Ⅳ．　研究成果の刊行物（論文別刷）

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同種造血幹細胞移植後のウイルス感染対策

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Key words : Viral infection, Cytomegalovirus (CMV), Varicella zoster virus (VZV), Human herpesvirus 6 (HHV6)

はじめに

同種造血幹細胞移植（Hematopoietic Stem Cell Transplantation: HSCT）は，白血病などの造血器疾患に対する治療として広く行われているが，graft-versus-host disease（GVHD）の予防・治療として免疫抑制剤やステロイドが使用されるため，細胞性免疫機能低下の状態が遷延化する。このため潜伏感染していたサイトメガロウイルス（CMV）の再活性化など，健常者では見られないような日和感染症が好発し，しばしば重篤化する。1980年代までは，移植後の感染症死亡の原因として，CMV感染症が最多で，CMV肺炎発症後の予後は非常に不良であった。しかしガンシクロビル投与によるCMV感染症予防が一般化した1990年代は，CMV肺炎などのCMV感染症の頻度は減少してきた[1]。近年，HLA不一致血縁ドナーや骨髄バンク・臍帯血など非血縁ドナーからの同種HSCTも増えてきており，移植方法の多様化によりCMV感染症のリスクは高くなる傾向にある。

日本造血細胞移植学会から，HSCT後のCMV感染症に関するガイドラインが1999年に出されたが（http://www.jshct.com/guideline/pdf/1999cmv.pdf），診断・治療薬の進歩も含めて2011年に改訂される予定である。また移植後早期感染管理に関するガイドラインも2011年に改定され，CMV以外のウイルス感染対策も追加される予定である。本総説では，同種HSCT後に最も多くみられるCMV感染症対策を中心に，その他のウイルスによる感染対策も含めて概説する。詳細に関しては，国内および欧米の造血幹細胞移植患者におけるウイルス感染対策ガイドラインや総説を参照されたい[2~5]。

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1. サイトメガロウイルス（cytomegalovirus: CMV）感染症

CMV感染・感染症の診断

末梢血CMV抗原血症の開発により「体内にCMVが存在すること（CMV感染）」の証明が容易になったが，「実際にCMVが肺炎などの臓器障害を発症している状態（CMV感染症）」とは区別して考える必要がある。

HSCT前にCMV感染既往の有無を評価するためにELISAを用いた抗CMV抗体の検出を行うが，日本人ではCMV抗体の保有率が欧米よりも高い。したがって，移植後にみられるCMV感染の多くは患者に潜伏感染しているCMVの再活性化である。以下のいずれかの所見が得られたとき，活動的なCMV感染（CMVの再活性化）と診断する。

(1) CMV分離，同定
(2) CMV抗原陽性多形核白血球の検出（CMV抗原血症）
(3) Polymerase chain reaction（PCR）あるいはreverse transcriptase-PCRによるCMV DNAまたはRNAの検出
(4) 細胞，組織病理学的にCMV感染細胞の証明

移植後は液性免疫能が低下しているため，CMV抗体自体は活動性CMV感染の診断法として有用性が低い。CMV抗原血症検査（CMV antigenemia）は，サイトスピンでスライドグラス上に付着させた末梢血白血球を，CMV pp65抗原に対するモノクローナル抗体（C7-HRPあるいはC10/C11）を用いて免疫染色を行い，目視にて定量的にCMV感染を評価する方法である[6~8]。CMV感染症の診断における感度および特異性が高く（>85%），CMV感染症の発症に先行して陽性化すること，また定量性もあることから，CMV感染のモニタリングや治療開始および治療終了の指標として広く国内で

用いられている。一方，CMV DNA を増幅し検出する定量 PCR 法は，CMV 抗原血症と同等の有用性が報告され，欧米で広く用いられているが[9~11]，国内では保険適応がなく標準的な検査法としては広まっていない。PCR は検査法によって得られる結果が異なり，必ずしも検出感度が高くない場合もある。

同種 HSCT 後の CMV 感染症の好発時期は，細胞性免疫が低下した移植後 3～12 週である。しかし最近は Day 100 以降に発症する晩期 CMV 感染症の報告も増えてきている[12, 13]。CMV 感染症の症状は多彩であり，発熱（38℃以上），倦怠感，関節痛，筋肉痛などの全身症状の他に，標的となる臓器によって異なる症状がみられる。CMV 肺炎では，乾性咳嗽，呼吸困難，CMV 胃腸炎では悪心，嘔吐，腹痛，下痢，下血，CMV 網膜炎では視力低下などの局所症状がみられる。CMV 感染症の検査所見には，白血球減少，血小板減少，異型リンパ球の出現，低蛋白血症などの全身所見の他に，CMV の侵襲部位によって，胸部異常（間質性）陰影，低酸素血症（CMV 肺炎），消化管潰瘍（CMV 胃腸炎），眼底出血（CMV 網膜炎），肝機能異常（CMV 肝炎），肝脾腫などの局所所見がある。

CMV 感染症の診断には，侵襲部位あるいは臓器に由来する症候に加えて，侵襲部位あるいは臓器で CMV 感染を証明する必要がある（ただし，CMV 網膜炎は特徴的な網膜所見のみでも診断されるため，CMV 感染の証明は必須ではない）。CMV 抗原血症を指標としたガンシクロビルを用いた早期治療（pre-emptive 治療）の導入により CMV 肺炎の頻度は著明に減少したが，相対的に CMV 胃腸炎の頻度が増加している[4]。

1）CMV 肺炎

発熱，呼吸困難，乾性咳嗽，低酸素血症，胸部異常（間質性）陰影等の肺炎の臨床所見と，気管支肺胞洗浄（BAL）液や生検肺組織など肺由来の検体から，CMV の分離培養，CMV の封入体を認めるか，免疫抗体法にて CMV の存在を証明することが必要である[14]。シェルバイアル法を用いた迅速分離同定法は，感度も高く，数日間で結果が得られる[15]。移植後の CMV 感染症のコンセンサスガイドラインによると，間質性肺炎像と，末梢血 CMV 抗原血症陽性のみ，あるいは BAL 液での PCR 陽性のみでは，CMV 肺炎の診断基準を満たさない[14]。CMV 肺炎では，ニューモシスティス・ジロベッチ，細菌，あるいは真菌などによる重複感染がしばしば認められ，可能な限り BAL を行うことで，他の病原体の有無を確認し，無駄な抗菌薬投与を中止することができる。BAL 液を用いたシェルバイアル法で CMV が検出された場合，CMV 肺炎の診断的価値は高い[16]。

2）CMV 胃腸炎

悪心，嘔吐，腹痛，下血などの臨床症状，消化管内視鏡による潰瘍，びらん，発赤，易出血性粘膜などの肉眼所見と，生検組織を用いて核内細胞封入体保有細胞の検出など組織病理学的に CMV 感染が証明される場合に診断する。生検組織の免疫染色による CMV 感染の証明は重要であるが，生検組織を用いた PCR 法による CMV DNA の検出は診断には不十分である。CMV 抗原血症検査は CMV 肺炎に対する感度は高いが，CMV 胃腸炎に対する感度は低く，30％の陽性率しかないとの報告もある[17, 18]。したがって，CMV 抗原血症が陰性であっても，CMV 胃腸炎を疑う臨床症状を認めた場合は，消化管内視鏡検査を行うことが極めて重要である。

CMV 胃腸炎の肉眼像として，深掘れ潰瘍（punched-out ulcer）がよく知られているが，HSCT 症例ではこのような潰瘍は意外に少なく，多くはびらん病変が散在性に多発することが多い[19, 20]。腸管 GVHD や CMV 腸炎は回腸末端部に好発するため，大腸内視鏡を行う場合は全大腸の観察が望ましい[21]。最近，注目を集めている小腸カプセル内視鏡は，11×26 mm 大のカプセルが消化管を通過する 8 時間以上の間，1 秒間に 2 枚ずつ撮影し，腹部に装着した電極から転送される。小腸カプセル内視鏡の最大の利点は苦痛を伴わずに小腸の肉眼所見を観察することができる点であり，欠点は生検ができない点である。しかし小腸カプセル内視鏡における CMV 腸炎の肉眼所見は，大腸内視鏡で観察する所見と極めて類似しており[22]，全身状態が悪く大腸内視鏡検査を行えない患者においては有用な検査法と言える。

