ていない。したがって、レベル2（GO 3mg/m^2）までで試験を終了する事とした。

過去20年間のAMLの治療成績の向上は、研究期間を通じて抗生物質や抗真菌剤の開発が進み、無菌室の普及も相俟ってAMLの治療の安全性が向上し、治療成績の向上に貢献しているものと考えられる。また、染色体異常による予後分類が提唱され、さらにJALSG Scoreなどの予後分類法も実用化された。これらの予後因子に基づいて、初回寛解期に造血幹細胞移植を施行することは、AML治療の基本的な戦略となって定着してきた。さらに遺伝子変異を加えた予後予測法が、AML治療の安全性と治療成績を向上させるものと思われる。しかしながら、初回治療不応例や再発例の存在は、治療成績の向上に対して未だ大きな障害となっている。本解析は、このような症例に対しても、造血幹細胞移植を積極的に行うことにより、予後が改善されることを示した。

データセンターの運営上の問題点としては、効率の良いモニタリングが上げられる。メールによるデータ入力依頼よりもFAXを用いたデータ入力依頼に対する反応が良好であり、忙しい臨床医に対する配慮を行うことも必要である。一方で新規加入施設の症例登録が少ない点も問題としてあげられた。臨床試験における患者登録は容易ではなく、容易ではないという共通認識を研究グループとしてまず共有することが重要である。患者登録には王道はないが、数多くの臨床試験を実施する研究グループであるほど、ノウハウの蓄積とそれを次の臨床試験に生かしていく体制づくりが重要である。そこで新規参加施設や世代交代した運営委員に対する新人教育を行う必要があると考えられ、臨床試験とJALSGの歴史、臨床試験の用語、登録症例の取り扱い、入力の重要性などについて研修会を行うことを計画している。

施設監査は現状では教育的な観点からの監査であり、懲罰的なものではない。しかし、今後の監査の具合によっては、施設審査委員会の格付けを経て、グループへの参加可否を審議する方向を考える必要がある。今回も記載不備例が多数認められ、監査通知を出すことにより記載が進んだ施設があった。

現在、登録症例における白血病検体の収集をすすめており、ゲノムワイド関連解析研究を準備している。現在はマイクロアレイによる解析が主に行われているが、今後は全ゲノムシーケンスから得られる情報により新たな展開が予想される。これらに基づいてゲノム、エピゲノムを標的とした治療薬の開発とともに、その臨床応用、至適投与法の検討が必要とされる。さらに白血病幹細胞を標的とした治療法の開発、微小残存病変に対する分子学的、免疫学的アプローチを含む寛解後療法、維持療法の最適化など今後解明すべき課題はきわめて多い。

以上、成人白血病に対する標準療法を確立するため、成人白血病多施設研究グループJALSGとの共同により研究を実施し着実な成果が得られている。

E. 結論

1. 未治療急性骨髄性白血病に対しては、AML201試験では、寛解導入療法におけるイダルビシンとダウノルビシン（増量）は同等の寛解率、生存率を示し、ダウノルビシン（増量）は経済効率が高いことが明らかになった。地固め療法におけるシタラビン大量群と従来の地固め療法群は同等であったが、CBF白血病ではシタラビン大量群が良い傾向を示した。従来の地固め療法群が経済効率は高いが、CBF白血病ではシタラビン大量群が良い。第1寛解期の移植症例の無再発生存率は有意に良く、全生存率も良い傾向があった。予後中間群では移植群が有意に良い。染色体・遺伝子変異に基づき造血幹細胞移植を含めた層別化治療の有効性と安全性の検討を行うAML209試験(予定症例数1500例)においては、これまでに236例の登録があり、順調に症例登録が行われている。

2. 再発・治療抵抗性急性骨髄性白血病に対し、

IDR+Ara-C および DNR+Ara-C の併用化学療法に、GO は安全に加えることができ、臨床第 II 相試験の GO 併用推奨治療は、IDR 12mg/m^2 (第 1-3 日)+Ara-C+GO 5 mg/m^2 (第 4 日)および DNR 50 mg/m^2 (第 1-5 日)+Ara-C+GO 3mg/m^2 (第 6 日)であった。

3. 急性前骨髄球性白血病に対し、維持療法において新規レチノイド化合物である Am80 と ATRA との比較第III相研究 APL204 は 349 例で症例登録を終了した。現在維持療法では ATRA 群 111 例、Am80 群 123 例が割付され治療進行中である。全登録症例の維持療法終了は 2013 年 6 月頃であり、最終解析を行う予定である。

4. 急性リンパ性白血病について、前 ALL97 試験の解析結果は従来の治療成績を凌駕できず、標準的治療確立のためには Ph 陰性 ALL には小児 protocol を参考にした治療の検討が必要と考えられた。Ph+ALL においては Ph+ALL202 試験により化学療法とイマチニブの併用を行う治療法が推奨され、55 歳以下では第一寛解期での同種造血幹細胞移植の有用性が示された。

5. 慢性骨髄性白血病に対する試験では、CML202 試験により本邦においてもイマチニブが第一選択薬であることが確認された。この試験では標準投与量 400mg 未満の症例が多く存在し、日本人の 300mg 投与症例でも 400mg と同等の成績である事が示された。イマチニブ血中濃度の検討では、日本人の 300mg 投与症例の平均値と分布は欧米人の 400mg をむしろ上回ることが判明した。一方、CML207 試験では初期耐性の克服を目的とした早期増量の試験を実施し登録を終了した。また有効性の極めて優れた分子寛解症例に対しては、投与中止の可能性を探るため、安全性を重視した間歇投与による減量試験を実施している。またイマチニブ耐性症例に対しては第2世代チロシンキナーゼ阻害薬ニロチニブとダサチニブの有効性、安全性、コンプライアンスを比較するランダム化第 II 相試験 CML210R を実施中である。

一方、イマチニブ耐性症例に対しては、BCR-ABL 変異スクリーニングを行い、日本における変異の種類と頻度を検討し、PCR インベーダー法がそのスクリーニングに有用である事、変異発現頻度は欧米と同等である事、P ループ変異が予後不良である事が明らかとなった。

6. 骨髄異形成症候群では大規模臨床コホート研究と、化学療法に G-CSF プライミングを用いた第II相試験が終了し、最終解析を行う予定である。

7. 再発・難反応性急性骨髄性白血病の標準的治療法の確立を目的とした臨床第 II 相試験 FLAGM 療法は有効な salvage 療法で 71%と高い奏功率を示した。この試験の結果から FLAGM療法が再発難治性 AML に対する標準的治療になり得る可能性が示唆された。

