1. 3 名ずつの患者を以下のように評価する。3 名で DLT 0 名なら次レベルに増量、1-2 名なら 3 名追加、3 名なら中止とする。
2. 3 名追加で 6 名になった場合は、DLT 1-2 名なら次レベルに増量し、3 名なら中止とする。

②対象患者の選択基準と除外基準の決定

1) 選択基準：以下の全てをみたすもの

1. 芽球の 20%以上が CD33 陽性の、既承認薬を用いた初回寛解導入療法による CR 後の再発(CR 後の初回再発)、もしくは、既承認薬による初回寛解導入療法にて CR に導入されない治療抵抗性 AML（FAB の M3 を除く）患者
2. GO 投与歴がない。
3. 年齢：65 歳以上、75 歳未満
4. PS：0～1（ECOG performance status score）
5. AST、ALT ともに開始時施設基準値上限の 2.5 倍以下
6. 総ビリルビン <1.5 mg/dL
7. 血清 Cre < 2.0 mg/dL
8. 十二誘導心電図にて虚血性変化・心房細動・治療を要する心室性不整脈のいずれも認めない。
9. 左心駆出率 > 50%（登録前 12 週以内の最新値）
10. 酸素非投与下で PaO_2>65 mmHg または SaO_2>93%（非観血的検査で可）
11. 2 ヵ月以上は生存が期待できる患者
12. 高齢者に対する多剤併用化学療法と GO の同時併用の経験やエビデンスは本邦では少ないことを十分に理解した上で、本人から文書による同意が得られた患者

2) 除外基準

1. 骨髄異形成症候群や骨髄増殖性疾患から進展した AML、もしくはこれらを合併する患者
2. 化学療法や放射線療法後の治療関連 AML の患者
3. 臨床診断で中枢神経浸潤がある（髄液検査、脳 MRI は必須ではない）患者
4. 自家および同種造血細胞移植を受けた患者
5. 緑内障の既往がある患者
6. インスリン治療中の糖尿病を合併する患者
7. コントロール不良の高血圧を合併する患者
8. 狭心症または心筋梗塞の既往のある、または心筋症を合併する、または抗不整脈薬で治療中の不整脈を有する患者
9. 間質性肺炎、肺線維症、高度の肺気腫を合併する患者
10. HBs 抗原、HCV 抗体、または HIV 陽性の患者
11. 活動性感染症を合併する患者
12. 臨床的に肝硬変と診断されている患者
13. 活動性の重複癌を合併する患者
14. 精神病または精神症状を合併しており試験への参加が困難と判断される Major tranquilizer・抗うつ薬・抗躁薬を服用中の患者

3) 再寛解導入療法後の治療

CR に到達しなかった場合の再寛解導入療法は規定しないが、GO の再投与は行わない。CR 患者では、薬剤投与開始から少なくとも 39 日以降に寛解後療法を行う。内容については規定しないが、造血細胞移植を実施する場合は、GO 投与後 115 日以降とする。

(2) 倫理的事項

①患者の保護

本研究実施にあたっては、ヘルシンキ宣言(1964)、東京改定(1975)、ベニス改定(1983)、香港改定(1989)の精神に基づくとともに、厚生労働省の臨床研究の倫理指針、疫学研究の倫理指針に則り行われる。

②説明と同意(インフォームドコンセント)
患者への説明事項

登録に先立って担当医師は患者本人に施設の倫理委委員会あるいは IRB で承認された説明文書を患者に渡し、以下の内容を口頭で詳細に説明する。

1)病気について
2)試験の概要
3)試験の背景と目的
4)試験の方法
5)試験への患者の予定参加期間
6)試験に参加患者予定人数
7)試験参加は患者の自由意思によること
8)健康に被害が生じた場合
9)試験の結果公表の場合も、プライバシーは守られること
10)試験に関する情報の随時連絡
11)研究の科学的・倫理的妥当性
12)予想される臨床上の利益および危険性または不便について
13)研究遂行にかかる費用について
14)参加者に対する金銭の支払いおよび参加者の費用の負担
15)知的財産権の帰属について
16)代諾者による承諾
17)担当医師
18)相談窓口について

同意

本臨床研究についての説明を行って翌日以降に、患者が研究の内容をよく理解したことを確認した上で、研究への参加について依頼する。

③プライバシーの保護と患者識別

登録患者の同定や照会は、登録時に発行される登録番号、年齢、性別、施設匿名化番号（または診療録番号）を用いて行われる。

④施設の倫理審査委員会の承認

本臨床研究の参加に際しては、本研究実施計画書および患者への説明文書が各施設の倫理審査委員会または IRB(機関審査委員会)で承認されなければならない。

⑤プロトコールの内容変更について

本臨床研究に参加する患者の危険(risk)を増大させる可能性があるか、研究の primary endpoint に関連するプロトコールの部分変更は改正と定義し、JALSG プロトコール委員会の承認、効果安全性評価委員の承認を得て、各施設の倫理委員会(あるいはIRB)の承認を必要とする。

C. 研究結果

平成 19 年 12 月より患者登録を開始した。平成 22 年 2 月までに、レベル 1 で 2 名の症例が登録された。1 例目は 65 歳女性で FAB 分類による診断は M5a、初回寛解導入療法にて治療抵抗性であった。好中球の最低値は 28/μL、好中球 500/μL 未満の期間は day5-31、血小板数の最低値は 1.8 万/μL、血小板数 5 万/μL 未満の期間は 10 日間、点滴関連毒性として O_2 飽和度低下(90%)を認め、副腎皮質ステロイド使用にて軽快した。発熱性好中球減少症を day12 に発症し、抗菌薬投与で 3 日目に解熱した。化学療法の効果は no response であったが、DLT は認めなかった。

2 例目は 74 歳男性で、FAB 分類の診断は M6、好中球の最低値は 0/μL、好中球 500/μL 未満の期間は day9-27 であった。血小板数の最低値は 0.5 万/μL、血小板数 5 万/μL 未満は 14 日間であった。耳下腺炎を day21 に発症し、抗菌薬投与で 6 日目に解熱した。化学療法後は完全寛解を得られ、DLT に相当する症状は認めなかった。

D. 考察

抗 CD33 モノクローナル抗体と殺細胞効果を有するカリケアマイシン(calicheamicin)を結合させた GO は、AML に対する効果が期待される。しかし、骨髄

抑制、点滴関連事象、静脈閉塞性肝疾患、肺障害などの副作用が報告されている。AML の高齢患者では従来の化学療法を行っても、満足すべき治療成績は得られていない。新たな治療に対する期待は大きく、今後の試験の進展が望まれる一方で、毒性評価が重要である。

