf-Hospital Mönchengladbach, Germany; [o]Department of Internal Medicine, University of Göttingen, Germany; [p]Department of Hematology/Oncology, University of Regensburg, Germany; [q]Department of Biostatistics, University of Münster, Germany

Received June 1, 2000; accepted June 6, 2000



Стандартная консолидация

Figure 1. Relapse-free survival in the 1981 AMLCG study: Patients aged 16 to 78 years received 1 to 2 courses of standard-dose 6-thioguanine-AraC-daunorubicin (TAD) for remission induction, and patients entering complete remission were randomized to receive 1 course of TAD for consolidation and no further treatment or the same consolidation followed by maintenance for 3 years. Maintenance included monthly courses of 5-day standard-dose cytosine arabinoside combined with a second drug, which rotated among daunorubicin, 5-thioguanine, or cyclophosphamide. Tick marks indicate patients alive without relapse at the most recent follow-up.

Интенсивная консолидация

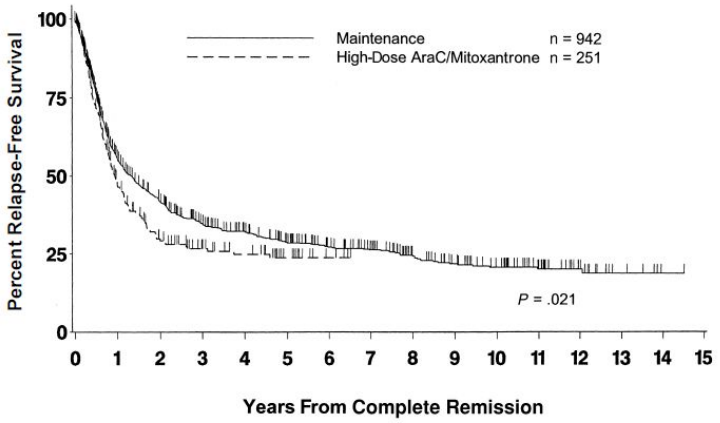


Figure 2. Relapse-free survival in the combined 1986 and 1992 AMLCG studies in patients aged 16 to 83 years. Induction treatment in patients aged <60 years was doubled with 2 courses of standard-dose TAD or TAD followed by high-dose Ara-C/mitoxantrone (HAM), and in patients aged ≥60 years, 1 to 2 courses of standard-dose TAD or HAM were used as the second course. All patients entering complete remission received 1 course of standard-dose TAD for consolidation and randomly received either 3 years of maintenance (see Figure 1) or 1 course of sequential HAM and no further treatment. Tick marks indicate patients alive without relapse at the last follow-up.

!Ротирующая схема!

Maintenance was determined by a study of Cancer and Leukemia Group B (CALGB) in which 5-day courses of standard-dose cytosine arabinoside (Ara-C) were given monthly and were combined by rotation with a second agent such as daunorubicin, 6-thioguanine (TG), or cyclophosphamide

Два пути с одинаковым результатом

- 1
  - Стандартная консолидация + поддерживающая терапия
- 2
  - Интенсивная консолидация без поддерживающей терапии

Российский опыт

- 1992 -1995 (ОМЛ-92)
  - 7+3+VP-16, 3 года поддерживающей терапии (ротация/7+3)
  - 7+3, 3 года поддерживающей терапии
- 1995 -1999 (ОМЛ-95)
  - 7+3 (45) , 3 года поддерживающей терапии
  - 7+3 (45), 1 года поддерживающей терапии
  - 7+3 (60), 1 год поддерживающей терапии
- 2001 – 2006 (ОМЛ-01.01)
  - 7+3+VP-16 N4, 1 год поддерживающей терапии
  - 7+3+VP-16 N2, 1 год поддерживающей терапии
  - 7+3+VP-16 N2, HAD N2
- 2006 – 2009 (ОМЛ-06.06)
  - 7+3, HAM, HAM/HiDAC, HiDAC N2
  - 7+3, HAM, HAM/HiDAC, HiDAC N2, поддерживающая терапия