8. 高齢者白血病については、GO は本邦での抗悪性腫瘍薬との併用は認められていないが、この研究成果により、治療選択の幅が広がることが期待される。予後不良とされる急性骨髄性白血病の高齢患者に対する有効な治療法が開発されることが期待される。

9. データ・センターでは全試験の登録症例に対するモニタリングとデータマネージメントを実施し web 登録プログラムの作成を行った。またデータ固定の終了した試験においては論文作成のための統計解析を行った。またデータ管理プログラムを作成し、JALSG データセンターの管理・運営を行った。

10. 効果・安全性評価委員会では、治療研究に直接タッチしない第三者による効果・安全性評価委員会を設置し、客観的立場より、プロトコールの意義と妥当性、ならびに、プロトコールが安全に施行されているか否か、phase I study における次レベルへの移行の可否、さらには結果解析の科学性を評価した。

11. 臨床試験の質の保証を行うために研究者相互間の施設監査を施設について実施した。現在までのところ、各施設でプロトコールが遵守されており、記載上もおおむね許容範囲の誤記に

とどまっている。来年度も引き続き各地域での監査を既存監査施設を中心に全施設に広げる予定である。

F．健康危険情報

1. 急性骨髄性白血病 AML201 試験

寛解導入療法開始後 60 日以内の死亡例は 36 例 (3.4%)で、感染症：19 例、出血：11 例、臓器障害：2 例、不明：4 例の報告があった。治療開始時に白血球数が異常高値の症例や 2 回の寛解導入療法を要した症例での死亡報告が多く、注意が必要である。地固め療法開始後 100 日以内の 14 例の死亡例が報告されている。C（HD-AC）群：7 例、D（JALSG）群：7 例で、8 例が敗血症によるものであった。Ara-C 大量療法は感染症を合併する頻度が高く、開始前の骨髄機能に基づいた減量規定の遵守と治療後の G-CSF の使用および早期の抗生物質療法の開始が重要である。そのほかの有害事象として敗血症性ショック（grade 4）、肺炎（grade 4）、腎不全（grade 4）、肺膿瘍（grade 3）が報告されている。これらは、いずれも化学療法後の骨髄抑制に伴って認められる既知の有害事象である。その他薬剤固有の有害事象として不整脈（grade 3）、末梢神経障害（grade2）が報告されている。

2 急性骨髄性白血病 AML206 試験

全体で 19 人の再発・治療抵抗性 AML が登録され、全例が CD33 陽性 AML であり、9 人が IAG 療法で、10 人が DAG 療法で治療された。IAG 群では、予想通りに Grade 3/4 の骨髄抑制が頻度高く認められ、IDR 12mg/m^2 (第 1-3 日)+Ara-C+GO 5 mg/m^2 (第 4 日)のレベル 3 では 3 人中 3 人に DLT が発現した。DAG 群では、Grade 3/4 の骨髄抑制は認められたが、DNR 50 mg/m^2 (第 1-5 日)+Ara-C+GO 3mg/m^2 (第 6 日)のレベル 3 では、DLT を認めなかった。しかし、GO 5 mg/m^2 の併用は IAG の結果より毒性が強いと判断されたため、効果安全性評価委員会の指示を受けてレベル 4 は施行しなかった。DAG で治療された 1 人が、治療効果を認めず AML の進行で 30 日以内に死亡したが、IAG 群および DAG 群では、致死的な肝機能障害や veno-occlusive disease (VOD)は認められなかった。

3. 急性前骨髄球性白血病 APL204 試験

有害事象は、急送有害事象 24 例、通常有害事象 22 例である。急送有害事象は寛解導入療法では、A 群 3 例（脳出血、肺出血、急性膵炎）、B 群 4 例（膵酵素上昇、脳出血、分化症候群 DS+脳出血）、C 群 7 例（脳梗塞+DS、白血球数著明高値+脳出血、脳出血+RA 症候群が 2 例、敗血症+DIC+脳出血、DIC+脳出血 2 例）、D 群 2 例（RA 症候群+感染症、RA 症候群+小脳出血）、である。地固め療法では、A 群 4 例（消化管血管奇形による一時的出血、敗血症+肺炎、肺炎）、B 群 2 例（敗血症、感染症+体液貯留+多臓器不全）、C 群 1 例（敗血症+ARDS）、である。維持療法では Am80 群 1 例で胆石性急性膵炎であるが治療との関連はないと思われた。

急送有害事象は 24 例で、うち 19 例が死亡している。寛解導入中では 4.0%(14/349)、地固め療法中では 1.5% (5/330)であり、APL97 に比し多い傾向はない (4.6%;13/283、4.0%;10/250)。しかしながら、寛解導入療法では出血予防管理やレチノイン酸症候群の早期診断治療が、地固め療法では骨髄抑制期の感染症対策がきわめて重要である。さらに APL204 の地固め療法の dose intensity は APL97 とほぼ同等に設定されていることから骨髄抑制は同等と思われ、特に地固め療法 3 コース目の骨髄抑制は遷延する傾向にあり注意が必要である。また地固め療法期に死亡した 5 例中 3 例は 60 歳以上の高齢であった。したがって地固め療法の 2 コース目と 3 コース目では、若年者はもちろん高齢者では特に注意深い治療が必要である。

通常有害事象は 22 例であり、A 群 13 例（一時的腎機能障害、腹腔内感染症、薬剤性肝障害、頸部蜂窩織炎、蜂窩織炎+網膜下出血、薬剤性腎障害、肛門部潰瘍、上室性頻拍、高 Ca 血症、

del 20 の染色体異常、肺出血、発熱性好中球減少症、中心静脈カテーテルによる血栓症)、B群5例(白血球上昇、肺炎、RA症候群+敗血症、RA症候群による呼吸不全、敗血症+G-CSFによる骨痛)、C群4例(白血球上昇+脳出血、RA症候群が2例、中枢神経系toxoplasma感染症)で、いずれも臨床的に管理可能であったが、APLに伴うDICとATRA治療による白血球上昇、地固め療法中の感染症コントロールは重要である。

維持療法では、現在ATRA群111例、Am80 123例である。寛解導入療法登録から維持療法割付までの期間中央値は195日(123-886)であった。有害事象の規定には該当しないが、Am80群で、1コース目にみられた軽度の発疹が2コース目に軽度増強したため被験者の希望により中止した1例があった。またFDPおよびDダイマーの一過性の上昇を認めたが臨床的には何も異常を認めない症例があった。現在、維持療法施行中の症例でDICマーカーの変化を調査中である。その他試験継続上問題となる有害事象の報告はない。