CMV 感染・感染症の治療

CMV 感染症と診断した場合は，ただちに抗ウイルス薬による治療を開始する必要がある。第一選択として用いる抗ウイルス薬はガンシクロビルであり，通常ガンシクロビル 5 mg/kg，1 日 2 回点滴を初期投与量として 3 週間，その後 5 mg/kg を 1 日 1 回の維持投与量が用いられる[2, 3]。CMV 肺炎に対しては，静注免疫グロブリンの併用が推奨されているが，CMV 腸炎などに対する有効性は認められていない[3]。また CMV 肺炎に対する副腎皮質ステロイド大量療法の有用性は確立していない。腎障害がある場合は，ガンシクロビルの投与量を調節する必要があり，クレアチニン・クリアランス（Ccr, m*l*/分）に応じて減量する（表 1）。クレアチニン・クリアランス実測値（m*l*/min），もしくは推定クレアチニン・クリアランスを血清クレアチニン値（mg/d*l*）を用いて下記式にて算出する。

男性 ＝（140－年齢［年］）×（体重［kg］）/72×（血清クレアチニン値［mg/d*l*］）

表 1 CMV 感染症に対するガンシクロビル治療

Ccr（ml/min）	初期治療		維持治療	
	用量（mg/kg）	投与間隔（時間）	用量（mg/kg）	投与間隔（時間）
≧70	5	12	5	24
50～69	2.5	12	2.5	24
25～49	2.5	24	1.25	24
10～24	1.25	24	0.625	24
＜10	1.25	透析後週 3 回	0.625	透析後週 3 回

女性 ＝（140－年齢［年］）×（体重［kg］）×0.85/72×（血清クレアチニン値［mg/dl］）

ガンシクロビルの副作用として，白血球減少，血小板減少，貧血，腎機能低下，神経障害などが報告されている。副作用の中では，白血球減少の頻度が最も高く，特に好中球減少が進行する場合は，ガンシクロビル投与の一時中止および G-CSF の併用を考慮する。それでも改善がない場合は，ホスカルネットへの変更を検討する[2～4]。

バルガンシクロビルは，ガンシクロビルの L-バリンエステル体で，吸収されて直ちにガンシクロビルになる。初期治療では，1 回 900 mg（450 mg 錠 2 錠）を 1 日 2 回，食後に内服，21 日まで投与，維持治療では，1 回 900 mg（450 mg 錠 2 錠）を 1 日 1 回，食後に内服する。薬物動態の検討では，経口バルガンシクロビル 900 mg/日が静注ガンシクロビル 5 mg/kg/日に相当するが，造血幹細胞移植後の患者では経口バルガンシクロビルの方が静注ガンシクロビル投与よりも血中濃度が高い傾向にある[23, 24]（特に体重が低値の場合，安全性に十分注意する必要がある）。しかし，下痢などの消化管症状が強い時は，適宜ガンシクロビル点滴静注に変更を考慮する。副作用はガンシクロビルと同様であり，特に 3 週間以上の初期治療量の場合，高度な白血球減少に注意を要する[25]。

ホスカルネットは，ガンシクロビルと同等の臨床効果が示されており，ガンシクロビルによる効果が不十分であったり，あるいは骨髄抑制などの忍容性に問題がある場合，第二選択薬となる。以前の適応は，AIDS 患者における CMV 網膜炎のみであったが，2011 年 5 月，造血幹細胞移植における CMV 血症及び CMV 感染症にも適応が拡大された。HSCT 患者における CMV 感染症に対する治療として用いる場合，初期治療では 90 mg/kg を 12 時間毎に 1 日 2 回 2 時間以上かけて，2～3 週間点滴静注，維持治療では 90～120 mg/kg 1 日 1 回 2 時間以上かけて点滴静注とされている。

HSCT 患者においては，腎毒性を誘発する恐れのある薬剤を併用している患者の割合が高いため，安全性に注意しながら低用量から開始することが望ましい。ホスカルネットは，腎機能に応じて用量調節が必要である（表 2）。本剤の用量調節ガイドでは，クレアチニンクリアランス実測値（ml/min）を体重（kg）で除するか，血清クレアチニン値（mg/dl）を用いて下記の計算式により，推定クレアチニン=クリアランス値を求める。

男性 ＝（140－年齢［年］）/72×（血清クレアチニン値［mg/dl］）

女性 ＝（140－年齢［年］）×0.85/72×（血清クレアチニン値［mg/dl］）

CMV 感染症の予防

ドナーまたはレシピエントの移植前 CMV 抗体陽性は，ドナー・患者ともに CMV 陰性の場合と比較して，同種 HSCT 後に CMV 感染・感染症を合併するリスクが高い。わが国における CMV 抗体保有率は欧米諸国に比して高く，日本人成人の 80～90％は CMV 抗体陽性であったが，最近の傾向として，若年者の CMV 抗体保有率は 60％台に低下傾向を示している[26]。ドナーとレシピエントの両方が CMV 抗体陰性の場合には，血液製剤を介した CMV 初感染を予防するため，可能な限り CMV 抗体陰性血液製剤を輸血する[27]。

ガンシクロビルによる CMV 感染症の予防は，生着後の全症例に予防投与をする方法（total prophylaxis）と，CMV 感染をモニターして，高リスクと考えられる症例だけに投与する早期（pre-emptive）治療に分類される[28]。ガンシクロビルの長期予防投与を用いることで，好中球

表2　CMV感染症に対するホスカルネット治療

Ccr/体重 (ml/min/kg)	初期治療		維持治療	
	用量 (mg/kg)	投与間隔 (時間)	用量 (mg/kg)	投与間隔 (時間)
＞1.4	90	12	90	24
1.0～1.4	70	12	70	24
0.8～1.0	50	12	50	24
0.6～0.8	80	24	80	48
0.5～0.6	60	24	60	48
0.4～0.5	50	24	50	48
＜0.4	投与しない		投与しない	

減少症に伴う細菌・真菌感染症が増加や，CMVに対する免疫回復の遅延から，移植後後期のCMV感染症が増加することも指摘されている。そこで，国内の多くの施設では，保険診療でも可能なCMV抗原血症を用いたモニタリングを行い，リスク群ごとに決めた陽性細胞数を基準に，ガンシクロビル投与を開始する早期（pre-emptive）治療（図1）が主流となっている[8, 29]。ただしCMV抗原血症の陽性・陰性に関わらず，CMV感染症の臨床所見がありCMV感染症と診断した場合には，すみやかにガンシクロビル治療を開始する。特にCMV胃腸炎やCMV網膜炎では，CMV抗原血症検査の検出感度が劣るため，CMV抗原血症が陰性を持続していても治療開始が遅れないように注意する必要がある。

CMV抗原血症を指標とした早期（pre-emptive）治療（図1）

同種HSCT症例では，通常，好中球生着時より週に1回の末梢血CMV抗原血症のモニタリングを開始する。モニタリングは通常，移植後day100まで行われてきたが，近年，移植後day100以降に発症するCMV感染症が問題となってきている[12, 13]。そこで慢性GVHDに対してステロイド投与中の症例や，Day100以前にCMV抗原血症陽性となった症例や，HLA不一致・非血縁移植などのハイリスク例では，Day100以降もCMV抗原血症モニタリングを続行することを考慮する[2, 3]。

Pre-emptive治療の開始基準に関しては，各施設で異なっており，一定した結論は得られていないが，CMV感染症を合併するリスクを十分に考慮した上で，治療開始遅延例を少なくし，かつガンシクロビル過剰投与を避けることを考慮することが重要である。CMV感染症の高リスク群として，患者あるいはドナーがCMV抗体陽性の非血縁者間移植，HLA不一致血縁者間移植，CD34陽性細胞移植，T細胞除去移植，抗胸腺細胞抗体（ATG）や抗CD52抗体が投与された例，GVHD合併例，全身ステロイド投与例などがあげられる。高リスク群では，CMV抗原陽性細胞数が1個でも陽性になったら，ガンシクロビル投与を開始する。低リスク群では，CMV抗原血症が陽性でも，陽性細胞数が基準値以下の場合には，3～7日後に抗原血症検査を再検し，増加傾向を認めない場合は，ガンシクロビルを投与せずにモニタリングを継続する方法が可能かもしれない。HLA一致血縁者間移植では50,000個の白血球中のCMV抗原陽性細胞（C7-HRP）が10個を越えるとCMV感染症の頻度が高くなるが，非血縁者間移植では陽性細胞が10個未満でもCMV感染症を発症することがあるため，治療開始基準の閾値は低くなる[8, 30]。