本研究では、再寛解導入療法として BH-AC(200mg/m^2, DIV ,days 1-8) + DNR (30 mg/m^2 ,IV ,days 1-3)に GO の併用療法を行い、GO の投与量で複数の用量レベルを設けている。海外では GO 併用化学療法を用いた研究がいくつか行われている。DeAngelo らは、62～78 歳の AML 新規 21 例を対象として cytarabine (Ara-C) 100 mg/m^2 (days1-7) + DNR 45 mg/m^2 (days 1-3)に GO 6 mg/m^2 (day 4)を投与し、その耐用性が示された。Kell らは、Ara-C 200 mg/m^2 x 2/day + DNR 50 mg/m^2 (days 1,3,5)+thioguanine 100mg/m^2/ day(day 1-10) に GO 3 mg/m^2 (day 1) 併用の feasibility を示している。高齢患者を対象とし、anthracyclin 系薬剤を含む化学療法と GO を併用した試験も行われている。Clavio らは 60~80 歳の AML 新規例 46 例を対象として、fludarabine 30mg/m^2 (days 1-3)+Ara-C 1 g/m^2 (days 1-3) + idarubicin 5 mg/m^2 (days 1-3)に GO 3 mg/m^2 (day 4) の併用を行った。Pirrotta らは 65~77 歳の AML 新規例 10 例を対象に、fludarabine 25mg/m^2 × 2 回/日 (days 1-3) + Ara-C 1g/m^2 (days 1-3) + idarubicin 5 mg/m^2 (days 1-3)に GO 3 mg/m^2 (day 4)を併用した。いずれの報告も GO 3 mg/m^2 と化学療法を併用している。これらの研究で用いられた化学療法に比べ本研究の BH-AC + DNR 療法の強度は勝らないと考えられる。また Kell らのそれよりも劣ると思われる。高齢者では毒性が高くなる可能性も考慮し、GO 1.5mg/m^2 + BH-AC (8 日間) +DNR (3 日間) をレベル 1 としている。現時点ではまだレベル 1 のみの登録であり、DLT に相当する毒性が認められていないのは、海外の研究結果と合致する。Kell らの研究では、GO 6 mg/m^2 (day 1) で毒性が増加したことを考慮し、本研究のレベル 3 は 5 mg/m^2 としている。

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。

E. 結論

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。

F. 健康危険情報

G. 研究発表

未発表

H. 知的財産権の出願・登録状況

該当事項はない。

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書

臨床試験のデザインおよび生存解析に関する研究

研究分担者　熱田　由子　名古屋大学大学院医学系研究科造血細胞移植情報管理・生物統計学　助教

研究要旨

臨床試験計画においては臨床医学のみではなく臨床試験方法論やデータ管理学などの知識が必要である。これは、臨床試験計画チームに専門家が必要であるのみならず、臨床試験を計画する臨床家が臨床試験方法論などに関して必要十分の知識をもつことが必要である。試験デザインやその背景となる統計学的事項に関して、臨床家が理解しにくい点などを整理し、教育的説明などを行うことにより、計画される臨床試験の質の向上のみならず、臨床試験計画時におけるプロセスをより合理化していくことができると考えられる。

A. 研究目的

臨床試験の立案から、プロトコールを固定し、実際の登録が始まるまでには、年単位での時間がかかることが多い。臨床試験の計画チーム内で十分な議論の時間を要すること、定義や治療内容の詳細にわたるプロトコールを作り上げるまでの膨大な作業量に要する時間なども理由に挙げられる。しかし、より重要な要素として、試験デザインを含むプロトコール骨子（プロトコールコンセプト）が固定するまでに時間がかかることが多く、対象・介入内容・評価内容・および試験デザインの臨床試験骨子自体が二転三転することによって、より時間がかかることがしばしば見られる。

臨床試験計画においては臨床医学のみではなく臨床試験方法論やデータ管理学などの知識が必要である。臨床試験計画チームに専門家が必要なだけではなく、臨床試験を計画する臨床家が臨床試験方法論などに関して必要十分の知識をもつことが必要である。臨床家が特に理解しておくべき事柄に関して整理し、臨床家の観点から説明を行う方法を研究することを本研究の目的とした。

B. 研究方法

臨床試験で最も重要な点は、最終解析でどのような解析をし、試験で用いられた介入内容を評価するか、という点である。臨床家は、臨床医学の知識が深いが故に、介入内容の詳細にこだわりがちで、試験計画の際に最終解析への注目度が薄れがちである。さらに、最終解析をどう行うか、ということと試験計画時の症例数算定は密接に結びついているが、統計用語が用いられる症例数算定の箇所は臨床家から嫌遠されがちである。症例数算定で用いられる数字のいくつかは統計家が判断するものであるが、キーとなる数字は臨床家が臨床的に判断しなければならないものが多い。Single arm phase II trial の場合と selection design の randomized phase II design において統計家が主に責任をもつ数字と、臨床家が主に責任を持つべき数字を区別し、最終解析と関連付けて説明する。

C. 研究結果

1. Single arm phase II trial

最終解析では、試験計画時に設定した閾値奏効割合を「下回ることはまずないだろう」と結論できれば、「Phase III trial で標準治療群と闘わせるにあたり十分に有望」と結論できることになる。

ここで、試験治療での効果が閾値奏効割合を下回らないことの検証は、割合であれば主に検定、生存率、無病生存率などの時間解析結果であれば推定の方法を用いる。

閾値奏効割合（率）は、医学的に判断され試験計画時に設定される数値である。設定方法は、通常標準治療における有効率と同程度、あるいは少し低めに設定する。試験計画時に医学的に判断して設定する数字として期待奏効割合（率）がある。これは試験治療の奏効割合としてどの程度期待できるか、という数値を設定する。これら二つの数値および統計担当者が主に担当するα値、β値から必要症例数が算定される。期待奏効割合（率）はそれまでのパイロットスタディーなどの結果から予測される奏効割合（率）を設定する。単一施設からの極めて良好な奏効割合をそのまま適応する際には注意が必要である。これらのパイロットスタディーにおける症例数は少なく、奏効割合の信頼区間は大きい。点推定値として良好な奏効割合が得られた場合はその成績が公表される確率が高くなるという公表バイアスを考慮する必要がある。

期待奏効割合（率）を高く設定しすぎる（期待しすぎる）ことによるリスクを示す。期待奏効割合が高い場合（=閾値奏効割合との間隔が広い場合）は、算定される必要症例数が少なくなる。臨床試験におけるスムーズな患者登録は、臨床試験においてもっとも重要な点の一つであり、試験計画時において必要症例数を可能な限り最小限にとどめたい、と臨床家は考える。倫理的にも確かに重要な要素である。試験最終解析での奏効割合の点推定値が60％の2つの例を示す。片方は、18 例中奏効例が 12 例の場合、および 60 例中 30 例だった場合である。同じ点推定値 60％でも、その信頼区間は、－％、－％と大きく異なる。最終解析の検定（片側検定）では、閾値奏効割合が40％だった場合に、前者は P=となり、後者は P=となる。つまり、前者においては帰無仮説を棄却することができず、閾値奏効割合を「下回ることはまずないだろう」と結論することができないことになる。

2. Randomized phase II trial, selection design

新薬が短期間の間にいくつか出ているような場合などにおいて、すべての新薬において大規模無作為比較第 III 相試験を実施することは困難である。標準治療と無作為比較第 III 相試験で比較するための最有力候補を選ぶというデザインの第 II 相試験であり、Simon らにより 1985 年に提案されている。2 群（あるいは 3 群以上）において、有効率がすぐれていた群の介入内容を、次期無作為比較第 III 相試験での試験群とする。

最終解析では、基本的にはアームどうしの差にかかわらず（"by any amount"）、最も有効性を示したアームが選ばれることに注意する必要がある。

症例数算定においては、方群の奏効割合の推定値と、もう一方の群がたとえば 15％その奏効割合が真に上回っていたとして、本当に優れているほうを"selection"する確率をたとえば 90％と設定して算定する。このうち、奏効割合の推定値、およびどの程度上回っているかとする数値は医学的に判断する。