4. 高齢者急性骨髄性白血病GML208試験

2009年12月に米国(SWOG S0106試験)で行われた研究の成果が発表された。未治療AMLを対象に、初回寛解導入療法でダウノルビシン塩酸塩とシタラビンの併用療法(DA療法)への本剤(GO) 6mg/m^{2}の併用効果、及び、大量シタラビン療法による地固め療法後の本剤の追加投与の効果が検討された。寛解導入期に治療との関連性を否定できない致死的有害事象の発現率は、本剤併用群で有意に高いという結果であった。この結果に基づき、米国では本剤の承認が製造・販売会社により自主的に取下げられることが決定した。

別添４

研究成果の刊行に関する一覧表

平成２０-２２年度

研究成果の刊行に関する一覧表

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研究成果の主な刊行物・別刷

Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study

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We conducted a multi-institutional randomized study to determine whether high-dose daunorubicin would be as effective as standard-dose idarubicin in remission-induction therapy for newly diagnosed adult patients younger than 65 years of age with acute myeloid leukemia. Of 1064 patients registered, 1057 were evaluable. They were randomly assigned to receive either daunorubicin (50 mg/m^2 daily for 5 days) or idarubicin (12 mg/m^2 daily for 3 days) in combination with 100 mg/m^2 of cytarabine by continuous infusion daily for 7 days as induction therapy. Complete remission was achieved in 407 (77.5%) of 525 patients in the daunorubicin group and 416 (78.2%) of 532 in the idarubicin group ($P = .79$). Patients achieving complete remission received intensive postremission therapy that consisted of either 3 courses of high-dose cytarabine or 4 courses of standard-dose therapy. Overall survival rates at 5 years were 48% for the daunorubicin group and 48% for the idarubicin group ($P = .54$), and relapse-free survival rates at 5 years were 41% and 41% ($P = .97$), respectively. Thus, high-dose daunorubicin and standard-dose idarubicin were equally effective for the treatment of adult acute myeloid leukemia, achieving a high rate of complete remission and good long-term efficacy. This study is registered at http://www.umin.ac.jp/ctrj/ as C000000157. (*Blood*. 2011;117(8): 2358-2365)

Introduction

The combination of anthracycline and cytarabine (Ara-C) with or without other antileukemia drugs is a standard induction therapy for acute myeloid leukemia (AML),[1-3] and a combination of daunorubicin at a dose of 45 to 50 mg/m^2 given daily for 3 days and Ara-C at a dose of 100 to 200 mg/m^2 given daily for 7 days generally has been used. In the late 1980s, however, idarubicin was introduced into clinics, and 3 randomized studies comparing idarubicin with daunorubicin reported significantly higher complete remission (CR) rates in favor of idarubicin.[4-6] A meta-analysis also confirmed a superior effect of idarubicin at a dose of 10 to 12 mg/m^2 for 3 days versus daunorubicin at a dose of 45 to 60 mg/m^2 for 3 days in the achievement of CR.[7] Nevertheless, the long-term follow-up of the above-mentioned 3 randomized studies comparing idarubicin with daunorubicin revealed that the idarubicin group had better overall survival (OS) than the daunorubicin group in only 1 study.[8]

The Japan Adult Leukemia Study Group (JALSG) used idarubicin and Ara-C as induction therapy in the AML95 and AML97 studies,[9-11] after idarubicin was registered and approved for the national health insurance system in 1995. Both studies resulted in satisfactorily high CR rates (80% and 79%, respectively); however, these CR rates were not superior to those of our earlier AML87, AML89, and AML92 studies, which used daunorubicin in combination with other antileukemia drugs.[12-14] In these 3 previous studies,

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daunorubicin and other drugs were administered in a response-oriented individualized manner; that is, additional drugs were given for a few days when the bone marrow at day 8 was not hypoplastic, containing a substantial number of blasts. Therefore, the total doses of daunorubicin administered during the first course of induction therapy were 240 to 280 mg/m^2 given for more than 5 to 7 days, which was more than the conventional dose of 40 to 60 mg/m^2 given for 3 days. Usui et al also reported that the optimal dose of daunorubicin in their induction therapy for newly diagnosed adult AML was approximately 280 mg/m^2 (40 mg/m^2 for 7 days).[15]

Because there had been no prospective randomized study comparing a higher dose of daunorubicin with the standard dose of idarubicin (12 mg/m^2) in adult AML, in the present multi-institutional randomized study, we prospectively compared idarubicin (12 mg/m^2 for 3 days) with daunorubicin (50 mg/m^2 for 5 days), in combination with Ara-C (100 mg/m^2 for 7 days), as induction therapy for previously untreated adult AML. High-dose daunorubicin resulted in the same CR rate and predicted 5-year OS compared with standard-dose idarubicin.

Methods

Patients

From December 2001 to December 2005, 1064 newly diagnosed adult patients 15 to 64 years of age with de novo AML were consecutively registered from 129 participating institutions. AML was first diagnosed by the French-American-British (FAB) classification at each institution. Peripheral blood and bone marrow smears from all registered patients were sent to Nagasaki University and examined by May-Giemsa, peroxidase, and esterase staining. Next, diagnosis was reevaluated by the central review committee. Patients with the FAB M3 subtype were not registered in the present study. Eligibility criteria included adequate function of liver (serum bilirubin level < 2.0 mg/dL), kidney (serum creatinine < 2.0 mg/dL), heart, and lung and an Eastern Cooperative Oncology Group performance status between 0 and 3. Patients were not eligible if they had prediagnosed myelodysplastic syndrome, but they were eligible if they had no definite diagnosis of myelodysplastic syndrome confirmed by bone marrow histologic analysis even when they had a previous history of hematologic abnormality. Cytogenetic abnormalities were grouped by standard criteria and classified according to the Medical Research Council classification.[16] The study was approved by the institutional review boards at each participating institution. Written informed consent was obtained from all patients before registration in accordance with the Declaration of Helsinki. The study was registered at http://www.umin.ac.jp/ctr/ as C000000157.

Treatments

Patients were randomly assigned by use of a centralized computer system to receive either idarubicin or daunorubicin. Randomization was stratified by age (younger or older than 50 years) and type of AML (FAB classification). All patients received 100 mg/m^2/d Ara-C by 24-hour continuous infusion from days 1 to 7. In the idarubicin group, patients received 12 mg/m^2/d idarubicin for 3 days, and in the daunorubicin group, they received 50 mg/m^2/d daunorubicin for 5 days. If patients did not achieve CR by the first course, the same induction therapy was repeated after an approximately 3- to 4-week interval. If patients did not achieve CR with 2 courses, they were judged as failure cases.