血漿CMV定量PCR法は感度が高く，CMV抗原血症の結果ともよく相関している[31～33]。特に好中球数1,000/μl以下の移植後早期はCMV抗原血症検査が使えないため，T細胞除去・CD34陽性細胞移植などのハイリスク群では，pre-emptive治療の指標として有用である。また血漿CMV定量PCR法は，CMV抗原血症よりも早期に陽性化するという報告もある[34]。しかし，PCR法は国内で保険適応がなく，pre-emptive治療の指標として国内で用いられる頻度は低い。

国内で，C10/C11法で2スライドのCMV抗原陽性細胞数が合計3個以上，定量IE-PCR法（血漿）では300コピー/mlを開始閾値とする無作為比較試験が行われ

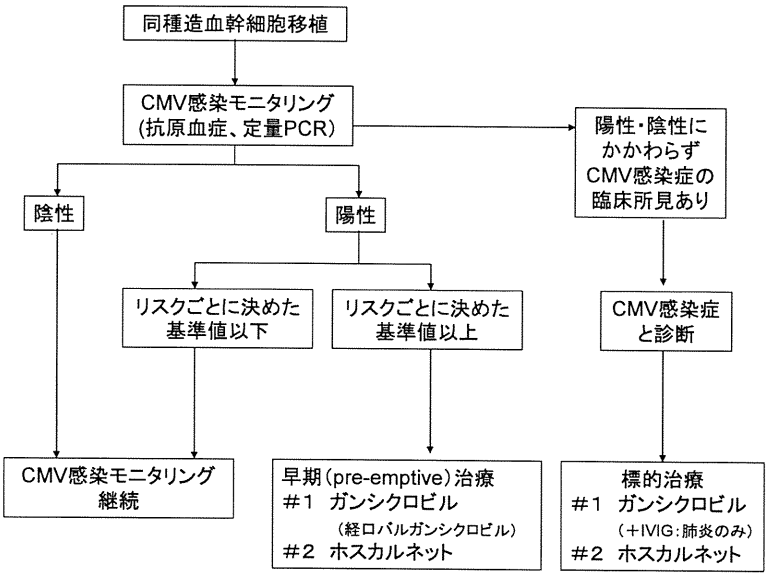

図 1 CMV 感染モニタリングを指標とした CMV 感染症の予防・治療の進め方（日本造血細胞移植ガイドラインより引用改変）

た[35]。いずれの方法でも効果的に CMV 感染症の発症は抑制できたが，感度が高いと言われている PCR 法でガンシクロビル早期投与が行われる割合が低かった。これは，C10/C11 法の開始閾値を 2 スライド合計 3 個以上とすると，過剰な抗ウイルス療法が行われた可能性が高く，より高い閾値設定が適切であることを示している。

Pre-emptive 治療時における，ガンシクロビル開始時の投与量は，欧米では 5 mg/kg，1 日 2 回投与を 1〜2 週間行い，抗原陽性細胞数の減少を確認後に，3 週以上の維持投与量を続行する方法がよく用いられる[2〜4]。一方，急性 GVHD が欧米より重篤でない日本では，5 mg/kg 1 日1 回より投与開始し，治療後のウイルス量の推移を注意深くモニターし，陽性細胞数が 50%以上上昇していた場合には 5 mg/kg 1 日 2 回に増量する方法が用いられることが多い[4, 36]。初期投与量を減量することにより，従来の方法と同じく CMV 感染症の効果的な発症抑制が可能であり，ガンシクロビル総投与量は従来法よりも有意に少なく，骨髄抑制などの副作用の減少が期待できる。

またガンシクロビル投与開始後にも CMV 抗原陽性細胞数が増加する場合があるが，ガンシクロビル耐性の CMV の頻度は少なく，ステロイドや ATG 投与などによる著明に低下した宿主免疫能が原因である場合が多い[37, 38]。こういうケースでは，抗原血症陽性細胞数の減少を確認するまで，ガンシクロビル 5 mg/kg 1 日 2 回の初期投与量を続行する必要がある。Pre-emptive 治療により CMV 抗原血症が陰性であることを確認した後に，投与中止する。

経口バルガンシクロビルによる早期投与（900 mg×2/日）は，静注ガンシクロビルとほぼ同等の有効性が示されている[39〜41]。国内の少数例の臨床試験でも，900 mg×2/日×3 週間の早期投与で 90%の奏功率が得られている[25]。副作用に関しては，ガンシクロビルと同様に，骨髄抑制による好中球減少が問題となる。

早期投与における抗ウイルス薬としては，ガンシクロビルが第一選択であるが，ガンシクロビルの治療効果が不十分または骨髄抑制などの副作用がある場合にホスカルネットは代替薬として用いられる[2〜4]。Pre-emptive 治療の設定で，ホスカルネット 60 mg/kg×2/日を 2 週間投与する群（110 名）と，ガンシクロビル 5 mg/kg×2/日を 2 週間投与する群（103 名）を無作為化比較する臨床試験が欧州で行われた[42]。CMV 感染症の発症は，両群とも 5 例で，ホスカルネットはガンシクロビルと同等の有効性が示された。副作用としては，ガンシクロビルでは骨髄抑制が有意に多く（11%），ホスカルネットでは腎機能障害（5%），電解質異常が多い傾向であった。このため，抗 CMV 治療を開始する前に好中球が減少している場合や，ガンシクロビルによって好中球減少を生じた際などにはホスカルネットが有用と考えられる。

国内での使用経験の後方視的解析では，320 名にホスカルネットが使用されており，投与量の中央値は 88 mg/kg/日で，投与量の分布では，90 mg/kg/日と 180 mg/kg/日にピークがみられた[43]。早期投与で使用された 248 名のうち 77%で CMV 抗原陽性細胞の消失がみられ，ガンシクロビルと同等の有効性が得られている。副作用としては，電解質異常が 11%，好中球減少 8%，

血小板減少 8%，腎機能障害は 3%であり，ホスカルネットはガンシクロビルに次ぐ第二選択薬として安全に使用できると報告されている。

2. 水痘帯状疱疹ウイルス（varicella zoster virus: VZV）感染症

VZV は初感染では水痘として発症するが，その際に知覚神経節へ潜伏感染する。同種 HSCT 後は免疫低下により VZV の再活性化を来たすことが多いため，移植前に高感度な EIA 法を用いた VZV 抗体価を測定する必要がある[2, 44]。VZV 再活性化を来たした大部分の症例では，帯状疱疹として発症するが，播種性または内臓 VZV 感染症を来たし重症化するリスクもある。このため VZV 抗体陽性の同種移植患者では，VZV 再活性化を予防するためにアシクロビル（ACV）投与が行われることが多い。

欧米のガイドライン[2, 44]では，VZV 抗体陽性の同種移植患者に対する移植後 1 年間の ACV 予防が A-II または B-I レベルで推奨されている（国内では保険適応外）。その根拠として，シアトルで行われたプラセボを対照とした無作為化比較試験において，ACV 予防投与（1,000 mg/日）を行うことにより移植 1 年後までは VZV 発症をほぼ抑制することが可能であった[45]。ただし ACV 予防投与中止後の VZV 感染症の発症が問題となるため，慢性 GVHD 合併患者や免疫抑制剤投与中は，ACV 予防をさらに長期間続行することが推奨されている[2, 45]。ACV 予防投与を中止するタイミングとして，免疫抑制剤中止後 6 ヶ月後，または CD4 陽性リンパ球が 200/μl 以上という報告もあるが[2, 46]，十分なエビデンスは確立していない。無作為化比較試験ではないが，ACV 予防投与量を 1 日あたり 200 mg～400 mg 投与へ減量して，同種移植後 1 年間，または免疫抑制剤を中止するまで投与することにより，VZV 感染症の発症が有意に減少したという国内からの報告がある（図 2）[47, 48]。