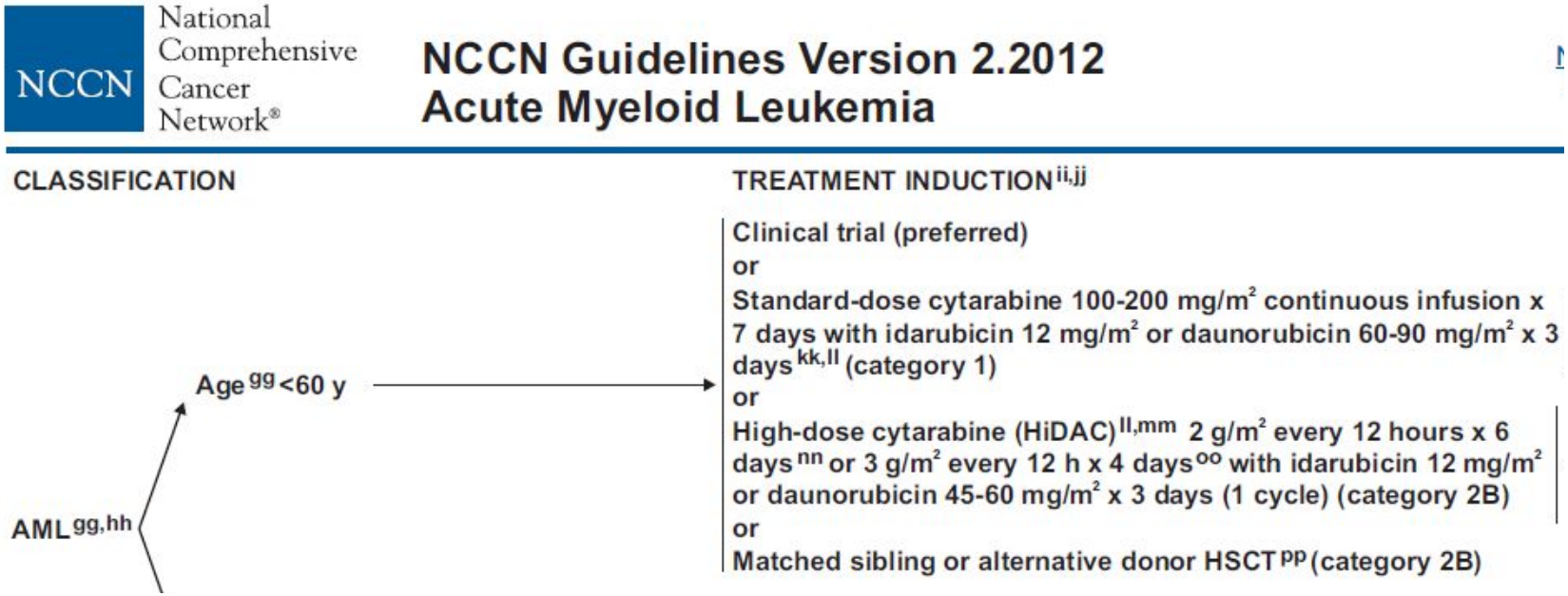
Результаты индукционного лечения больных ОМЛ в разных исследованиях

Показатели	Исследование			
	ОМЛ-92 (n=185)	ОМЛ-95 (n=251)	ОМЛ-01.01* (n=354)	ОМЛ-06.06 (n=109)
Полная ремиссия, %	63,4	61,0	н.д.	78,0
после 1 курса	51,9	48,6	55,4	51,0
Резистентность,%	15,1	21,9	34,1	3,0
Ранняя летальность, %	21,5	17,1	10,5	19,0
Смерть в ремиссии,%	18,1	15,3	10,0	13,0