All patients who achieved CR were again randomized to receive either 4 courses of conventional consolidation therapy or 3 courses of high-dose Ara-C therapy. In the conventional consolidation-therapy group, the first course consisted of mitoxantrone (7 mg/m^2 by 30-minute infusion on days 1 to 3) and Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5). The second course consisted of daunorubicin (50 mg/m^2 by 30-minute infusion on days 1 to 3) and Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5). The third course consisted of aclarubicin (20 mg/m^2 by 30-minute infusion on days 1 to 5) and Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5). The fourth course consisted of Ara-C (200 mg/m^2 by 24-hour continuous infusion on days 1 to 5), etoposide (100 mg/m^2 by 1-hour infusion on days 1 to 5), vincristine (0.8 mg/m^2 by bolus injection on day 8), and vindesine (2 mg/m^2 by bolus injection on day 10). Each consolidation was administered as soon as possible after the neutrophils, white blood cells (WBCs), and platelets recovered to more than 1.5×10^9/L, 3.0×10^9/L, and 100×10^9/L, respectively. In the high-dose Ara-C group, 3 courses of 2.0 g/m^2 Ara-C were given by 3-hour infusion every 12 hours on days 1 to 5. Each course was administered 1 week after the neutrophils, WBCs, and platelets recovered to the above counts.

The best supportive care, including administration of antibiotics and platelet transfusions, was given as indicated. When patients had life-threatening documented infections during neutropenia, the use of granulocyte colony-stimulating factor was permitted.

After completion of consolidation therapy, no patients received further chemotherapy. Allogeneic stem cell transplantation (SCT) was offered during the first CR to patients 50 years of age or younger and with a histocompatible donor in the intermediate or adverse cytogenetic risk groups.

Definitions and study end points

Responses were evaluated according to the recommendations of the International Working Group.[17] CR was defined as the presence of all of the following: fewer than 5% blasts in bone marrow, no leukemic blasts in peripheral blood, recovery of peripheral neutrophil counts to more than 1.0×10^9/L and platelet counts to more than 100×10^9/L, and no evidence of extramedullary leukemia. Relapse after CR was defined as the presence of at least 1 of the following: reappearance of leukemic blasts in the peripheral blood, recurrence of more than 5% blasts in the bone marrow not attributable to any other cause (eg, bone marrow regeneration after consolidation therapy), and appearance of extramedullary leukemia.

This was a multi-institutional, randomized, phase 3 study with a 2×2 factorial design. The primary end point of the first randomization was CR rate. The result of the second randomization is reported here in part but will be presented fully in a separate paper. OS was calculated from the date of entry into the study until death due to any cause and was censored at the last follow-up. Relapse-free survival (RFS) for patients who achieved CR was measured from the date of CR until the date of AML relapse or death of any cause and was censored at the last follow-up. Patients who underwent allogeneic SCT were not censored at the date of SCT.

Statistical analysis

This study was prospectively powered to demonstrate noninferiority of daunorubicin compared with idarubicin. With a sample size of 420 patients per group (840 in total), the study had a power of 90% at a 1% level of significance to demonstrate noninferiority (assuming an 80% CR rate for both groups). Statistical testing for the noninferiority trial was performed according to the method of Blackwelder.[18] The Kaplan-Meier method was used to estimate probabilities of OS and RFS.[19] To test factors that predict CR, the χ^2 test and Wilcoxon rank sum test were used for univariate analysis, and the multiple logistic regression model was used for multivariate analysis. For comparison of OS and RFS, the log-rank test was used for univariate analysis and the proportional hazard model of Cox for multivariate analysis.[20,21] Cumulative rates of CR, neutrophil recovery, and platelet recovery were estimated according to the Kaplan-Meier method and were evaluated with the log-rank test. The JMP program (SAS Institute Inc) was used for these analyses. All analyses were performed according to the intention-to-treat principle. All statistical tests except the method of Blackwelder were 2-sided, and the significance level was set at .05.

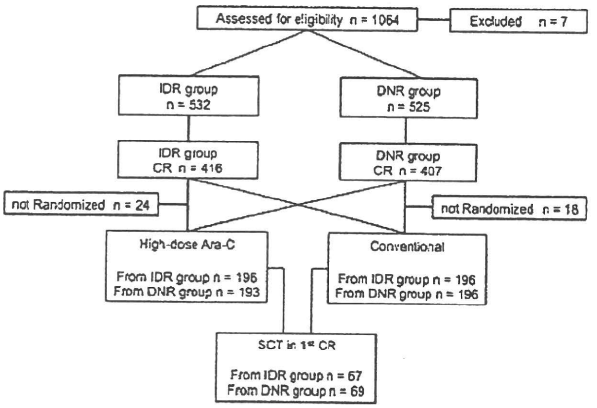

Figure 1. CONSORT flow diagram. IDR indicates idarubicin; DNR, daunorubicin; CR, complete remission; Ara-C, cytarabine; and SCT, stem cell transplantation.

Results

Patient characteristics

Among 1064 registered patients, 7 did not meet the inclusion criteria (misdiagnosis, 1; infectious complication, 1; without therapy, 1; and withdrawal of consent, 4). The study population thus comprised 1057 patients (Figure 1). Patient characteristics are presented in Table 1. Median age was 47 years (range, 15-64 years). Cytogenetics data were available for 1021 patients (96.6%). Among these, 247 (24.2%) were classified in the favorable-risk group, 681 (66.7%) in the intermediate-risk group, and 93 (9.1%) in the adverse group. Five hundred thirty-two patients were assigned to the idarubicin group and 525 to the daunorubicin group. The 2 groups were well balanced with regard to pretreatment characteristics such as age, initial WBC counts, FAB classification, and cytogenetic prognostic grouping.

Table 1. Patient characteristics

	IDR group (n = 532)	DNR group (n = 525)	*P*
Median age, y (range)	47 (15-64)	47 (15-64)	.781
≤ 50	310	306	
> 50	222	219	.996
Median WBC count, ×10⁹/L (range)	13.7 (0.1-382)	15.3 (0.1-334)	.769
≤ 20 × 10⁹/L	304	297	
20= ≤ 50 × 10⁹/L	95	104	
> 50 × 10⁹/L	125	121	
Unknown	8	3	.427
FAB type			
M0	30	30	
M1	95	94	
M2	232	233	
M4	100	100	
M5	56	51	
M6	17	16	
M7	2	1	.997
Cytogenetic group			
Favorable	128	119	
Intermediate	335	346	
Adverse	49	44	
Unknown	20	16	.561
MPO-positive blasts, %			
< 50	169	187	
≥ 50	307	292	
Unknown	56	46	.330
Performance status			
0, 1, 2	512	509	
3	20	16	.524

Values are number of patients unless otherwise indicated.
IDR indicates idarubicin; DNR, daunorubicin; WBC, white blood cell count; FAB, French-American-British classification; and MPO, myeloperoxidase.