ACV 予防が行われている期間中は，VZV 感染症を合併することは稀であるが，VZV 再活性化により皮膚病変が出現した場合，擦過検体を用いた蛍光抗体法による抗原検出は有用である（保険適応あり）。VZV 再活性化を疑う皮膚病変を認めた時は，バラシクロビル（Val-ACV）内服または ACV 点滴による治療をすみやかに開始する必要がある[2]。限局性の帯状疱疹に対しては ACV 5 mg/kg を 8 時間ごとに点滴静注，または Val-ACV 1,000 mg を 1 日 3 回経口投与する。

VZV 抗体陰性の患者においては，ACV 予防投与は原則として不要である[2]。ただし VZV 感染症を発症した者と接触した場合は 96 時間以内に，（海外では VZV 抗体高力価製剤が推奨されている）免疫グロブリン製剤を投与することが推奨される[2]。免疫グロブリン製剤投与が困難な場合は，暴露後の ACV または Val-ACV 予防投与を考慮する[2, 44]。移植予定患者に帯状疱疹を疑う皮疹を認めた場合，すみやかに ACV または Val-ACV による治療を開始することが推奨される[2, 44]。播種性の帯状疱疹または水痘を発症した患者は，陰圧個室に隔離し空気感染予防策を行う[2, 44]。

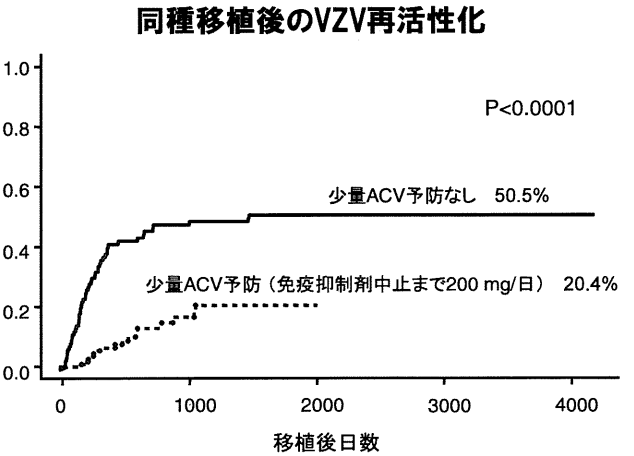

図 2　同種移植後の VZV 再活性化は，少量アシクロビル（ACV 200 mg/日）予防により有意に減少する（文献 48 より引用改変）

ACV 少量長期予防を行わない場合は，VZV 再活性化による播種性 VZV または内臓 VZV 感染症に十分に注意する必要がある。同種 HSCT 患者では，皮膚病変が出現する前に，播種性または内臓 VZV 感染症による急激な腹痛，肝障害，DIC が急速に進行し致死的となることが報告されている[49]。播種性 VZV または内臓 VZV 感染症を疑った時は，血液定量 PCR 検査（保険適応外）を提出し，すみやかに大量 ACV 点滴投与による治療開始を考慮する。播種性の帯状疱疹や内臓性 VZV 感染症に対しては ACV 10 mg/kg を 8 時間ごとに点滴静注する。ACV は腎排泄のため，腎障害を合併した患者では減量が必要であり，大量投与時には十分な補液を行うことが推奨される。ACV 予防投与中に VZV 感染症を合併した場合には，大量 ACV 点滴投与を行うか，代替治療薬としてホスカルネット点滴を用いた治療を考慮する[2, 44]。

3. ヒトヘルペスウイルス 6 型（human herpesvirus 6: HHV-6）感染症

HHV-6 は CMV と同じく β ヘルペスウイルスに属し，A と B の 2 つのサブタイプがあるが，実際に病原性が明らかになっているのはほとんどがサブタイプ B であり，移植後の再活性化も 97%がサブタイプ B である。HHV-6 は新生児期にみられる突発性発疹の原因ウイル

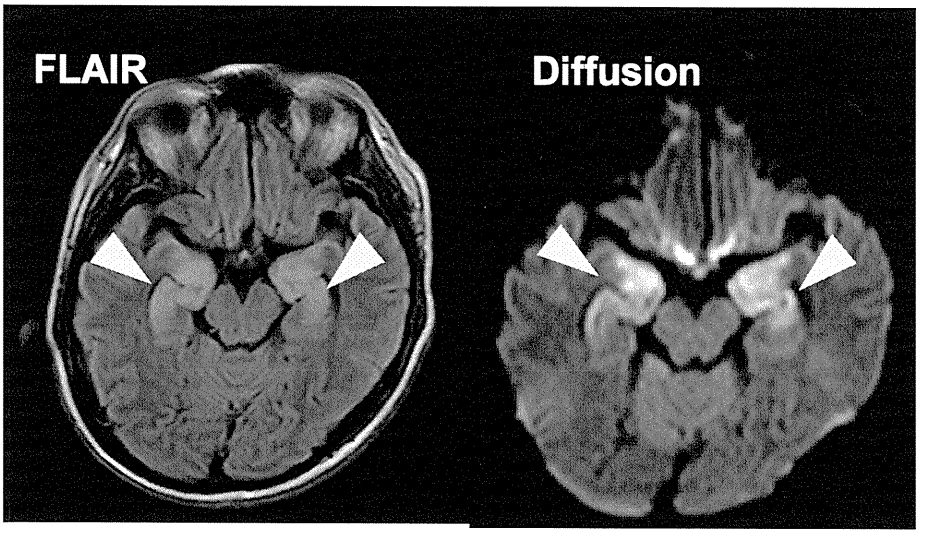

図3 HHV6脳炎の頭部MRI画像（臍帯血移植26日後）
（左）FLAIR，（右）Diffusion。髄液中のHHV-6 DNAは20万9677コピー/m*l*と増加していた。（画像提供：大分大学・緒方正男先生）

スで，初感染後に末梢血リンパ球や唾液腺などに潜伏する[50,51]。同種移植後は，特に好中球生着前後の時期にHHV-6の再活性化を認めることが多く，特に臍帯血移植後は高頻度である[52,53]。

このHHV-6の再活性化により，発熱，皮疹，肺炎，骨髄抑制，脳炎など，多彩な臨床症状を呈することが知られているが，臨床的に最も重要なのはHHV-6による辺縁系脳炎である[50]。中枢神経障害を呈し，髄液よりHHV-6が証明され，ほかの要因が除外された症例がHHV-6脳炎と診断される[3,54,55]。症状として，見当識障害や短期記憶障害，発熱，頭痛，性格変化以外にも，意識障害や痙攣など致死的な経過となることもある[54]。同種HSCT後の生着前後の時期は，免疫抑制剤による脳症，敗血症やDIC，肝障害，腎障害にともなう中枢神経障害，精神的ストレスや拘禁反応，オピオイドやステロイド投与の副作用など，中枢神経症状を呈する鑑別診断が数多く存在する時期であるが，HHV-6脳炎で高頻度にみられる短期記憶障害や痙攣などの臨床症状とMRI所見は非常に特徴的である。見当識障害や短期記憶障害は，海馬・辺縁系を中心とした障害によるものと考えられており，MRIのFLAIR画像や拡散強調（diffusion）画像で同部位に異常を認めたHHV-6脳炎症例が報告されている（図3）[56,57]。

HHV-6脳炎に対する治療として，ガンシクロビルまたはホスカルネットが抗ウイルス作用を持つが，至適投与量や投与期間は確立していない[2,3]。HHV-6による脳炎は痙攣・昏睡へと急速に進行したり，短期記憶障害が後遺症として残存することも多いため，HHV-6脳炎を疑う場合には，MRI検査や髄液のPCR検査を行うと共に，すみやかに抗ウイルス治療を開始することが推奨される。