繰り返しになるが、これはどちらかの群が優れている、ということを検証するものではないことを強調することが臨床家にと

って重要である。あくまでも標準治療と無作為比較第 III 相試験で比較するための最有力候補を絞り込むためのデザインである。例えば、Randomized phase II trial で、真の群間の奏効率の差が 15%（40% vs. 55%）であった場合に優れている群を選択できる確率を 80%、85%、90%とした場合は方群 16 例、23 例、36 例の症例数が必要になる。Randomized phase II trial では、このように方群が 20－40 例程度（全体で 100 例未満）で運用されることが多いが、方群が数十例だった場合に、それぞれおける優位差検定時の統計学的パワーを下表に示す。これからも、どちらかの群を検証するものではない、ということが明らかである。

S1	S2	N (片群)	Power (%)
40	55	30	22
40	55	40	28
40	55	50	33
40	55	80	49
40	55	100	58
40	55	150	75
40	55	200	86

D. 考察

試験デザインやその背景となる統計学的事項に関して、臨床家が理解しにくい点などを整理し、教育的説明などを行うことにより、計画される臨床試験の質の向上のみならず、臨床試験計画時におけるプロセスをより合理化していくことができると考えられる。

E. 結論

試験デザインやその背景となる統計学的事項に関して、臨床家が理解しにくい点などを整理し、教育的説明などを行うことにより、臨床試験計画時におけるプロセスをより合理化していくことが重要である。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

Imahashi N, Inamoto Y, Seto A, Watanabe K, Nishiwaki S, Yanagisawa M, Shinba M, Yasuda T, Kuwatsuka Y, Atsuta Y, Kodera Y, Miyamura K. Impact on relapse of corticosteroid therapy after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia. Clin Transplant. in press.

Muramatsu H, Kojima S, Yoshimi A, Atsuta Y, Kato K, Nagatoshi Y, Inoue M, Koike K, Kawase T, Ito M, Kurosawa H, Tanizawa A, Tono C, Hamamoto K, Hotta N, Watanabe A, Morishima Y, Kawa K, Shimada H. Outcome of 125 children with CML who received transplants from unrelated donors: the Japan Marrow Donor Program (JMDP). Biol Blood Marrow Transplant. 2010;16: 231-8.

Yazaki M, Atsuta Y, Kato K, Kato S, Taniguchi S, Takahashi S, Ogawa H, Kouzai Y, Kobayashi T, Inoue M, Kobayashi R, Nagamura-Inoue T, Azuma H, Takanashi M, Kai S, Nakabayashi M, and Saito H, for the Japan Cord Blood Bank Network. Incidence and Risk Factor of Early Bacterial Infections after Unrelated Cord Blood Transplantation. Biol Blood Marrow Transplant. 2009;15:439-46.

Kuwatsuka Y, Miyamura K, Suzuki R, Kasai M, Maruta A, Ogawa H, Tanosaki R, Takahashi S, Koda K, Yago K, Atsuta Y,

Yoshida T, Sakamaki H, Kodera Y. Hematopoietic stem cell transplantation for core binding factor acute myeloid leukemia: t(8;21) and inv(16) represent different clinical outcomes. Blood. 2009;113: 2096 -103

Atsuta Y, Suzuki R, Nagamura-Inoue T, Taniguchi S, Takahashi S, Kai S, Sakamaki H, Kouzai Y, Kasai M, Fukuda T, Azuma H, Takanashi M, Okamoto S, Tsuchida M, Kawa K, Morishima Y, Kodera Y, and Kato S, for the Japan Marrow Donor Program and the Japan Cord Blood Bank Network. Disease-specific analyses of unrelated cord blood transplant compared with unrelated bone marrow transplant in adult patients with acute leukemia. Blood. 2009;113: 1631-8.

Nishida T, Murayama T, Hirai H, Okamoto S, Sao H, Hara M, Kanamori H, Atsuta Y, Matsuo K, Morishima Y, Kodera Y. Phase II study of tacrolimus and methotrexate for prophylaxis of acute graft-versus-host disease after HLA-A, B, and DRB1 genotypically mismatched unrelated bone marrow transplantation among Japanese patients. Int J Hematol. 2009;89:98-105

Azuma H, Hirayama J, Akino M, Miura R, Kiyama Y, Imai K, Kasai M, Koizumi K, Kakinoki Y, Makiguchi Y, Kubo K, Atsuta Y, Fujihara M, Homma C, Yamamoto S, Kato T, and Ikeda H. Reduction in adverse reactions to platelets by the removal of plasma supernatant and resuspension in a new additive solution (M-sol).Transfusion.2009; 49:214-18.

2. 学会発表

Comparison of unrelated cord blood transplantation and human leucocyte antigen mismatched unrelated bone marrow transplantation for adult patients with hematological malignancy.
Yoshiko Atsuta, Ritsuro Suzuki, Tokiko Nagamura-Inoue, Shuichi Taniguchi, Satoshi Takahashi, Shunro Kai, Hisashi Sakamaki, Yasushi Kouzai, Masaharu Kasai, Takahiro Fukuda, Hiroshi Azuma, Minoko Takanashi, Shinichiro Okamoto, Masahiro Tsuchida, Keisei Kawa, Yoshihisa Kodera, Yasuo Morishima, and Shunichi Kato, for the Japan Marrow Donor Program and the Japan Cord Blood Bank Network.
2010 BMT Tandem Meetings
Best Abstracts Plenary Session
February 26, 2010（口演）

熱田由子、鈴木律朗、山下卓也、福田隆浩、宮村耕一、坂巻壽、小寺良尚
成人血縁者間造血幹細胞移植における二次性固形腫瘍
第 71 回　日本血液学会総会
2009 年 10 月 25 日　OS-3-30（口演）

H. 知的財産権の出願・登録状況

なし

別添５

研究成果の刊行に関する一覧表

平成 21 年度

研究成果の刊行に関する一覧表

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ohtake S, Miyawaki S, Miyazaki Y, Takeuchi J, Ohnishi K, Naoe T, Ohno R. et al.	Randomized trial of response-oriented individualized versus fixed -schedule induction chemotherapy with idarubisin and cytarabine in adlut acute myeloid leukemia: the JALSG AML95 study.	Int J Hematol.		[Epub ahead of print]	2010
Morita Y, Kanamaru A, Miyazaki Y, Ohnishi K, Naoe T, Ohno R. et al.	Comparative analysis of remission induction therapy for high-risk MDS and AML progressed from MDS in the MDS200 study of Japan Adult Leukemia Study Group.	Int J Hematol.	91	97-103	2010
Sakamaki H, Miyawaki S, Ohtake S, Miyazaki Y, Ohno R. et al.	Allogeneic stem cell transplantation versus chemotherapy as post-remission therapy for intermediate or poor risk adult acute myeloid leukemia: results of the JALSG AML97 study.	Int J Hematol.		[Epub ahead of print]	2010
Sakamaki H, Usui N, Miyawaki S, Naoe T, Miyazaki Y, Ohnishi K, Ohno R. et al.	Phase 1/2 clinical study of dasatinib in Japanese patients with chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia.	Int J Hematol.	89	332-341	2009
Kobayashi Y, Takeuchi J, Miyawaki S, Naoe T, Usui N, Ohno R. et al.	Phase I/II study of humanized anti-CD33 antibody conjugated with calicheamicin, gemtuzumab ozogamicin, in relapsed or refractory acute myeloid leukemia: final results of Japanese multicenter cooperative study.	Int J Hematol.	89	460-469	2009
Tojo A, Kobayashi U, Miyazaki Y, Usui N, Naoe T, et al.	A Phase I/II study of nilotinib in Japanese patients with imatinib-resistant or -intolerant Ph+ CML or relapsed/refractory Ph+ ALL	Int J Hematol.	89	679-688	2009
Shiotsu Y, Naoe T. et al.	KW-2449, a novel multi-kinase inhibitor, suppresses the growth of leukemia cells with FLT3 mutations or T315I-mutated BCR/ABL translocation.	Blood.	114	1607-17	2009
Ishikawa Y, Miyawaki S, Miyazaki Y, Naoe T. et al.	Comprehensive analysis of cooperative gene mutations between class I and class II in de novo acute myeloid leukemia.	Eur J Haematol.	83	90-98	2009
Sanz MA, Naoe T. et al.	Management of acute promyelocytic leukemia: Recommendations from an expert panel on behalf of the European LeukemiaNet.	Blood.	113	1875-91	2009
Fujita H, Ohnishi K, Miyawaki S, Naoe T, et all.	Management of infection in patients with acute leukemia during chmotherapy in Japan:questionnaire analysis by the Japan Adult Leukemia Study Group	Int J Hematol.	90	191-198	2009
Kuwatsuka Y, Atsuta Y, et al.	Hematopoietic stem cell transplantation for core binding factor acute myeloid leukemia: t(8;21) and inv(16) represent different clinical outcomes.	Blood.	113	2096-103	2009
Atsuta Y. et al.	Disease-specific analyses of unrelated cord blood transplant compared with unrelated bone marrow transplant in adult patients with acute leukemia.	Blood	113	1631-38	2009