Table 2. Results of induction therapy

	IDR group, n (%)	DNR group, n (%)
Patients	532	525
CR	416 (78.2)	407 (77.5)
CR by 1 course	341 (64.1)	321 (61.1)
CR by 2 courses	75 (14.1)	86 (16.4)
95% CI	74.5-81.5	73.8-80.9

IDR indicates idarubicin; DNR, daunorubicin; and CR, complete remission.

Response to induction therapy

Overall, of 1057 evaluable patients, 823 (77.9%) achieved CR. Of 532 patients in the idarubicin group, 416 (78.2%) achieved CR, and of 525 in the daunorubicin group, 407 (77.5%) obtained CR ($P = .79$). Noninferiority for the primary end point was assessed by determining whether the lower bound of the 95% confidence interval (CI) of the difference between the CR rates for the daunorubicin and idarubicin groups was less than −10%. The CR rate of the daunorubicin group was noninferior to that of the idarubicin group (Table 2). In the idarubicin group, 341 patients (64.1%) achieved CR after the first course, and in the daunorubicin group, 321 (61.1%) did so ($P = .39$). The average period to achieve CR was 33.8 days (95% CI 32.9 to 34.6 days) in the idarubicin group and 32.4 days (95% CI 31.6 to 33.2 days) in the daunorubicin group ($P = .038$). CR rates related to FAB classification, age, and cytogenetics are shown in Table 3. Although they were few, patients with FAB M6 responded better to idarubicin: 78% of 17 patients in the idarubicin group and 38% of 16 in the daunorubicin group achieved CR ($P = .037$). There were no differences in CR rate between the 2 groups in other FAB subtypes, cytogenetic risk groups, age, myeloperoxidase positivity of blasts, initial WBC count, or performance status (Table 3). Overall, logistic regression analysis revealed that induction regimen was not an independent prognostic factor but that cytogenetic group and percentage of myeloperoxidase-positive blasts were significant independent factors for achieving CR (Table 4). A cutoff value of WBCs at 20 or 50 × 10⁹/L did not change the result.

OS and RFS

At a median follow-up of 48 months, 5-year predicted OS rates were 48% for the idarubicin group (95% CI 43% to 53%) and 48% for the daunorubicin group (95% CI 43% to 53%; $P = .54$; Figure 2A), and 5-year predicted RFS rates of CR patients were 41% (95% CI 36% to 46%) and 41% (95% CI 35% to 45%), respectively ($P = .97$; Figure 2B). Significant unfavorable prognostic features for OS by the Cox proportional hazard model were adverse cytogenetic risk group, age greater than 50 years, WBC count more than 20 × 10⁹/L, myeloperoxidase-positive blasts less than 50%, and FAB classification of either M0, M6, or M7; for RFS, the significant unfavorable prognostic features were adverse cytogenetic risk group, WBC count more than 20 × 10⁹/L, myeloperoxidase-positive blasts less than 50%, lactate dehydrogenase of 500 IU/L or more, and age greater than 50 years. Induction regimen was not an independent prognostic factor for either OS or RFS by this multivariate analysis.

Table 3. CR rates by induction therapy

	CR rate, %		
	IDR group (n = 532)	DNR group (n = 525)	*P*
FAB type			
M0	43	63	.195
M1	86	79	.236
M2	80	82	.718
M4	81	79	.86
M5	77	75	.96
M6	76	38	.037
M7	50	100	.999
Cytogenetic group			
Favorable	91	96	.134
Intermediate	79	76	.359
Adverse	51	43	.534
Unknown	50	69	.257
Age, y			
≤ 50	83	77	.108
> 50	73	78	.225
Myeloperoxidase-positive blasts, %			
< 50	68	66	.709
≥ 50	87	88	.699
WBC at diagnosis, ×10⁹/L			
≤ 20	79	76	.767
20= ≤ 50	82	82	.993
> 50	74	77	.824
Performance status			
0, 1, 2	79	78	.762
3	80	75	.999

CR indicates complete remission; IDR, idarubicin; DNR, daunorubicin; FAB, French-American-British classification; and WBC, white blood cell count.

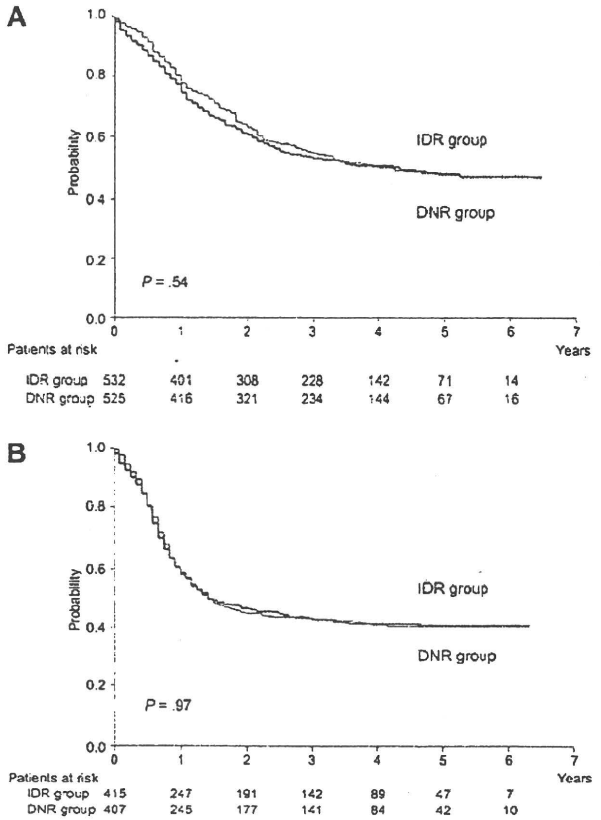

Figure 2. OS and RFS. (A) Predicted 5-year overall survival (OS) was 48% for the idarubicin group (IDR; n = 532; red line) and 48% for the daunorubicin group (DNR; n = 525; blue line; *P* = .54). (B) Predicted 5-year relapse-free survival (RFS) was 41% for the idarubicin group (IDR; n = 416; red line) and 41% for the daunorubicin group (DNR; n = 407; blue line; *P* = .97).

Adverse events

Patients receiving idarubicin required a slightly but significantly longer time to recover from neutropenia and thrombocytopenia. Median duration with a neutrophil count less than 1.0×10^9/L was 28 days for the idarubicin group and 27 days for the daunorubicin group ($P = .0011$; Figure 3A). Median duration with a platelet count less than 100×10^9/L was 25 days for the idarubicin group and 24 days for the daunorubicin group ($P = .0034$; Figure 3B). Sepsis occurred more frequently in the idarubicin group than in the daunorubicin group (8.7% and 4.9%, respectively; $P = .02$). Early death within 60 days occurred more frequently in the idarubicin group than in the daunorubicin group (4.7% and 2.1%, respectively; $P = .03$; Table 5).