血漿を用いた定量PCR検査でHHV-6コピー数が高いとき（10,000コピー/m*l*以上）に脳炎の発症が多いという国内からの報告がある[58]。血漿定量PCR検査によるモニタリングを週1回行ってガンシクロビルによるpre-emptive治療を開始する臨床試験では，29例中9例で高レベルのHHV-6再活性化を認め，2例で脳炎を発症した[59]。HHV-6脳炎の高リスクである臍帯血移植患者においては，ホスカルネット予防投与によるベネフィットがリスクを上回る可能性があるが，現時点ではエビデンスは確立しておらず，臨床試験として行うことが推奨される[2]。

著者のCOI（conflicts of interest）開示：本論文発表内容に関連して特に申告なし

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Comparison of Allogeneic Hematopoietic Cell Transplantation and Chemotherapy in Elderly Patients with Non-M3 Acute Myelogenous Leukemia in First Complete Remission

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The benefits of allogeneic hematopoietic cell transplantation (allo-HCT) for patients with acute myelogenous leukemia (AML) in first complete remission (CR1) have mostly been evaluated in younger patients. Although favorable outcomes of allo-HCT over chemotherapy have been reported with the use of reduced-intensity conditioning (RIC) regimens in elderly patients with AML in CR1, information is still limited, especially on the effects of cytogenetic risks and donor sources. We collected data from AML patients aged 50 to 70 years who achieved CR1, and compared the outcome in 152 patients who underwent allo-HCT in CR1 (HCT group) to that in 884 patients who were treated with chemotherapy (CTx group). The cumulative incidence of relapse in the HCT group was significantly lower than that in the CTx group (22% versus 62%). Both overall survival (OS) and relapse-free survival (RFS) were significantly improved in the HCT group (OS: 62% versus 51%, $P = .012$), not only in the whole population, but also in the intermediate-risk group. Among patients who had a suitable related donor, the outcomes in the HCT group were significantly better than those in the CTx group. The introduction of appropriate treatment strategies that include allo-HCT may improve the outcome in elderly patients with AML in CR1.

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KEY WORDS: Acute myelogenous leukemia, Elderly patients, Allogeneic hematopoietic cell transplantation, First complete remission

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INTRODUCTION

The biologic characteristics of acute myelogenous leukemia (AML) change as the patient becomes older, because such patients are more often associated with unfavorable profiles such as antecedent hematologic disorder (AHD), expression of P-glycoprotein in blasts, and unfavorable-risk cytogenetic abnormalities [1-4]. In addition, elderly patients are more likely to have a worse performance status and an increased risk of comorbidities, which makes it difficult for them to undergo aggressive therapies [5,6]. Consequently, the reported probability of achieving a first complete remission (CR1) is lower than that in younger patients. In most previous studies, the duration of remission has been reported to be 6 to 8 months, with a 3-year survival rate of <20% [7-10].

Although allogeneic hematopoietic cell transplantation (allo-HCT) is an effective strategy for decreasing the risk of relapse in younger patients, an increase in the risk of treatment-related toxicity is inevitable. Although >50% of the reported AML patients are 50

years of age or older, most previous studies have investigated treatment strategies that include allo-HCT in related younger donor/patient pairs by allocating treatment options based on donor availability. Over the past decade, several studies showed that allo-HCT with reduced-intensity conditioning (RIC) is acceptably safe and effective in elderly patients [11-18]. Allo-HCT with RIC has also been reported to be superior to conventional chemotherapy in elderly AML patients in CR1, particularly when they have a matched related donor [19,20]. However, most of these studies included small numbers of patients, and there is still limited information available on the effects of risk factors of AML, differences in donor sources, and conditioning regimens. To address these critical questions, we performed a nationwide retrospective survey.

PATIENTS AND METHODS

Data Source

The study protocol was approved by the institutional review board at the National Cancer Center Hospital. The targeted population was adult patients who were diagnosed with AML between 1999 and 2006, aged 50 to 70 years, and who had achieved CR1 after 1 or 2 courses of induction chemotherapy. The diagnosis of AML was determined by the WHO classification and included myelodysplastic syndrome with 20% or more bone marrow (BM) blasts. CR was evaluated according to standard criteria for hematologic CR, which was defined as a normocellular BM aspirate containing 5% or less blasts with normal maturation. The presence of minimal residual disease was not molecularly examined in this study. Among them, patients with acute biphenotypic leukemia who were treated with chemotherapy for acute lymphoblastic leukemia, those who had extramedullary AML without BM invasion or extramedullary lesion that did not totally disappear after remission induction chemotherapy, those with acute promyelocytic leukemia, and those who received autologous HCT in CR1 were excluded from the analysis. Information about the disease risks at diagnosis, clinical course, HLA typing and donor availability during CR1, conditioning regimen, and donor source of allo-HCT were collected. Related donors included an HLA-matched or 1-antigen (Ag)-mismatched related donor. A haploidentical related donor who had 2 or more Ag mismatches was considered as an alternative donor. Unrelated donors included volunteer BM donors with 0 or 1-Ag mismatches and unrelated cord blood with three or less-Ag mismatches. As HLA typing for unrelated BM donors was predominantly performed by matches at serum levels in this era, detailed information on allele-level matches was not completely available.

Statistical Analysis

Data were retrospectively reviewed and analyzed as of December 2009. Background differences between the 2 groups was examined with the chi-square test for categoric variables, and with t-test for metric variables. The primary endpoints of the study were relapse-free survival (RFS) and overall survival (OS) from when CR1 was achieved. The unadjusted probabilities of RFS and OS were estimated using the Kaplan-Meier product limit method according to the treatment group, and 95% confidence intervals (CIs) were calculated using the Greenwood formula. To compare RFS and OS between the treatment groups, the log-rank test was used. We performed landmark analyses by excluding patients who died or relapsed within 60 days from CR1 for those who were treated with chemotherapy alone. Cumulative incidences were estimated for relapse and nonrelapse mortality (NRM) to take into account competing risks. The Pepe and Mori's test was used to evaluate the differences between groups. RFS, OS, incidences of relapse, and NRM were estimated as probabilities at 3 years from CR1. Associations between treatment groups and outcome were evaluated using Cox proportional hazard regression models. In addition to whether allo-HCT in CR1 was performed or not, the following factors were considered as covariates: cytogenetic classification according to the Southwest Oncology Group (SWOG), FAB classification, the number of courses of chemotherapy required to achieve CR1, initial white blood cell (WBC) count, and dysplasia at diagnosis. We considered 2-sided P-values of $<.05$ to be statistically significant. Statistical analyses were performed with the SPSS software package and SAS version 9.1.3 (SAS, Cary, NC, USA).

RESULTS

Patients

Clinical data for around 1300 patients were collected from 67 institutions. After excluding 45 patients who received autologous HCT in CR1 or other ineligible patients as described in Patients and Methods, 1036 were eligible for this study (Table 1). The median follow-up of the surviving patients was 44 months. As a remission induction therapy, 89% of elderly patients had received cytarabine- and anthracycline (daunorubicin or idarubicin)-based regimens. Low-dose cyatarabine-based regimens were performed in 8% of the elderly patients. Consolidation therapy was continued with cytarabine-based regimens with or without maintenaice therapy at the discretion of physicians.