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kiguchi T, Ito Y. et al.	Compliance with taking imatinib mesylate in patients with chronic myeloid leukemia in the chronic phase.	Leuk Res.	33	506-508	2009
Hirano I, Ohnishi K. et al.	Depletion of pleckstrin homology domain leucine-rich repeat protein phosphatase 1 and 2 by Bcr-Abl promotes chronic myelogenous leukemia cell proliferation through continuous phosphorylation of Akt isoforms.	J Biol Chem.	284	22155-65	2009
Nakamura S, Ohnishi K et al..	Development and pharmacologic characterization of deoxybromophospha sugar derivatives with antileukemic activity.	Invest New Drugs.		[Epub ahead of print]	2009
Takeshita A, Ohnishi K, Naoe T, Ohno R. et al.	CMC-544 (inotuzumab ozogamicin) shows less effect on multidrug resistant cells: analyses in cell lines and cells from patients with B-cell chronic lymphocytic leukaemia and lymphoma.	Br J Haematol.	146	34-43	2009
Takeshita A, Naoe T, Ohnishi K, Ohno R. et al.	CMC-544 (inotuzumab ozogamicin), an anti-CD22 immuno-conjugate of calicheamicin, alters the levels of target molecules of malignant B-cells.	Leukemia.	23	1329-36	2009
Suzuki R, Ohtake S, Takeuchi J, Miyawaki S, Ohno R, Naoe T. et al.	The clinical characteristics of $CD7^{+}CD56^{+}$ acute myeloid leukemias other than M0.	Int J Hematol.		[Epub ahead of print]	2010
Suzuki M, Naoe T. et al.	BCR-ABL-independent and RAS / MAPK pathway-dependent form of imatinib resistance in Ph-positive acute lymphoblastic leukemia cell line with activation of EphB4.	Eur J Haematol.	84	229-238	2010
Inamoto Y, Naoe T. et al.	Donor single nucleotide polymorphism in the CCR9 gene affects the incidence of skin GVHD.	Bone Marrow Transplant.	45	363-369	2010
Tanizaki R, Naoe T. et al.	Irrespective of CD34 expression, lineage-committed cell fraction reconstitutes and re-establishes transformed Philadelphia chromosome-positive leukemia in NOD / SCID / IL-2Rgammac mice.	Cancer Sci.	101	631-638	2009
Sugimoto T, Naoe T. et al.	Escape mechanisms from antibody therapy to lymphoma cells: downregulation of CD20 mRNA by recruitment of the HDAC complex and not by DNA methylation. 390: 48-53, 2009.	Biochem Biophys Res Commun.	390	48-53	2009
Hiraga J, Naoe T. et al.	Down-regulation of CD20 expression in B-cell lymphoma cells after treatment with rituximab-containing combination chemotherapies: its prevalence and clinical significance.	Blood.	113	4885-93	2009
Doi Y, Miyazaki Y. et al.	High-resolution melting analysis for a reliable and two-step scanning of mutations in the tyrosine kinase dkmain of the chimeical *bcr- abl* gene.	Int J Hematol.	90	37-43	2009
Sakai M, Miyazaki Y.et al.	Long-term efficacy of imatinib in a practical setting is correlated with imatinib trough concentration that is influenced by body size: a report by the Nagasaki CML Study Group.	Int J Hematol.	89	319-325	2009

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
Iwanaga M, Miyazaki Y. et al.	Relationship between Monoclonal Gammopathy of Undetermined Significance and Radiation Exposure in Nagasaki Atomic Bomb Survivors.	Blood	113	1639-50	2009
Tanaka M, Miyawaki S, et al.	The cytotoxic effects of gemtuzumab ozogamicin (mylotarg) in combination with conventional antileukemic agents by isobologram analysis in vitro.	Anticancer Res.	29	4589-96	2009
Ishizawa K, Ohnishi K.. et al.	Safety and efficacy of rasburicase (SR29142) in a Japanese phase II study.	Cancer Sci.	100	357-362	2009
Yanada M, Ohno R, Naoe T.	Recent advances in the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia.	Int J Hematol.	89	3-13	2009
Espinoza JL, Ohtake S. et al.	NKG2D gene polymorphism has a significant impact on transplant outcomes after HLA-fully-matched unrelated bone marrow transplantation for standard risk hematologic malignancies.	Haematologica.	94	1427-34	2009
Matsuda A, Miyazaki Y, et al.	Differences in the distribution of subtypes according to the WHO classification 2008 between Japanese and German patients with Refractory Anemia according to the FAB classification in Myelodysplastic Syndromes.	Leukemia Res.		[in press]	
宮崎泰司	JALSGにおける急性骨髄性白血病治療研究	臨床血液	50	611-616	2009
石川裕一、宮崎泰司、宮脇修一、直江知樹　他	WHO分類に基づく急性骨髄性白血病における網羅的遺伝子変異の解析.	臨床血液	50	597-603	2009
Mori M, Kobayashi Y. et al.	The indolent course and high incidence of t(14;18) in primary duodenal follicular lymphoma.	Ann Oncol.		[in press]	2009
Watanabe T, Kobayashi Y. et al.	Potential efficacy of the oral histone deacetylase inhibitor vorinostat in a phase I trial in follicular and mantle cell lymphoma.	Cancer Sci.	101	196-200	2010
Yamaguchi M, Kobayashi Y, Usui N, et al.	Phase I/II study of concurrent chemoradiotherapy for localized nasal NK/T-cell lymphoma: Japan Clinical Oncology Group Study JCOG0211.	J Clin Oncol.	27	5594-600	2009
Kobayashi Y.	Recent advances in the treatment of follicular lymphoma.	Int J Clin Oncol.	14	191-196	2009
Kato M, Kobayashi Y. et al.	Frequent inactivation of A20 in B-cell lymphomas.	Nature.	459	712-716	2009
Maeshima A M, Kobayashi Y. et al.	Secondary CD5+ diffuse large B-cell lymphoma not associated with transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma (Richter syndrome).	Am J Clin Pathol.	131	339-346	2009