Postremission therapy

Of the 823 CR patients, 781 were randomly assigned to receive either 4 courses of conventional standard-dose consolidation therapy (392 patients) or 3 courses of high-dose Ara-C therapy (389 patients), and 136 patients (16% of CR patients) underwent allogeneic SCT in the first CR. There was no significant difference in OS or RFS by postremission therapy between the idarubicin and daunorubicin groups (Table 6). In the idarubicin group, predicted 5-year OS rates were 57% for the conventional standard-dose consolidation arm (95% CI 49% to 65%) and 58% for the high-dose Ara-C arm (95% CI 51% to 66%; $P = .79$; Figure 4A). In the daunorubicin group, predicted 5-year OS rates were 56% (95% CI 48% to 63%) and 58% (95% CI 50% to 65%; $P = .71$; Figure 4B), respectively. If 2 groups were evaluated together, predicted 5-year OS rates were 56% (95% CI 51% to 62%) and 58% (95% CI 53% to 62%; $P = .95$), and predicted 5-year RFS rates were 39% (95% CI 34% to 44%) and 43% (95% CI 38% to 48%), respectively ($P = .72$). The detailed results of this consolidation phase will be reported in a separate paper.[22]

Table 4. Factors that predicted CR in all evaluable patients by multivariate analysis

Variables	Odds ratio	*P*
Cytogenetic group		
Favorable	10.39	< .0001
Intermediate	4.67	< .0001
Myeloperoxidase-positive blast ≥ 50%	2.64	< .0001
Induction therapy: IDR arm	0.97	.854

CR indicates complete remission; and IDR, idarubicin.

Discussion

The present randomized study demonstrates that if the dose intensity is increased appropriately, daunorubicin is as effective as a standard dose of idarubicin for adults less than 65 years of age

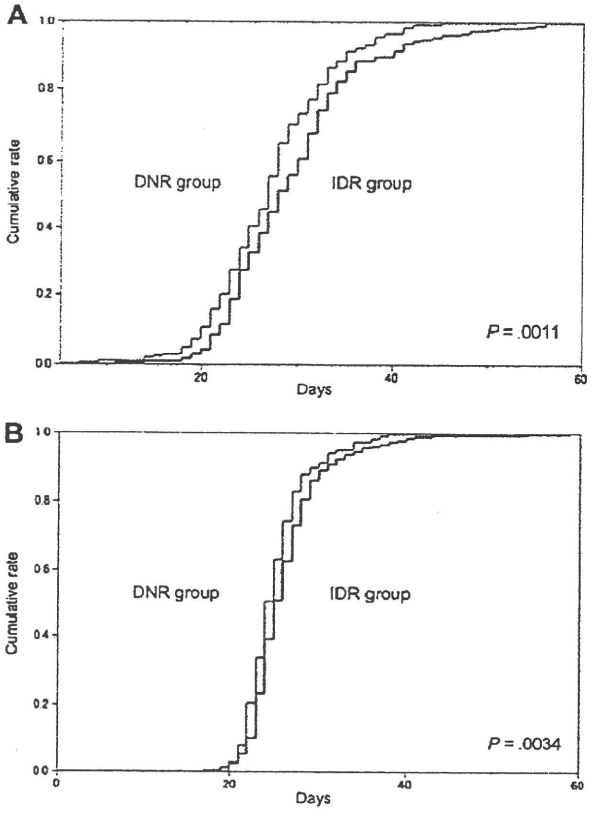

Figure 3. Hematologic recovery. (A) Day of recovery from neutropenia after the first induction course. Neutropenia was defined as neutrophil count $< 1.0 \times 10^9$/L. Median duration until recovery was 28 days for the idarubicin group (IDR; red line) and 27 days for the daunorubicin group (DNR; blue line; $P = .0011$). (B) Day of recovery from thrombocytopenia after the first induction course. Thrombocytopenia was defined as platelet count $< 100 \times 10^9$/L. Median duration until recovery was 25 days for the idarubicin group (IDR; red line) and 24 days for the daunorubicin group (DNR; blue line; $P = .0034$).

who have been newly diagnosed with AML. Remission-induction therapy with 50 mg/m^2 of daunorubicin for 5 days resulted in almost the same CR rate and long-term outcome as seen with 12 mg/m^2 of idarubicin for 3 days in combination with 100 mg/m^2 of Ara-C for 7 days. Generally, daunorubicin is used at a dose of 45 to 50 mg/m^2 for 3 days in combination with 100 to 200 mg/m^2 of Ara-C for 7 days, and 50% to 70% of newly diagnosed adult patients with AML achieve CR. As stated in the "Introduction," JALSG used a response-oriented individualized induction therapy in the AML87, AML89, and AML92 studies for AML, which permitted the additional daunorubicin and other antileukemia drugs

Table 5. Adverse events (World Health Organization grades 3 to 5) after the start of induction therapy

	IDR group, no. of patients (%)	DNR group, no. of patients (%)	*P*
Sepsis	46 (8.7)	26 (4.9)	.021
Early death*	25 (4.7)	11 (2.1)	.026
Bleeding	19 (3.6)	23 (4.4)	.532
Febrile neutropenia	416 (78.2)	406 (77.4)	.761
Acute cardiac toxicity	10 (1.9)	4 (0.8)	.112
Late-onset cardiac failure	2 (0.38)	2 (0.38)	.998

IDR indicates idarubicin; and DNR, daunorubicin.
*Death within 60 days after the start of induction therapy.

Table 6. Effect of induction therapy on outcome by postremission therapies

	5-year OS		5-year RFS	
Consolidation arm	IDR group	DNR group	IDR group	DNR group
Conventional standard-dose, %	57	56	41	37
P	.759		.332	
High-dose Ara-C, %	58	58	42	44
P	.725		.658	
Allogeneic SCT in first CR, %	59	59	58	64
P	.469		.394	

Number of patients in the conventional standard-dose arm was 196 in the IDR group and 196 in the DNR group; in the high-dose Ara-C arm, the numbers were 196 and 193, respectively; and in the SCT group, the numbers were 67 and 69, respectively, as shown in Figure 1.

OS indicates overall survival; RFS, relapse-free survival; IDR, idarubicin; DNR, daunorubicin; Ara-C, cytarabine; and CR, complete remission.

to be administered according to bone marrow status on day 8 or later.[12-14] The CR rates in these 3 studies ranged from 77% to 80%, and the median total dose of daunorubicin was 240 mg/m^2.