Donor Availability and Consideration of allo-HCT in CR1

Information on HLA typing during CR1 and the availability of related donors was obtained in 953

Table 1. Patient Characteristics

Characteristics	All Patients n = 1036	Allo-HCT in CR1 n = 152 (%)	No HCT in CR1 n = 884 (%)	P
Median age				
years, (range)	60 (50-70)	55 (50-70)	61 (50-70)	<.001
Median time from diagnosis to CR1				
days, (range)	40 (26-283)	48 (26-242)	39 (13-283)	<.001
Disease				
M0, 6, 7	102	24 (16)	78 (9)	<.001
AHD	37	19 (13)	18 (2)	<.001
Cytogenetic risks (SWOG)				<.001
Favorable	164	5 (3)	159 (18)	
Intermediate	589	93 (61)	496 (56)	
Unfavorable	166	27 (18)	139 (16)	
Unknown	99	25 (16)	74 (8)	
Remission induction				0.13
2 courses	199	36 (24)	163 (18)	
WBC (/μL)				<.001
Higher than 20,000	335	28 (18)	307 (35)	
Dysplasia				<.001
Yes	268	74 (49)	194 (22)	

Allo-HCT indicates allogeneic hematopoietic cell transplantation; CR1, first complete remission; AHD, antecedent hematologic disorder; WBC, white blood cell; SWOG, Southwest Oncology Group.

elderly patients. Among these patients, HLA typing was performed in 331 patients in CR1 (35%) and these patients were younger than those who did not have their HLA typed during CR1 (median, 56 years versus 62 years) (Table 2 and Figure 1). Patients who had their HLA typed were associated with more unfavorable features, such as unfavorable FAB types, AHD, a requirement of 2 courses of remission induction therapy, dysplasia at diagnosis, and a lower frequency of favorable-risk AML by the SWOG classification. Related donors (HLA-matched and 1-Ag-mismatched related donors) were found in 134 patients (40%). No significant difference was found in the distribution of age and risk factors between patients who found a related donor and those who did not after HLA typing (Table 2). Among the patients who had a related donor, 76 (57%) actually underwent allo-HCT during CR1. Among the 197 patients who did not find a related donor, 76 (39%) received allo-HCT from an alternative donor in CR1 (Figure 1).

Patients Who Received allo-HCT in CR1

Of the total 1036 patients, 152 underwent allo-HCT in CR1 (15%). Patients who received allo-HCT in CR1 were younger and associated with more unfavorable characteristics than those who did not (Table 1). As shown in Table 3, 49% of the patients

Table 2. Donor Search and Transplantation

		HLA Check in CR1, n = 331				Statistical Differences		
Characteristics	No HLA Check in CR1 N = 622 (%)	Related Donor Available/HCT+*[a] n = 76 (%)	Related Donor Available/HCT−[b] n = 58 (%)	Related Donor not Available/HCT+[c] n =76 (%)	Related Donor not Available/HCT−[d] n =121 (%)	P*	P†	P‡
Age, median, years	62	55	55	55	57	<.001	.396	.906
Disease								
M0, 6, 7	47 (8)	17 (22)	5 (9)	7 (9)	13 (11)	0.008	.170	.160
AHD	11 (2)	4 (5)	2 (3)	15 (20)	2 (2)	<.001	186	.450
Cytogenetic risks (SWOG)						<.001	.561	.045
Favorable	118 (19)	4 (5)	12 (21)	1 (1)	19 (16)			
Intermediate	354 (57)	43 (57)	28 (48)	50 (66)	69 (57)			
Unfavorable	92 (15)	13 (17)	9 (16)	14 (18)	17 (14)			
Unknown	48 (8)	16 (21)	9 (16)	11 (14)	14 (12)			
Remission induction						.009	.541	.871
2 courses	103 (17)	19 (25)	14 (24)	17 (22)	29 (24)			
WBC (/μL)						.021	.178	.004
Higher than 20,000	223 (36)	11 (14)	19 (33)	17 (22)	39 (32)			
Dysplasia						<.001	.991	.117
Yes	127 (20)	31 (41)	16 (28)	43 (57)	26 (21)			

CR indicates complete remission; HCT, allogeneic hematopoietic cell transplantation; AHD, antecedent hematologic disorder; WBC, white blood cell; SWOG, Southwest Oncology Group.

*P-value of comparing "No HLA check in CR1" versus "HLA check in CR1."

†P-value of comparing "Related donor available[a+b]" versus "Related donor not available[c+d]".

‡P-value of comparing "HCT+[a]" versus "HCT-[b]" among those who had a related donor.

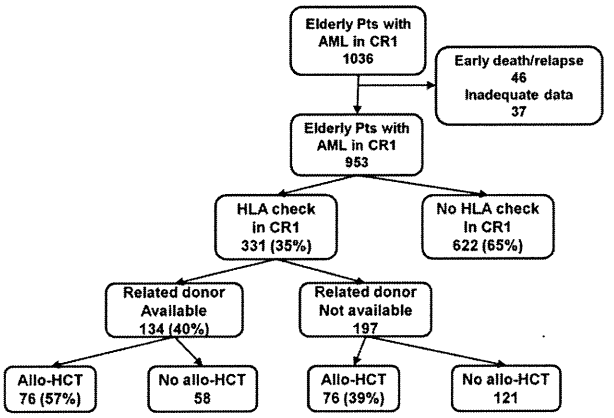

Figure 1. Patient flow. Among 953 patients for whom information was available, HLA typing was performed in 331 patients in CR1 (35%). Related donors were found in 134 patients (40%). Among the patients who had a related donor, 76 (57%) actually underwent allo-HCT in CR1. Among the 197 patients without a related donor, 76 (39%) received allo-HCT from an alternative donor in CR1.

received allo-HCT in CR1 from an HLA-matched or 1-Ag-mismatched related donor. The median interval from CR1 to allo-HCT was 139 days. An RIC regimen was given to 93 patients (61%) with a higher median age of 58 years compared to those who received a myeloablative (MA) regimen, 52 years. Extensive chronic graft-versus-host disease (cGVHD) developed in 61 patients (45%) among 135 who lived and had a follow-up period of longer than 100 days.

Comparison of the Outcomes of allo-HCT versus Chemotherapy in CR1

The outcome in patients who received allo-HCT in CR1 (HCT group) was compared to that in patients who did not receive allo-HCT in CR1 (CTx group). Landmark analyses were performed in all subgroups by excluding 46 patients from the CTx group who relapsed or died within 60 days after achieving CR1. In the CTx group, 183 patients ultimately received salvage allo-HCT after relapse (33% of relapsed patients). The cumulative incidence of relapse in the HCT group was significantly lower than that in the CTx group (22% versus 62% at 3 years from CR1, $P < .001$) (Figure 2). The cumulative incidence of NRM in the HCT group was higher than that in the CTx group (21% versus 3%, $P < .001$). The 3-year RFS in the HCT group was significantly higher than that in the CTx group (56% versus 29%, $P < .001$). Although the difference between the HCT and CTx groups decreased, the 3-year OS in the HCT group was also significantly higher than that in the CTx group (62% versus 51%, $P = .012$). Multivariate analyses for survival showed that performance of allo-HCT, a single course of induction therapy to achieve CR1, lack of dysplasia, WBC below 20,000/μL at diagnosis, and a more favorable cytogenetic risk were significantly associated with better RFS and OS (Table 4). We also used the Cox proportional hazards model with time-dependent variables after taking into account the time from CR1 to allogeneic HCT. By adjusting the influence of waiting time to allogeneic HCT in this analysis, we found that allogeneic HCT in CR1 was also independently associated with better OS.

In a subset analysis according to the cytogenetic risk, patients with intermediate-risk AML showed the similar trends in relapse, NRM, RFS, and OS to the entire patient population (OS: 67% versus 54%, $P = .024$) (Figure 3A). Among patients with unfavorable-risk AML, 27 received allo-HCT in CR1 and 125 did not. In this group of patients, relapse incidence in the HCT group was also substantial (Figure 3B) (41% at 3 years; 95% CI, 21%-61%), which led to OS that did not differ significantly compared to that in the CTx group (OS: 47% versus 35%, $P = .206$).

We also evaluated the outcome in relation to donor availability (Figure 4). Among 134 patients

Table 3. Characteristics of Transplantation in CR1

Characteristics	Allo HCT in CR1 n = 152 (%)	Median Age, Years (Range)	Median Interval from CR1 to HCT, Days (Range)
Total		55 (50-70)	139 (14-981)
Donor			
Matched related	64 (42)	55 (50-70)	121 (14-574)
1-Ag-mismatched related	10 (7)	57 (50-60)	99 (15-436)
Haplo-identical	3 (2)	51 (50-54)	144 (21-147)
Unrelated bone marrow	52 (34)	55 (50-64)	177 (40-981)
Cord blood	23 (15)	55 (50-67)	127 (14-650)
Conditioning			
Myeloablative			
TBI regimen	16 (11)	52 (50-58)	167 (52-436)
Non-TBI regimen	40 (26)	52 (50-59)	141 (14-361)
Reduced-intensity			
Flu/Bu-based	48 (32)	58 (50-70)	147 (15-574)
Flu/Mel-based	29 (19)	58 (50-66)	126 (14-981)
Others	16 (11)	58 (50-69)	99 (23-304)

Allo-HCT indicates allogeneic hematopoietic cell transplantation; CR, complete remission; Ag, antigen; TBI, total body irradiation; Flu, fludarabine; Bu, busulfan; Mel, melphalan.