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
Maeshima A M, Kobayashi Y. et al.	Histological and immunophenotypic changes in 59 cases of B-cell non-Hodgkin's lymphoma after rituximab therapy.	Cancer Sci.	100	54-61	2009
Maeda Y, Kanamaru A. et al.	Relationship between expression of mutant type glutathione S-transferase theta-1 gene and reactivity of rapamycin in myelodysplastic syndrome.	Hematology	14	266-270	2009
Wada N, Kanamaru A. et al.	Diffuse large B-cell lymphoma with a high number of epithelioid histiocytes (lymphoepithelioid B-cell lymphoma): a study of Osaka Lymphoma Study Group.	Virchows Arch.	455	285-293	2009
Hirase C, Kanamaru A. et al.	Hypersensitivity of Ph-positive lymphoid cell lines to rapamycin: Possible clinical application of mTOR inhibitor.	Leuk Res.	33	450-459	2009
Tamura K, Kanamaru A et al.	Efficacy and safety of micafungin, an echinocandin antifungal agent, on invasive fungal infections in patients with hematological disorders.	Leuk Lymphoma.	50	92-100	2009
Yamaguchi Y, Usui N, et al.	Gemtuzumab ozogamicin (GO) in relapsed/refractory patients with acute myeloid leukemia.	Gan To Kagaku Ryoho	36	1105-09	2009
Yahagi Y, Usui N, et al.	Fractionated administration of gemtuzumab ozogamaicin for refractory acute myeloid leukemia	臨床血液	50	1601-05	2009
Miura K, Takeucni J, et al.	Feasibility and eligibility of retreatment with rabbit anti-T lymphocyte globulin for aplastic anemia previously treated with horse anti-thymocyte globulin.	Int J Hematol	90	426-428	2009
Kiguchi T, Ito Y, et al.	Restoration of cardiac function by an iron chelator, deferasirox, in a patient with aplastic anemia and cardiac iron overload.	Int J Hematol	89	546-548	2009
Yazaki M, Atsuta Y, et al.	Incidence and Risk Factor of Early Bacterial Infections after Unrelated Cord Blood Transplantation.	Biol Blood Marrow Transplant.	15	439-446	2009
Nishida T, Atsuta Y. et al.	Phase II study of tacrolimus and methotrexate for prophylaxis of acute graft-versus-host disease after HLA-A, B, and DRB1 genotypically mismatched unrelated bone marrow transplantation among Japanese patients.	Int J Hematol.	89	98-105	2009
Azuma H, Atsuta Y. et al.	Reduction in adverse reactions to platelets by the removal of plasma supernatant and resuspension in a new additive solution (M-sol).	Transfusion	49	214-218	2009

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
Imahashi N, Atsuta Y, et al.	Impact on relapse of corticosteroid therapy after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia.	Clin Transplant.		[in press]	
Muramatsu H, Atsuta Y, et al.	Outcome of 125 children with CML who received transplants from unrelated donors: the Japan Marrow Donor Program (JMDP).	Biol Blood Marrow Transplant.		[in press]	

研究成果の主な刊行物・別刷

Int J Hematol
DOI 10.1007/s12185-009-0480-5

ORIGINAL ARTICLE

Randomized trial of response-oriented individualized versus fixed-schedule induction chemotherapy with idarubicin and cytarabine in adult acute myeloid leukemia: the JALSG AML95 study

Shigeki Ohtake · Shuichi Miyawaki · Hitoshi Kiyoi · Yasushi Miyazaki · Hirokazu Okumura · Shin Matsuda · Tadashi Nagai · Yuji Kishimoto · Masaya Okada · Masatomo Takahashi · Hiroshi Handa · Jin Takeuchi · Shinichi Kageyama · Norio Asou · Fumiharu Yagasaki · Yasuhiro Maeda · Kazunori Ohnishi · Tomoki Naoe · Ryuzo Ohno

Received: 11 May 2009 / Revised: 11 December 2009 / Accepted: 21 December 2009

Abstract A multicenter, prospective, randomized study was conducted to compare a response-oriented individualized remission induction therapy with a standard fixed-schedule induction therapy, using idarubicin (IDR) and cytarabine (Ara-C), in adult patients with acute myeloid leukemia (AML). Newly diagnosed patients with AML of age less than 65 were randomly assigned to receive either of the two schedules. Both groups received IDR (12 mg/m^2) for 3 days and Ara-C (100 mg/m^2) for 7 days. In the individualized group, if the bone marrow on day 8 did not become hypocellular with less than 15% blasts, patients received additional IDR for one more day and Ara-C for 2 or 3 more days. Patients achieving complete remission (CR) received the same post-remission therapy. The CR rate was 79.4% for the individualized group ($n = 209$) and 81.9% for the fixed group ($n = 221$) ($p = 0.598$). At a median follow-up of 81 months, 7-year predicted overall survival was 37% for the individualized group and 39% for

For the Japan Adult Leukemia Study Group (JALSG).

S. Ohtake (✉) · H. Okumura
Department of Hematology, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa 920-8641, Japan
e-mail: sohtake@med3.m.kanazawa-u.ac.jp

S. Miyawaki
Division of Hematology, Saiseikai Maebashi Hospital, Maebashi, Japan

H. Kiyoi · T. Naoe
Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Y. Miyazaki
Department of Hematology and Molecular Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

S. Matsuda
Center for Hematopoietic Disorders, Ohta Nishinouchi Hospital, The Ohta Foundation, Kohriyama, Japan

T. Nagai
Division of Hematology, Jichi Medical University, Shimotsuke, Tochigi, Japan

Y. Kishimoto
The First Department of Internal Medicine, Kansai Medical University, Moriguchi, Japan

M. Okada
Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

M. Takahashi
Division of Hematology and Oncology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

H. Handa
Department of Medicine and Clinical Science, Gunma University Graduate School of Medicine, Maebashi, Japan

J. Takeuchi
Department of Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan

S. Kageyama
Department of Hematology and Oncology, Mie University Graduate School of Medicine, Tsu, Japan

Published online: 07 January 2010

the fixed group ($p = 0.496$), and 7-year predicted event-free survival was 22% for the individualized group and 23% for the fixed group ($p = 0.546$). Thus, the present study could not demonstrate any advantage of a response-oriented individualized induction therapy over a fixed-schedule induction therapy in this protocol setting.

Keywords Acute myeloid leukemia · Response-oriented individualized induction therapy · Idarubicin · Cytarabine

1 Introduction

In Japan, a response-oriented individualized induction therapy has been used for adult acute myeloid leukemia (AML) since the reporting of the success of DCMP two-step therapy using daunorubicin (DNR), cytarabine (Ara-C), 6-mercaptopurine (6MP) and prednisolone (PSL), by Uzuka et al. in the mid 1970s [1]. They reported a complete remission (CR) rate of more than 80% in adult AML, which is currently not surprisingly high but was remarkable in the mid 1970s even for a single institutional study. A subsequent multi-institutional study conducted at the Koseisho Leukemia Study Group using this DCMP two-step protocol could not replicate the high CR rate, but a subset analysis revealed the first-step alone could induce almost the same CR rate as the two-step therapy [2]. Accordingly, a response-oriented individualized induction therapy, the BHAC-DMP therapy, using enocitabine (BHAC), Ara-C, 6MP, and PSL, was developed, and Ohno et al. [3] reported more than 80% CR in adult AML by a single institutional study.

