Джеффри Е. Рубнитц в 1979 г. с отличием окончил Висконсинский университет в Мадисоне (США) по специальности «Молекулярная биология», после чего работал в области изучения биологических основ рекомбинации белка. В 1987 г. Джеффри Е. Рубнитц получил степень доктора философии (PhD) по биологии, в 1988 г. – звание доктора медицины (MD) в Калифорнийском университете в Сан-Диего (США). В 1991 г. он завершил интернатуру по педиатрии, а в 1994 г. – ординатуру по детской гематологии-онкологии в Детской больнице Люсиль Пакард в Стэнфорде (США), где впоследствии работал врачом до 1995 г.

В 1995 г. начинается карьера профессора Рубнитца в Госпитале Святого Иуды (Мемфис, США), где он прошел путь от врача до директора отдела лейкемии/лимфомы. За время работы в госпитале Джеффри Е. Рубнитц руководил подготовкой врачей-ординаторов, в настоящее время он является профессором отдела педиатрии Университета Теннесси (США).

Профессор Рубнитц член ряда профессиональных организаций, среди которых Детская онкологическая группа (Children's Oncology Group – COG), Американское общество гематологов (American Society of Hematology – ASH), Американское общество клинической онкологии (American Society of Clinical Oncology – ASCO) и др.

Он является обладателем наград в области изучения лейкемии, в том числе и ASCO.

Джеффри Е. Рубнитц автор 168 оригинальных статей, 36 книг и глав в книгах, он регулярно выступает на ведущих форумах в области детской гематологии-онкологии.

Основная область научных интересов профессора Рубнитца – оптимизация диагностики и лечения острого миелоидного лейкоза. Под его руководством ведутся сразу несколько протоколов по лечению данного заболевания, среди которых AML-08, PANAML и др.

На Конгрессе SIOP Asia – 2016 профессор Рубнитц представил в пленарной сессии свой доклад «Острый миелоидный лейкоз и трансплантация гемопоэтических стволовых клеток».

Modern strategies in AML treatment*

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Acute myeloid leukemia (AML) is a complex disease that is characterized by diverse genetic and epigenetic abnormalities. The heterogeneity of AML subtypes implies that improvements in clinical outcome will require the development of therapies that are specific for each subtype of the disease and the design of novel clinical trials to test these strategies. In this review, we briefly summarize recent clinical trials, the genetic diversity of AML, and the use of minimal residual disease in the treatment of AML.

Key words: *acute myeloid leukemia, children, treatment, minimal residual disease*

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Introduction

Improvements in supportive care, refinements in risk classification based on a deeper understanding of the biology and genetics of acute myeloid leukemia (AML), and the monitoring of minimal residual disease (MRD) to assess response to therapy, have all contributed to improvements in outcome for children with this disease. Here, we discuss the results of recent clinical trials, the genetic diversity of AML, and the use of MRD in the treatment of patients with AML.

Results of recent clinical trials

Complete remission and overall survival rates are now greater than 90% and 60%, respectively, for children with AML who are treated on contemporary clinical trials.[1] Cooperative group studies conducted over the past 20 to 30 years have sought to determine the optimal anthracycline dose and agent during induction therapy, the benefit of cytarabine intensification during induction therapy, the ideal duration of postremission therapy, the effects of new agents, and the value of MRD monitoring. Although most therapeutic interventions were determined to be safe, nearly all randomized clinical trials demonstrated similar results between treatment arms. For example, 521 children with AML were randomly assigned to receive liposomal daunorubicin (80 mg/m^2/day for 3 days) or idarubicin (12 mg/m^2/day for 3 days) in combination with cytarabine and etoposide during induction therapy on the AML-BFM 2004 trial.[2] Although the results were outstanding, there were no differences in survival between patients treated with liposomal daunorubicin (76%) compared to those treated with idarubicin (75%). The COG AAML0531 trial investigated the effects of two doses of gemtuzumab ozogamicin added to a standard chemotherapy backbone.[3] As in the BFM study, excellent treatment outcomes were observed, but there were no significant differences in survival between treatment arms (69% for patients who received gemtuzumab versus 65% for those who did not). Other large randomized trials that produced similar treatment results between study arms include the MRC AML12[4] and the St. Jude AML02[5] trials. In the MRC trial, mitoxantrone was not associated with an improvement in survival compared to daunorubicin, and in the St. Jude trial, low-dose and high-dose cytarabine induction regimens produced similar results. Together, these and other recent trials highlight the limitations of randomized studies of non-specific agents performed in a heterogeneous disease with small patient subgroups. As recently discussed, further progress in the treatment of childhood AML will require international collaboration.[1]

Genetic heterogeneity of AML

AML is an incredibly heterogeneous disease that is characterized by genetic alterations that can be grouped into at least eight functional categories.[6] Some lesions have prognostic significance, whereas others provide therapeutic targets.[7–9] Genetic alterations that are associated with a favorable outcome include t(8;21)(q22;q22), inv(16)(p13.1;q22), and t(16;16)(p13.1;q22). However, a recent international collaborative study revealed that there is heterogeneity even among patients with t(8;21): those with del(9q) or +4 may have a worse outcome than other patients with t(8;21).[10] Abnormalities that are associated with a high risk of relapse in childhood AML include monosomy 7 and internal tandem duplications of the *FLT3* gene, as well as less common alteration such as *NUP98-NSD1, DEK-NUP214, KAT6A-CREBBP,* and *RUNX1-CBFA2T3.* Among patients with rearrangements of the *MLL* gene, those with t(6;11)(q27;q23), t(10;11)(p12;q23) and t(10;11)(p11.2;q23) have high rates of relapse, whereas those with t(1;11)(q21;q23) have an excellent outcome.[11]