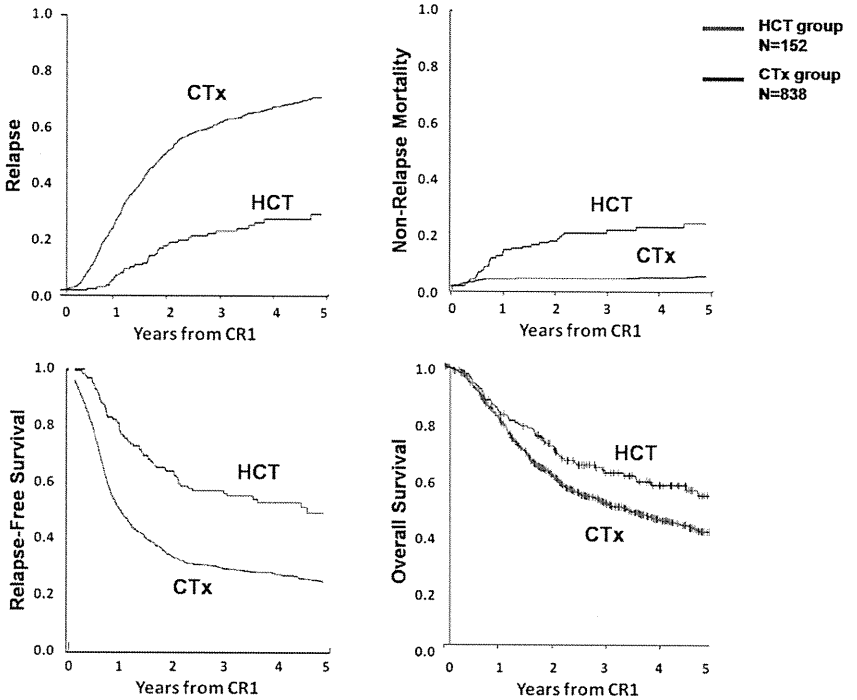

Figure 2. Outcomes according to treatment in CR1 (total elderly patients). Relapse (upper left), nonrelapse mortality (upper right), relapse-free survival (bottom left), and overall survival (OS) (bottom right) of patients who underwent allogeneic hematopoietic cell transplantation in CR1 and those who did not are shown. Forty-six patients who died or relapsed within 60 days from CR1 were excluded as described in the Statistical Analysis. OS was significantly improved in the HCT group ($P = .012$).

who had a related donor, 76 underwent allo-HCT in CR1. The incidence of NRM among the patients who received allo-HCT from a related donor was 14%, which was significantly lower compared to that observed in the whole HCT group. On the other hand, patients who found a related donor but did not undergo allo-HCT in CR1 had a substantial incidence of relapse (80%; 95% CI, 70%-90%). These results led to significant differences in RFS and OS between the HCT and CTx groups (RFS: 64% versus 11%, $P < .001$, OS: 66% versus 43%, $P = .001$) (Figure 4A). These results did not change when 622 patients who did not have their HLA typed (those who were not known to have a suitable related donor) were included in the CTx group (66% versus 54%, $P = .011$) (Appendix 1-A) or when landmark was extended to 5 months from CR1 for the patients in the CTx group who had a related donor (66% versus 54%, $P = .068$) (Appendix 1-B). We also performed the same comparison limited to intermediate-risk AML patients who had a related donor, and found significant differences between the HCT and CTx groups (RFS: 78% versus

Table 4. Multivariate Analysis

	RFS		OS	
Variables	HR (95% CI)	P	HR (95% CI)	P
Allo HCT in CR1 (versus Yes)				
No	2.58 (1.97-3.37)	<.001	1.81 (1.35-2.42)	<.001
Cytogenetic Risk (versus Favorable)				
Intermediate	1.14 (0.90-1.44)	.283	1.10 (0.84-1.45)	.487
Unfavorable	1.70 (1.28-2.24)	<.001	1.89 (1.37-2.59)	<.001
Unknown	1.62 (1.18-2.23)	.003	1.34 (0.92-1.95)	.132
FAB (versus M1, 2, 4, 5)				
M0, 6, 7	1.25 (1.00-1.57)	.052	1.38 (1.07-1.77)	.014
Remission Induction (versus 1 course)				
2 courses	1.52 (1.26-1.84)	<.001	1.61 (1.31-1.99)	<.001
Dysplasia (versus No)				
Yes	1.21 (0.98-1.48)	.075	1.29 (1.02-1.63)	.033
WBC (versus 20,000 or lower)				
Higher than 20,000	1.29 (1.09-1.54)	.004	1.24 (1.01-1.51)	.038

HR indicates hazard ratio; RFS, relapse-free survival; CI, confidence interval; OS, overall survival; allo-HCT, allogeneic hematopoietic cell transplantation; CR, complete remission; WBC, white blood cell count.

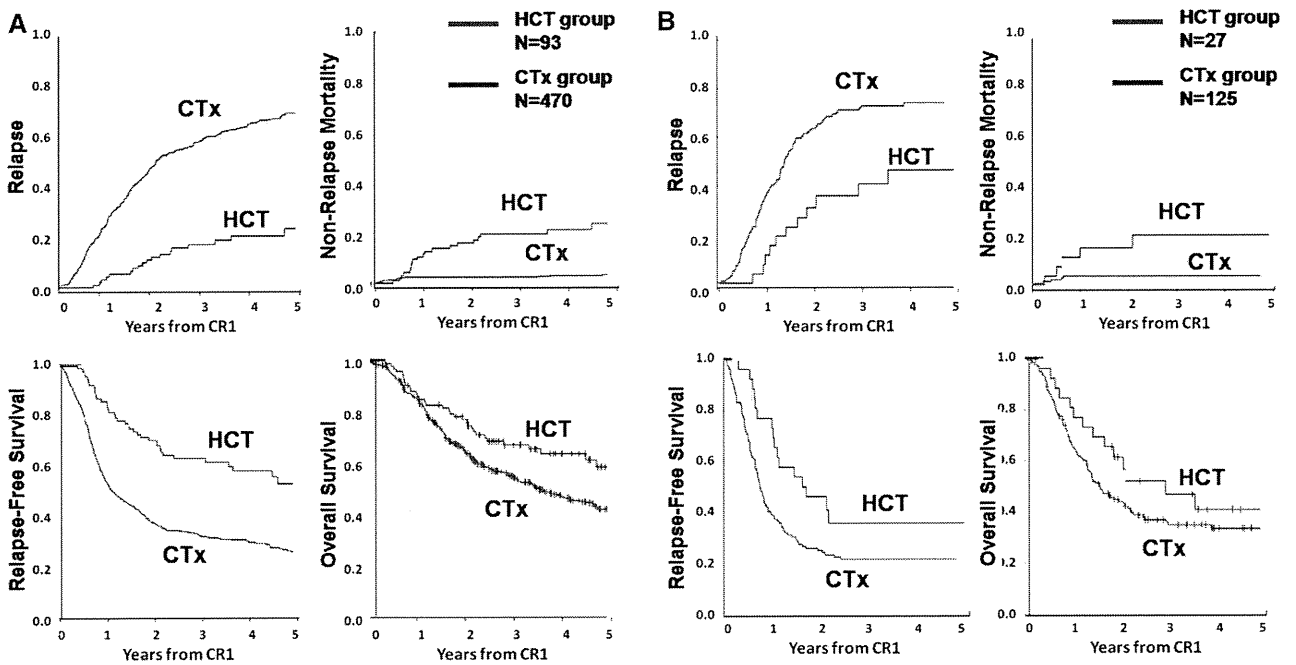

Figure 3. Outcomes according to treatment in CR1 (cytogenetic risks). Relapse (upper left), nonrelapse mortality (upper right), relapse-free survival (bottom left), and overall survival (OS) (bottom right) of patients who underwent allogeneic hematopoietic cell transplantation in CR1 and those who did not are shown among (A) intermediate-risk AML and (B) unfavorable-risk AML. (A) OS was significantly improved in the HCT group among patients with intermediate-risk AML. (B) Relapse incidence was high even after HCT, and OS in the HCT group did not significantly differ from that in the CTx group.