On the basis of these experiences and also because of the regulation of our national medical insurance system, we used a dose and schedule of daunorubicin of 50 mg/m^2 for 5 days, that is, a total dose of 250 mg/m^2. In addition,we avoided higher daily doses, such as 80 mg/m^2 for 3 days, because higher plasma concentration might cause more cardiotoxicity in older patients.[23]

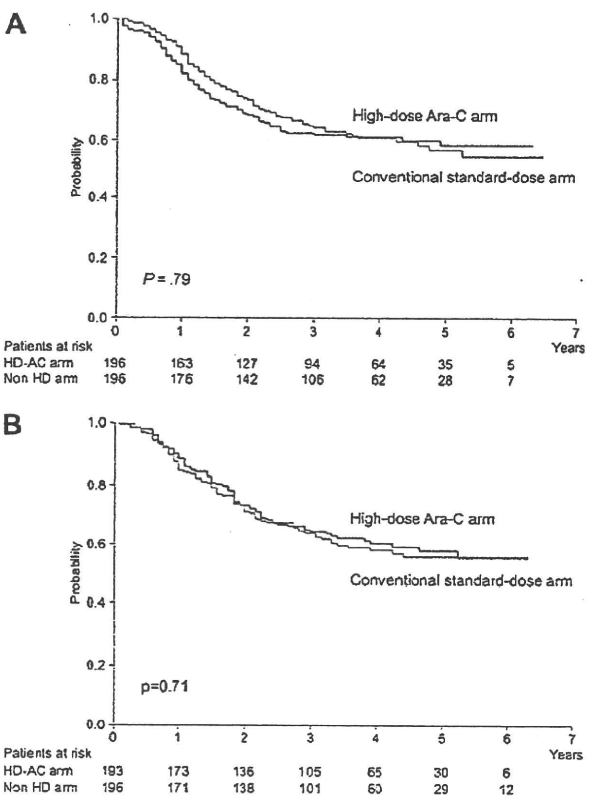

Figure 4. OS of CR patients randomized to receive consolidation therapy. (A) In the idarubicin group, predicted 5-year OS was 58% for the high-dose Ara-C arm (n = 196; red line) and 57% for the conventional standard-dose arm (n = 196; blue line; $P = .79$). (B) In the daunorubicin group, predicted 5-year OS was 58% for the high-dose Ara-C arm (n = 193; red line) and 56% for the conventional standard-dose arm (n = 196; blue line; $P = .71$). Ara-C indicates cytarabine; HD-AC arm, high-dose Ara-C arm; and Non HD arm, conventional standard-dose arm.

Three randomized studies in the early 1990s[4-6] and subsequent studies[24,25] and meta-analyses[7] reported a superior effect of idarubicin (12 to 13 mg/m^2 × 3 days) over that of daunorubicin (45 to 50 mg/m^2 × 3 days), in combination with Ara-C, and AML patients receiving idarubicin obtained 70% to 80% CR without a significant increase in toxic mortality, whereas those receiving daunorubicin achieved 58% to 65% CR.[4-6] However, because the duration of neutropenia and thrombocytopenia was longer in the idarubicin groups, it was questioned whether the doses used in these comparisons were equivalent in terms of levels of toxicity and whether any observed advantage represented an inherent biological advantage of idarubicin rather than biological dose equivalence.[1,2]

In these randomized studies, Wiernik et al reported that patients with initial WBC counts > 50 × 10^9 cells/L obtained only 32% CR by the daunorubicin regimen compared with 68% CR by the idarubicin regimen, whereas patients with WBC counts < 50 × 10^9/L obtained 65% and 69% CR, respectively.[5] Berman et al also reported that patients in the idarubicin group did well regardless of their initial WBC count, whereas patients in the daunorubicin group had a decreased response rate as the WBC count increased.[4] In the present study, however, a total of 250 mg/m^2 of daunorubicin resulted in almost the same CR rate as a total dosage of 36 mg/m^2 of idarubicin regardless of initial WBC counts and other prognostic factors such as cytogenetics, age, and FAB classification except M6. Although among patients with FAB M6, 16 patients in the daunorubicin group had a significantly lower CR rate than 17 patients in the idarubicin group, we have no clear explanation for this observation, because the small number of patients made further analysis difficult. Thus, the increased total dosage of daunorubicin administered in 5 days would be responsible for almost the same satisfactory CR rate and long-term outcome as idarubicin administered in 3 days in the present study. As for adverse events, the recovery from neutropenia and thrombocytopenia was slightly but significantly delayed in the idarubicin group, and sepsis and early mortality occurred more frequently in the idarubicin group, as shown in Figure 3 and Table 5.

Before we initiated the present AML201 study, there was no evidence that a higher dose of daunorubicin was more effective than its standard dose because of the lack of a prospective randomized study. In the sequential studies reported by Southwest Oncology Group, however, the CR rate with daunorubicin at a dose of 70 mg/m^2 was better than that with 45 mg/m^2.[26,27] Very recently, 2 groups reported that a higher dose of daunorubicin improved the CR rate and OS in prospective randomized studies.[28,29] A collaborative group composed of the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology, the German AML Study Group, and the Swiss Group for Clinical Cancer Research compared 3-day daunorubicin at 90 mg/m^2 with 3-day daunorubicin at 45 mg/m^2, in combination with 7-day Ara-C, in elderly patients 60 to 83 years of age who had AML or high-risk refractory anemia and reported a higher CR rate for the escalated-treatment group (52% vs 35%, $P = .002$).[28] Although survival end points did not differ significantly overall, among patients 60 to 65 years of age, the CR rate (73% vs 51%) and OS rate (38% vs 23%) were significantly higher for the 90-mg/m^2 group. The Eastern Cooperative Oncology Group also compared 3-day daunorubicin at 90 mg/m^2 with 3-day daunorubicin at 45 mg/m^2, in combination with 7-day Ara-C, in patients 17 to 60 years of age with AML and reported a higher CR rate (70.6% vs 57.3%, $P < .001$) and longer OS (median 23.7 vs 15.7 months, $P = .003$) for the high-dose group.[29] Given these previous reports and the present report, the optimal total dose of daunorubicin is still to be explored but may rest somewhere between 250 and 270 mg/m^2. Because we used the FAB classification in the present study, we did not include either patients with 20% to 30% of blasts in the bone marrow or those with refractory anemia with excess blasts; therefore, it is unclear whether the present result is applicable to those patients.