Minimal residual disease

Perhaps the best predictor of outcome in patients with AML is response to therapy, which reflects features specific to the leukemia (e. g., genetic alterations), characteristics of the patient (e. g., pharmacogenomics), and the intensity and components of therapy. However, morphologic examination of the bone marrow lacks the sensitivity and specificity required to accurately assess response. Modern methods to measure MRD rely on leukemia-specific features that distinguish residual leukemia cells from normal hematopoietic precursors, and include flow cytometric detection of aberrant immunophenotypes,[5, 12] RNA-based PCR analysis of leukemia-specific transcripts,[13] and genomic assessment of mutation clearance.[14] In the St. Jude AML02 trial,[5] the presence of MRD as measured by flow cytometry after one course of induction was associated with a 3-year cumulative incidence of relapse of 39%, compared to only 17% for without detectable MRD. The relapse rate was particularly high for patients with MRD > 1% after one course of therapy and for those with any detectable MRD (> 0.1%) after two courses of therapy. Similar results were recently reported by investigators from the Nordic Society of Paediatric Haemato-Oncology (NOPHO) study group.[12] Patients who were MRD negative after one course of therapy had event-free and overall survival rates of 65% and 77%, compared to only 22% and 51% for those who were MRD positive. Patients who remained MRD positive at the start of consolidation therapy fared extremely poorly, with event-free and overall survival rates only 11% and 28%. In a multivariable analysis, MRD at the start of consolidation therapy was the strongest predictor of survival. In a study of 346 adult patients with *NPM1*-mutated AML, response to therapy was measured by quantitative RT-PCR analysis of *NPM1*-mutated transcripts.*13* Persistence of transcripts in blood after the

second cycle of chemotherapy was associated with a high risk of relapse (82%, compared to 30% for patients with no detectable transcripts) and was the only independent prognostic factor for survival. Although technically more challenging, a recent report suggests that detection of leukemia-specific mutations by deep sequencing may provide a sensitive and widely applicable method of MRD detection that also produces important information about the clonal structure of each patient's leukemia.[14] In this study, the detection of persistent leukemia-associated mutations in at least 5% of bone marrow cells in remission samples obtained at day 30 was associated with a significantly increased risk of relapse.[14] Although performed in adults with AML, it is likely that this method will be applicable to pediatric AML cases as well.

Conclusion

The topics of hematopoietic stem cell transplantation and the development of new agents are beyond the scope of this article, but the reader is referred to several recently published reviews.[15–17] Promising therapeutic approaches include the use of epigenetic modifiers, targeted kinase inhibitors, immunotherapy, Bcl-2 inhibitors, and selective inhibitors of nuclear export. As these modalities are being developed, we must strive to provide the best care possible using agents that are currently available. Key components of optimal therapy include a full molecular diagnostic evaluation to identify patients who are at high risk of relapse, the close monitoring of response to therapy as assessed by MRD, rigorous supportive care, and the selective use of hematopoietic stem cell transplantation.

Современные стратегии лечения острого миелоидного лейкоза*

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Острый миелоидный лейкоз (ОМЛ) – это комплексное заболевание, которое характеризуется широким спектром генетических и эпигенетических аномалий. Гетерогенность подтипов ОМЛ подразумевает, что улучшение клинических исходов требует разработки методов терапии, которые будут специфичными для каждого подтипа, и создания новых клинических исследований для подтверждения их целесообразности. В данном обзоре кратко представлены последние клинические исследования, генетическое разнообразие ОМЛ и мониторинг минимальной остаточной болезни.

Ключевые слова: *острый миелоидный лейкоз, дети, лечение, минимальная остаточная болезнь*

Введение

Улучшение результатов лечения детей с острым миелоидным лейкозом (ОМЛ) обусловлено оптимизацией поддерживающей терапии, уточнением классификации по группам риска, основанной на более глубоком понимании биологии и генетики, а также мониторингом минимальной остаточной болезни (МОБ) в целях оценки ответа на лечение. В данном обзоре рассмотрены результаты последних клинических исследований, генетическое разнообразие ОМЛ, а также мониторинг МОБ.

Результаты последних клинических исследований

Для пациентов с ОМЛ, которые получают лечение в рамках современных клинических исследований, показатели достижения полного ответа на терапию и общей выживаемости в настоящее время превышают 90 % и 60 % соответственно [1]. В исследованиях кооперативных групп, проведенных в течение последних 20–30 лет, ученые и клиницисты пытались определить оптимальную дозу антрациклинов и препаратов для индукционной терапии, роль цитарабина в ее интенсификации, оптимальную продолжительность постре-

**Оригинальный обзор. Подготовлен по данным доклада, представленного на Конгрессе SIOP Asia – 2016. Обзор публикуется впервые в нашем журнале. Стиль и оформление англоязычной версии статьи сохранены.*