The multi-institutional AML87 study conducted by the Japan Adult Leukemia Study Group (JALSG) confirmed the high CR rate of response-oriented individualized BHAC-DMP therapy in adult AML, reporting an 80% CR rate [4]. Subsequent JALSG studies, AML89 [5] and AML92 [6], also employed the response-oriented individualized induction therapy, and reported 81 and 77% CR rates, respectively, in adult patients of age less than 65 years with non-M3 type AML. These CR rates were around 10% higher than those reported from cooperative study groups in the USA and Europe, where fixed-schedule induction therapies are used [7]. Therefore, even though the necessity for a randomized study was seriously discussed among JALSG members, it was not possible to find any fixed-schedule regimen worth comparing with the present individualized therapy.

In the above 3 JALSG studies, DNR was used as one of the key drugs. However, in the late 1980s, a new DNR analogue, idarubicin (IDR), was introduced clinically, and in the early 1990s, one single [8] and 2 multi-institutional studies [9, 10] reported that IDR plus Ara-C regimens could produce 70–80% CR rates in adult AML by fixed-schedule therapy, which were significantly higher than the 58–59% CR rates of DNR plus Ara-C regimens.

Consequently, after IDR had been approved in Japan in 1995, a randomized study using IDR and Ara-C was conducted, comparing a response-oriented individualized induction therapy with a fixed-schedule therapy in previously untreated adult patients with AML.

2 Patients and methods

2.1 Patients

From August 1995 to December 1997, 437 newly diagnosed adult patients with AML, aged 15–64 years, were consecutively registered from 79 institutions, which participated in JALSG. The enrolled number of patients per hospital varied from 1 to 23 with median number of 4, and about 60% of patients were registered from major hospitals listed in the institutions of the authors.

AML was 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. Then, diagnosis was reevaluated by the central review committee. FAB-M3 was not registered in this study. Eligibility criteria included adequate functioning of the liver (serum bilirubin level < 2.0 mg/dL), kidney (serum creatinine < 2.0 mg/dL), heart, and lungs, and an Eastern Cooperative Oncology Group performance status between 0 and 3. Patients were not eligible if they had prediagnosed myelodysplastic syndrome (MDS), but were eligible if they had no definite diagnosis of MDS, as confirmed by bone marrow histological analysis even when they had a previous history of

N. Asou
Department of Hematology, Kumamoto University School of Medicine, Kumamoto, Japan

F. Yagasaki
Department of Hematology, Saitama Medical School, Hidaka, Japan

Y. Maeda
Department of Hematology, Kinki University School of Medicine, Osaka-Sayama, Japan

K. Ohnishi
Oncology Center, Hamamatsu University School of Medicine, Hamamatsu, Japan

R. Ohno
Aichi Cancer Center, Nagoya, Japan

hematological abnormality. Cytogenetic analyses were performed at either laboratories in participating hospitals or authorized commercial laboratories according to standard methods of G-banding. Cytogenetic abnormalities were grouped by standard criteria and classified according to the MRC classification [11]. The protocol was approved by institutional review board of each hospital. Informed consent was obtained from all patients before registration.

2.2 Treatment regimens

Patients were assigned randomly to receive either a response-oriented individualized induction therapy or a fixed-schedule induction therapy, using a centralized telephone procedure. All patients received IDR (12 mg/m^2/day, intravenously) from days 1 to 3 and Ara-C (100 mg/m^2/day, by 24-h continuous infusion) from days 1 to 7. Examination of bone marrow on the day 8 was evaluated at each participating hospital and the decision was made by the attending physician in charge of the hospital. In the individualized group, bone marrow aspiration was performed on day 8, and if the marrow was not severely hypoplastic and had more than 15% blasts, additional IDR was given on day 8 and Ara-C on days 8 to 10, or if the marrow was severely hypoplastic and had more than 15% blasts, additional IDR was given on day 8 and Ara-C on days 8 and 9. If patients suffered from documented infection on day 8, cancellation of additional chemotherapy was permitted according to the judgment of the attending physician (Fig. 1). The main aim of the individualized therapy was to give highly intensive but not too toxic doses of anti-leukemia drugs, especially IDR, to make the bone marrow severely hypoplastic, reduce the percentage of blasts to less than 5% within 10 days and obtain CR by the first course of induction therapy. In the fixed-schedule group (fixed group), patients did not receive additional doses regardless of their marrow status at day 8. If patients did not achieve CR by the first course, the same induction therapy was repeated at approximately 3- to 4-week intervals. If patients did not achieve CR with two courses, they were judged as failure cases.

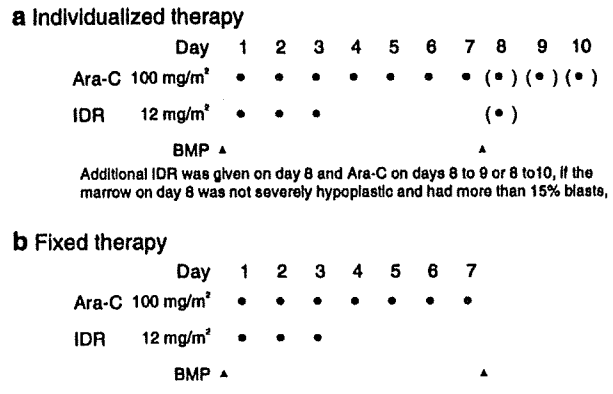

Fig. 1 Treatment scheme of induction therapy

All patients in both groups who had achieved CR planned to receive the same 3 courses of consolidation therapy. The first course consisted of mitoxantrone (MIT; 7 mg/m^2 by 30-min infusion on days 1–3) and Ara-C (200 mg/m^2 by 24-h continuous infusion on days 1–5). The second consisted of BHAC (200 mg/m^2 by 3-h infusion on days 1–7), DNR (50 mg/m^2 intravenously on days 1–3), 6MP (70 mg/m^2 orally on days 1–7), and etoposide (ETP; 100 mg/m^2 by 1-h infusion on days 1–5). The third consisted of BHAC (200 mg/m^2 on days 1–7) and aclarubicin (ACR; 14 mg/m^2 intravenously on days 1–7). Each consolidation course was given as soon as possible after WBC and platelet counts had recovered to more than 3,000/μL and 100,000/μL, respectively. Intrathecal methotrexate (15 mg), Ara-C (40 mg), and PSL (10 mg) were given after the second consolidation therapy for the prophylaxis of central nervous system leukemia.

After the completion of consolidation therapy, all patients planned to receive 6 courses of maintenance/intensification therapy every 2 months. The first course consisted of BHAC (170 mg/m^2 on days 1–5), DNR (40 mg/m^2 on days 1 and 4), and 6MP (70 mg/m^2 on days 1–7). The second consisted of BHAC (170 mg/m^2 on days 1–5) and MIT (5 mg/m^2 on days 1 and 2). The third consisted of BHAC (170 mg/m^2 on days 1–5), ETP (80 mg/m^2 on days 1, 3, and 5), and vindesine (2 mg/m^2 intravenously on days 1 and 8). The fourth consisted of BHAC (170 mg/m^2 on days 1–5), ACR (14 mg/m^2 on days 1–4) and 6MP (70 mg/m^2 on days 1–7), the fifth was the same as the first, and the sixth was the same as the third. Each course was given at 2-month intervals.

Best supportive care, including administration of antibiotics and platelet transfusion from blood cell separators, was given if indicated. When patients had life-threatening infections during neutropenia, the use of granulocyte colony-stimulating factor was permitted.