Долгосрочные результаты Российских клинических исследований по лечению ОМЛ

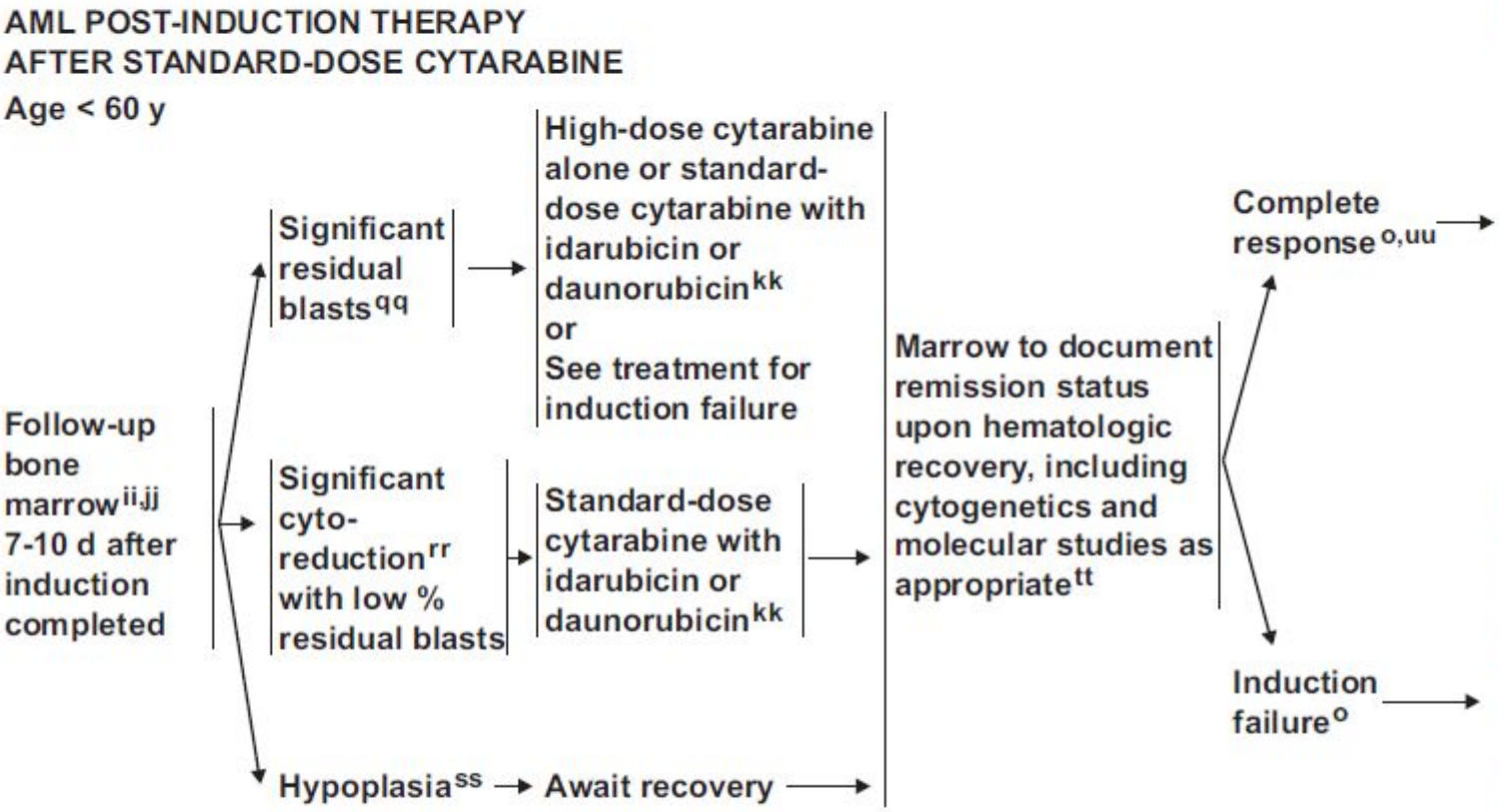
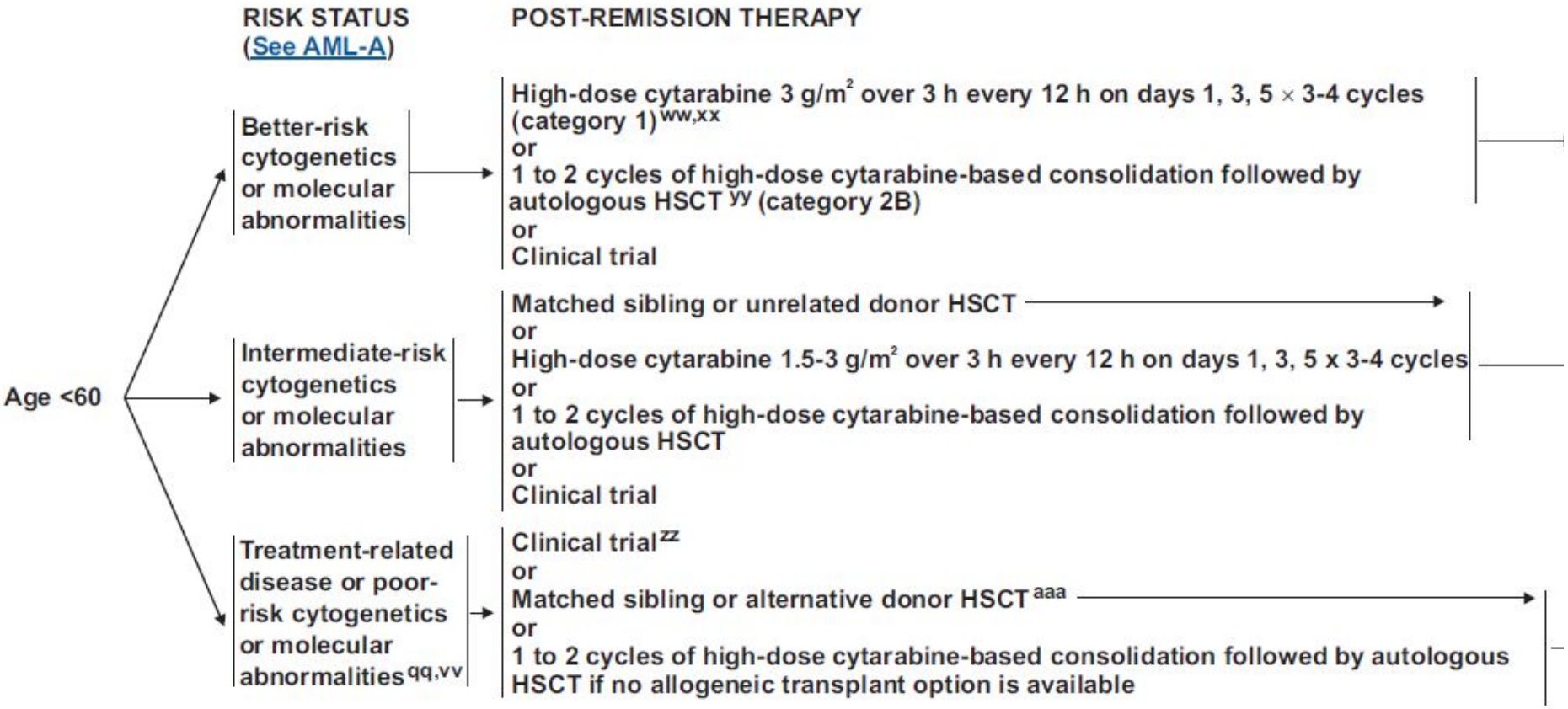
Показатели	Исследование			
	ОМЛ-92	ОМЛ-95	ОМЛ-01.01	ОМЛ-06.06
3-летняя общая / безрецидивная выживаемость,%	27 / 38	30 / 46	38 / 45	38 / 20
5-летняя общая/ безрецидивная выживаемость,%	25/ 35	25 / 28	25,5 / 25	Н.д.
7-летняя общая/ безрецидивная выживаемость,%	18 / 29,5	н.д.	19 / 21	Н.д.

Американские рекомендации: индукция



DNR 60-90 мг/м²

Американские рекомендации: посиндукционный курс



Американские рекомендации: консолидация