Idarubicin is a derivative of daunorubicin and differs from its parent compound by the deletion of a methoxy group at position 4 of the chromophore ring. In vitro and preclinical data have shown that idarubicin is more lipophilic, is faster in cellular uptake, exhibits increased cellular retention, is lower in susceptibility to P-glycoprotein–dependent resistance, and is less cardiotoxic than daunorubicin. Both idarubicin and daunorubicin undergo conversion to their respective alcohol metabolites, idarubicinol and daunorubicinol. Unlike the latter, idarubicinol has a prolonged plasma half-life and is thought to have a pharmacologic advantage.[30-33]

The pediatric Berlin-Frankfurt-Münster group previously compared idarubicin 12 mg/m^2 for 3 days with daunorubicin 30 mg/m^2 twice daily for 3 days, in combination with Ara-C and etoposide, and reported almost the same CR rates (85% vs 86%, respectively) and predicted 5-year event-free survival (55% vs 49%, respectively, $P = .29$) in newly diagnosed childhood AML.[34] Furthermore, daunorubicin at a dose of 60 mg/m^2 for 3 days and idarubicin at a dose of 12 mg/m^2 for 3 days achieved similar CR rates in the studies by Eastern Cooperative Oncology Group that consisted of a large number of adult patients.[35,36]

Recently, the French Acute Leukemia Association reported a randomized study comparing standard doses of idarubicin (12 mg/m^2 for 3 days) with high doses of daunorubicin (80 mg/m^2 for 3 days) or idarubicin (12 mg/m^2 for 4 days) for remission induction in newly diagnosed elderly patients 50 to 70 years of age (median 60 years old) with AML.[37] CR rates were significantly higher for the standard-dose idarubicin group (83%) than for the high-dose daunorubicin group (70%, $P = .007$) but not for the high-dose idarubicin group (78%, $P = .12$). Although OS, relapse incidence, and event-free survival were not different among the 3 arms of the study, daunorubicin (80 mg/m^2 for 3 days) did not improve the CR rate of elderly AML patients to the level of the standard-dose idarubicin regimen.

With regard to adverse events, recovery from myelosuppression was faster and sepsis was less frequent in the daunorubicin group. Both acute and late-onset cardiotoxicity were reported only in a small number of patients in both groups. Given that there was no increase in severe cardiac toxicities in patients receiving high-dose daunorubicin (90 mg/m^2 for 3 days) compared with standard-dose daunorubicin (45 mg/m^2 for 3 days) in the Eastern Cooperative Oncology Group study (7.9% and 7.2%, respectively),[29] daunorubicin may not necessarily be administered for 5 days as in the present study (50 mg/m^2 for 5 days), although further follow-up observation is needed for late-onset cardiotoxicity.

Since the landmark study of the Cancer and Leukemia Group B,[38] it has been believed that high-dose Ara-C is superior to consolidation therapy with intermediate (400 mg/m^2 for 5 days) or conventional (100 mg/m^2 for 5 days) doses of Ara-C. In the present study, we prospectively compared high-dose Ara-C with consolidation therapy that included a conventional dose of Ara-C and non–cross-resistant agents. Our results clearly demonstrate that there is no difference in RFS and OS between the 2 consolidation arms, regardless of whether idarubicin or daunorubicin is used as induction chemotherapy.

In conclusion, the intensified dose of daunorubicin in the present setting, that is, 50 mg/m^2 for 5 days, proved to be biologically equivalent in terms of efficacy and no more toxic in terms of myelosuppression than the standard dose and schedule of idarubicin, that is, 12 mg/m^2 for 3 days, for remission-induction therapy in newly diagnosed younger patients (15 to 64 years old, median 47 years) with AML.

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Authorship

Contribution: S.O. designed and performed research, collected and interpreted data, and wrote the manuscript; S.M. designed and performed research, analyzed data, and participated in writing the manuscript; H.F., H.K., K.S., N.U., H.O., K.M., C.N., Y.M., A.F., T. Nagai, T.Y., M. Taniwaki, M. Takahashi, F.Y., Y.K., N.A., H.S., and H.H. performed research; S.H. analyzed data; K.O. and T. Naoe conducted and performed research; and R.O. conducted research, interpreted data, and participated in writing the manuscript.

For a complete list of the members of the JALSG, see the supplemental Appendix (available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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A randomized comparison of 4 courses of standard-dose multiagent chemotherapy versus 3 courses of high-dose cytarabine alone in postremission therapy for acute myeloid leukemia in adults: the JALSG AML201 Study

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We conducted a prospective randomized study to assess the optimal postremission therapy for adult acute myeloid leukemia in patients younger than 65 years in the first complete remission. A total of 781 patients in complete remission were randomly assigned to receive consolidation chemotherapy of either 3 courses of high-dose cytarabine (HiDAC, 2 g/m² twice daily for 5 days) alone or 4 courses of conventional standard-dose multiagent chemotherapy (CT) established in the previous JALSG AML97 study. Five-year disease-free survival was 43% for the HiDAC group and 39% for the multiagent CT group ($P = .724$), and 5-year overall survival was 58% and 56%, respectively ($P = .954$). Among the favorable cytogenetic risk group (n = 218), 5-year disease-free survival was 57% for HiDAC and 39% for multiagent CT ($P = .050$), and 5-year overall survival was 75% and 66%, respectively ($P = .174$). In the HiDAC group, the nadir of leukocyte counts was lower, and the duration of leukocyte less than 1.0×10^9/L longer, and the frequency of documented infections higher. The present study demonstrated that the multiagent CT regimen is as effective as our HiDAC regimen for consolidation. Our HiDAC regimen resulted in a beneficial effect on disease-free survival only in the favorable cytogenetic leukemia group. This trial was registered at www.umin.ac.jp/ctr/ as #C000000157. (*Blood*. 2011;117(8): 2366-2372)

Introduction

Approximately 70% to 80% of the newly diagnosed younger adult patients with acute myeloid leukemia (AML) achieve complete remission (CR) when treated with an anthracycline, usually daunorubicin (DNR) or idarubicin (IDR), and cytarabine (Ara-C); however, only approximately one-third of these patients remain free of disease for more than 5 years.[1-5] If CR patients are left untreated, almost all of them will relapse and die.[6] Therefore, postremission therapy is indispensable. Postremission therapy is divided into consolidation and maintenance therapy. In the previous studies of Japan Adult Leukemia Study Group (JALSG) for adult AML (AML87, 89, 92, and 95),[1-3,5] we administered 3 courses of consolidation therapy and 6 courses of intensified maintenance therapy. In the AML97 study,[7] we conducted a randomized study to compare the conventional 3-course consolidation and 6-course maintenance therapies with 4 courses of intensive consolidation therapy without maintenance and demonstrated no difference in overall survival (OS) and disease-free survival (DFS). Therefore, the 4 courses of conventional standard-dose multiagent chemotherapy (CT) became the standard regimen in Japan. On the other hand, multiple cycles of high-dose cytarabine (HiDAC) have been commonly used as consolidation therapy in the United States and other countries. However, our national medical insurance system did not allow us to use HiDAC until 2001, and thus we could not use HiDAC in the previous treatment regimens for leukemia. We therefore conducted this prospective, multicenter cooperative

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