2.3 Response criteria and statistical analysis

CR was defined as the presence of all of the following: less than 5% of blasts in bone marrow, no leukemic blasts in peripheral blood, recovery of peripheral neutrophil counts over 1,000/μL and platelet counts over 100,000/μL, and no evidence of extramedullary leukemia. CR had to continue for at least 4 weeks, but the date of CR was defined as the first day when these criteria were fulfilled. Relapse was defined as the presence of at least one of the following: recurrence of more than 10% leukemic cells in bone marrow, any leukemic cells in peripheral blood, and appearance of extramedullary leukemia.

Overall survival (OS) was calculated from the first day of induction therapy to death by any cause and censored at the last follow-up. Event-free survival (EFS) was computed from the first day of induction therapy to relapse or death by any cause and censored at the last follow-up, and the survival time of patients who did not achieve CR was defined as 0 days. Relapse-free survival (RFS) for patients who achieved CR was measured from the date of CR to relapse or death by any cause and censored at the last follow-up. Patients who underwent allogeneic bone marrow transplantation (BMT) were censored at the date of BMT or not censored according to the object of the analysis. Kaplan–Meier product-limit estimates were used to determine OS, EFS, and RFS. To test factors to predict CR, χ^2 test and Wilcoxon rank-sum test were used for univariate analysis and the multiple logistic regression model for multivariate analysis. For comparison of OS, EFS, and RFS, the log-rank test was used for univariate analysis and Cox's proportional hazard model for multivariate analysis. JMP software (SAS Institute Inc., Cary, NC, USA) was used for the analysis; p values less than 0.05 (two-sided) were considered statistically significant. Analysis was done on an intent-to-treat basis.

3 Results

3.1 Patient population and characteristics

Of 437 patients registered, 7 patients were judged as ineligible by the central review committee because of other diseases: one refractory anemia with excess of blast, 5 mixed-lineage leukemia, and one acute lymphoblastic leukemia (ALL), with 430 patients considered evaluable. Two hundred nine patients received the individualized therapy and 221 the fixed-schedule therapy. Pretreatment characteristics are presented in Table 1. There were no major imbalances between the two randomized groups. Overall, the median age was 44 years, and 154 patients (36%) were of age 50 years or older. Cytogenetic analysis was reported in 414 patients (96%), and the cytogenetic prognostic groups were equally distributed in both arms.

3.2 Overall treatment results

Of 430 evaluable patients, 347 (80.7%) achieved CR. Of 209 patients in the individualized group, 166 (79.4%) achieved CR, and of 221 in the fixed group, 181 (81.9%) obtained CR ($p = 0.516$) (Table 2). CR rates related to FAB classification, age, and cytogenetics are shown in Table 2, and there were no statistically significant differences between the two groups. In the individualized group, of 41 patients with favorable chromosomes, 39 (95%) achieved CR, of 133 with intermediate chromosomes, 109 (79%) achieved CR, and of 28 with adverse chromosomes, 17 (61%) achieved CR. In the fixed group, of 49 patients with favorable chromosomes,

Table 1 Pretreatment characteristics

	Individualized group ($n = 209$)	Fixed group ($n = 221$)
Median age (range)	44 years (15–64)	44 years (15–64)
PS 0	34.9%	38.5%
PS 1	42.6%	45.2%
PS 2	14.4%	9.5%
PS 3	8.1%	6.8%
Leukocyte counts > 50,000/μL	17.7%*	29.9%*
Peroxidase positivity ≥ 50%	62.8%	64.2%
Presence of Auer body (%)	37.5%	46.1%
Presence of trilineage dysplasia	25.4%	21.2%
LDH ≥ 500 IU/L	65.9%	69.1%
Cytogenetics		
Favorable	19.6%	22.2%
Intermediate	63.6%	59.7%
Adverse	13.4%	14.0%
Unknown	3.3%	4.1%

* $p < 0.05$

Table 2 CR rates related to FAB classification, age, and cytogenetics

	All cases		Individualized group		Fixed group	
	No.	CR (%)	No.	CR (%)	No.	CR (%)
FAB						
M 0	16	62.5	8	62.5	8	62.5
M 1	80	85.0	41	85.4	39	84.6
M 2	192	82.3	95	77.9	97	86.6
M 4	108	78.7	55	80.0	53	77.4
M 5	20	90.0	5	100.0	15	86.7
M 6	8	50.0	2	50.0	6	50.0
M 7	6	66.7	3	66.7	3	66.7
Age						
15–19	40	90.0	19	100.0	21	81.0
20–29	65	78.5	29	75.9	36	80.6
30–39	71	81.7	41	75.6	30	90.0
40–49	100	83.0	45	77.8	55	87.3
50–59	105	77.1	53	79.2	52	75.0
60–64	49	77.6	22	77.3	27	77.8
Cytogenetics						
Favorable	90	93.3	41	95.1	49	91.8
Intermediate	265	80.8	133	78.9	132	82.6
Adverse	59	62.7	28	60.7	31	64.5
Unknown	16	75.0	7	71.4	9	77.8
Total	430	80.7	209	79.4	221	81.9

45 (92%) achieved CR, of 132 with intermediate chromosomes, 109 (83%) achieved CR, and of 31 with adverse chromosomes, 20 (65%) achieved CR.

In the individualized group, 149 patients (71%) achieved CR after the first course, and 79 (38%) patients who had received additional chemotherapy during the first course, 56 (71%) achieved CR. In the fixed group, 159 (72%) achieved CR after the first course (Table 3; Fig. 2). CR rates between patients who had equal to or more than 15% of blasts in bone marrow on day 8 and those had less than 15% were not significantly different in the individualized group (75 and 63%, respectively; $p = 0.09$), but were significantly different in the fixed group (81 and 56%, respectively; $p < 0.001$).

Myelosuppression judged by the nadir of leukocyte counts and the period of leukocyte count less than 1,000/μL after the first course of induction therapy was significantly more severe in the individualized group, as shown in Table 4. Early death within 30 days occurred in 10 (4.8%) in the individualized group and 4 (1.8%) in the fixed group ($p = 0.105$). There were no statistically significant differences in the distribution or frequency of complications between the two groups.

Significant favorable prognostic features for the achievement of CR were cytogenetic risk group (favorable or intermediate), blast peroxidase positivity of 50% or more, and pretreatment LDH value of less than 500 IU/L. These features were independent by the logistic regression analysis and not different between the two groups.

All courses of consolidation therapy were administered to 72% of patients in the individualized group and 80% in the fixed group ($p = 0.087$), and all courses of maintenance therapy were administered to 36 and 41% ($p = 0.365$), respectively. The most common reason for these cancellations was relapse in both groups (34 and 42 patients, respectively). The second common reason was BMT in the first remission (22 and 12 patients, respectively).

At a median follow-up of 81 months, 23 patients underwent BMT in the first remission, 29 after relapse and 4 without remission in the individualized group, and 15, 32 and 7 patients, respectively, in the fixed group. If patients who underwent BMT were censored at the date of transplantation to decrease the influence of BMT, 7-year predicted OS was 37% for the individualized group and 39% for the fixed group ($p = 0.496$) (Fig. 3a), and 7-year predicted EFS was 22 and 23%, respectively ($p = 0.546$) (Fig. 3b). If patients who underwent BMT were not censored, 7-year predicted OS was 35 and 35%, respectively

Table 3 Effect of individualized induction therapy

	Patients (%)	CR after first course	
		n	%
Individualized group	209	149	71
Additional chemotherapy −	130 (62)	93	72
Additional chemotherapy +	79 (38)	56	71
Fixed group	221	159	72

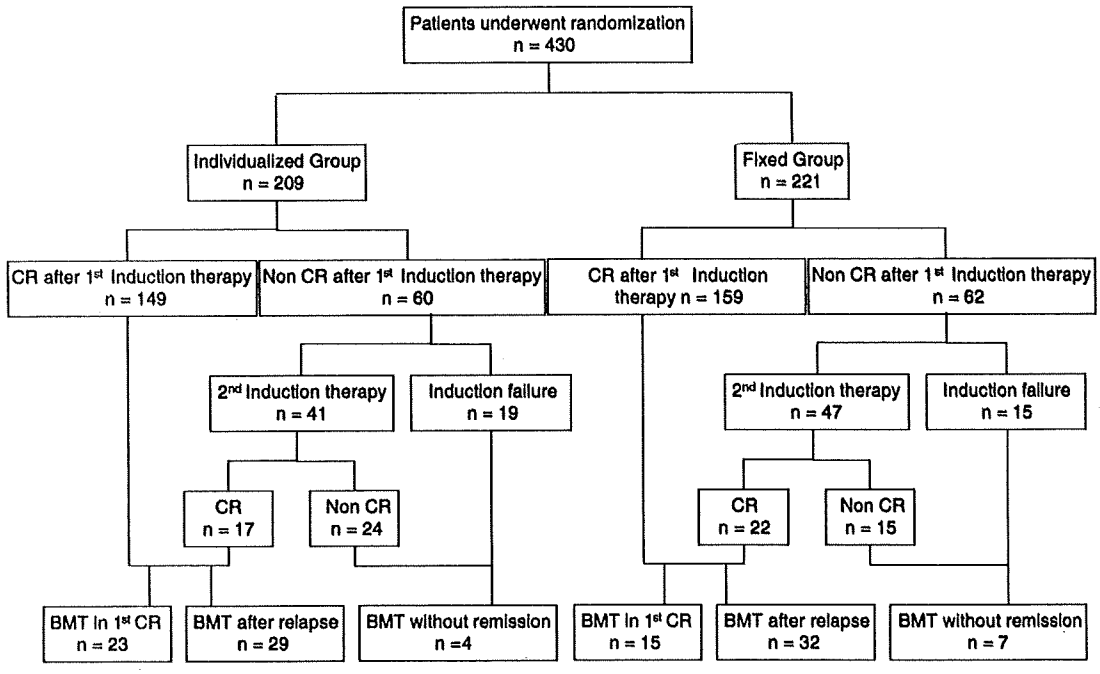

Fig. 2 Flow diagram: study design and outcome

Table 4 Comparison of treatment outcome

	Individualized group ($n = 209$)	Fixed group ($n = 221$)	p
CR rate (%)	79.4	81.9	0.516
After the first course	71.3	71.9	
After the second course	8.1	10.0	
Marrow blasts at day 8	12.9 ± 17.8%	11.1 ± 18.4%	0.021
Nadir of WBC[a]	328 ± 205/μL	394 ± 215/μL	0.0002
Period of WBC < 1,000/μL[a]	19.6 ± 9.8 days	17.8 ± 8.5 days	0.024
Days to CR[a]	38.9 ± 17.5	38.5 ± 16.2	0.802
Days till the consolidation therapy	49 ± 22	46 ± 18	0.157
Early death rate			
Within 30 days	4.8%	1.8%	0.105
Between 30 and 60 days	0.9%	1.4%	
Overall survival at 7 years	37%	39%	0.496
Event-free survival at 7 years	22%	23%	0.546

Data with ± denotes mean ± standard deviation

[a] After the initial course of induction therapy

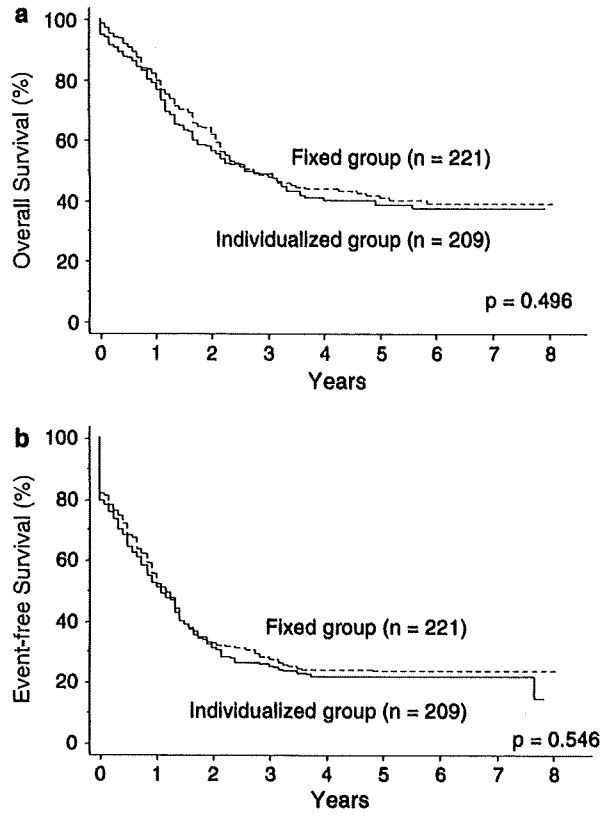

Fig. 3 Overall survival (**a**) and event-free survival (**b**). Predicted 7-year OS was 37% for the individualized group ($n = 209$) (*solid line*) and 39% for the fixed group ($n = 221$) (*dotted line*) ($p = 0.496$), and EFS was 22% for the individualized group (*solid line*) and 23% for the fixed group (*dotted line*) ($p = 0.546$)

($p = 0.840$), and 7-year predicted EFS was 23 and 24%, respectively ($p = 0.717$). Significant adverse prognostic features for OS were absence of Auer body, cytogenetic risk group (adverse), and age more than 30 years, and those for EFS were blast peroxidase positivity less than 50%, cytogenetic risk group (adverse), pretreatment LDH value equal or more than 500 IU/L, and FAB classification (M0, M6, or M7). When patients who underwent BMT were censored, RFS of CR patients was 27% for the individualized group and 29% for the fixed group ($p = 0.712$). Significant adverse prognostic features for RFS of CR patients were cytogenetic risk group (adverse) and FAB classification (M0, M6, or M7). There were no significant differences in these prognostic features between the two groups. However, among patients of age 50 years or older, the individualized group had significantly lower RFS (17%) than the fixed group (34%, $p = 0.026$), but there was no such difference of RFS (34 and 25%, respectively, $p = 0.194$) among patients of age less than 50 years.

4 Discussion

Most drug therapies are generally carried out in a response-oriented and individualized manner. Physicians adjust the dosage and treatment period depending on the response of patient's disease to the administered drugs. The reason why cancer chemotherapy is generally carried out by fixed dosage and period is because myelosuppression, the most important toxic effect of cytotoxic drugs, appears 7–10 days after the discontinuation of drugs. Myelosuppression is usually judged by leukocyte or platelet counts in the peripheral blood. However, if it is judged by bone marrow itself it is possible to obtain information on myelosuppression directly and earlier. Although the present individualized therapy requires frequent bone marrow aspirations and a prompt decision by attending physicians, well-trained hematology oncologists have little difficulty in