13%, $P < .001$, OS: 78% versus 63%, $P = .048$) (Appendix 1-C).

Among 197 patients who did not have a related donor, 76 underwent allo-HCT from an alternative donor in CR1. Alternative donors included 51 unrelated BM, 22 unrelated CB, and 3 haploidentical related donors. Patients who received allo-HCT in CR1 from an alternative donor had a higher incidence of NRM than those who received allo-HCT from a related donor (28% versus 14% at 3 years, $P = .029$). Additionally, incidence of relapse in allo-HCT from an alternative donor was not reduced compared to that in a related donor transplant setting (22% versus 22%, $P = .743$). Consequently, if we compare the outcomes of the HCT and CTx groups among patients who did not have a related donor, OS did not significantly differ between the two groups (57% versus 47%, $P = .388$) (Figure 4B).

As shown in Table 3, 39% of the patients in the HCT group received an MA regimen. Except for the younger age in those who received an MA regimen, there was no difference in the disease risk between the MA and RIC groups. Additionally, the OS did not significantly differ between the two groups (3-year OS from CR1: 63% versus 61%, $P = .571$) (Appendix 2-A). We also found that OS was not significantly different according to the application of total body irradiation (TBI) (TBI regimen versus non-TBI: 67% versus 61%, $P = .932$) (Appendix 2-B) or among different RIC regimens (fludarabine + busulfan-based, 56%; fludarabine + melphalan-based, 67%; others, 68%, $P = .862$) (Appendix 2-C).

DISCUSSION

We performed retrospective analyses with a 60-day landmark to compare allo-HCT and CTx in 1036 patients aged 50 to 70 years with non-M3 AML in CR1. The results of this study revealed that, overall, elderly patients with AML who received allo-HCT in CR1 had improved outcomes compared to those who were treated with conventional chemotherapy alone. Based on cytogenetic subgroup analyses, patients with intermediate-risk AML had a significantly better OS when they received allo-HCT in CR1. On the other hand, patients with unfavorable-risk AML had a higher risk of relapse even after allo-HCT in CR1, which diminished the benefit of allo-HCT. We also observed that patients who had a related donor had a significantly improved outcome when they received allo-HCT in CR1.

Our results that allo-HCT in CR1 provided an improved OS agree with previously reported comparisons of allo-HCT versus chemotherapy in elderly patients with AML in CR1. Mohty et al. [20] performed a retrospective comparison of "donor" versus "no donor" based on their consistent policy of considering allo-HCT with RIC in CR1 when a patient with high-risk AML had an HLA-matched sibling. They reported superior survival rates not only in the "transplant group" compared to the "no transplant group," but also in the "donor group" compared to the "no donor group." Furthermore, Estey et al. [19] reported the first prospective

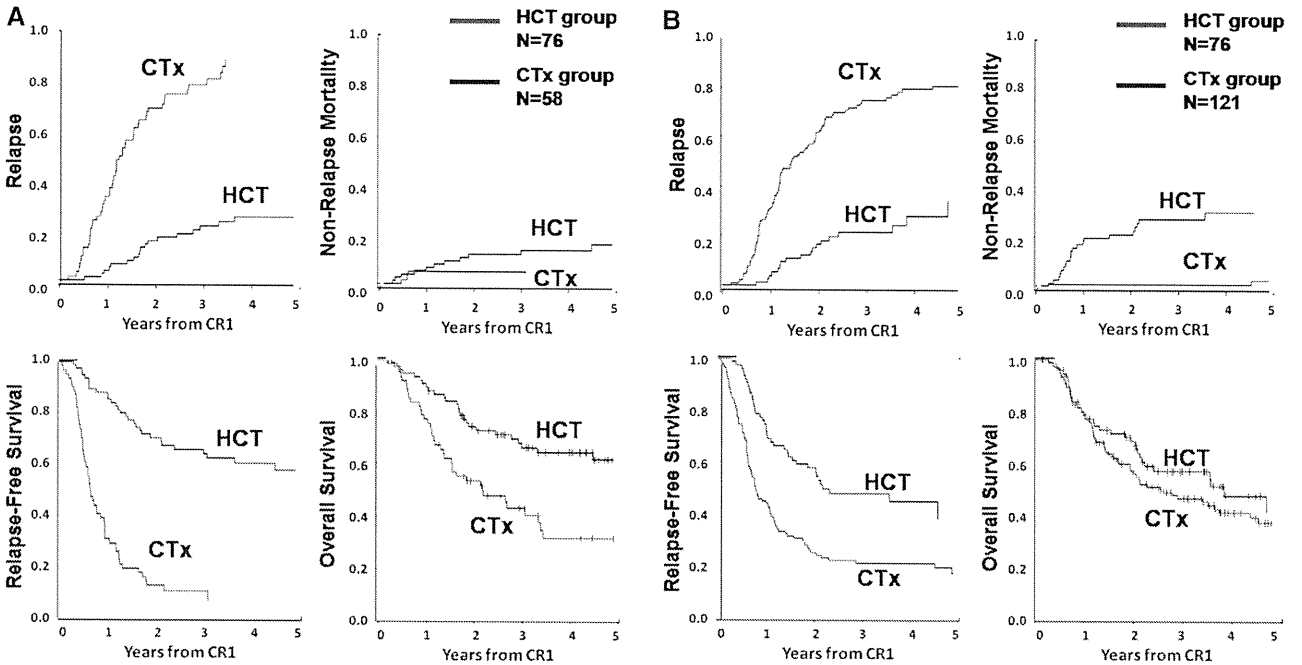

Figure 4. Outcomes according to treatment in CR1 (donor availability). Relapse (upper left), nonrelapse mortality (NRM) (upper right), relapse-free survival (bottom left), and overall survival (OS) (bottom right) of patients who underwent allogeneic hematopoietic cell transplantation in CR1 and those who did not are shown among (A) patients who had a suitable related donor and (B) patients who did not have a suitable related donor. (A) NRM was reduced in related donor transplant and survival probabilities were significantly improved in the HCT group. (B) OS in alternative donor transplant did not significantly differ from that in the CTx group.

observation of allo-HCT with RIC versus chemotherapy in elderly patients. Although the proportions of patients who were referred for transplantation (54%) and those who actually underwent allo-HCT in CR1 (14%) were relatively small, they presented an encouraging outcome that supported the benefit of allo-HCT.

In elderly patients with intermediate-risk AML, we also found improved OS when they received allo-HCT in CR1. This finding is consistent with the result indicated by a meta-analysis by Koreth et al. [21], although their report mostly included prospective studies that targeted younger patients. No previous studies have reported the effects of cytogenetic risks in the transplant setting for elderly patients. In the intermediate-risk group, we found a 60% relapse incidence at 3 years from CR1 when the patients were treated with chemotherapy alone. We also revealed that the incidence of relapse was reduced by 40% with the use of allo-HCT in CR1 without a significant increase in NRM compared to younger patients, which led to a significant improvement of OS.

Our current study did not show a significant benefit of allo-HCT among patients with unfavorable-risk AML. Although fewer patients were analyzed in this subgroup, which may have led to the unlikelihood of yielding a statistical significance, this result may also be explained by the fact that elderly patients tend to be given less-aggressive chemotherapy before allo-HCT because of concerns about toxicity [7,9]. Because no other realistic option can offer a chance of cure for patients with unfavorable-risk AML, many physicians would consider that allo-HCT is optimal for these patients. However, we clearly need to seek novel strategies to reduce the risk of relapse, for example, by reducing the tumor burden before allo-HCT with more intensified chemotherapy or conditioning regimen, or by prevention of recurrence after allo-HCT by vaccination strategy [22-27]. The role of new drugs such as clofarabine or hypomethylating agents should also be estimated for elderly patients with poor-risk AML who are vulnerable to intensive treatments [28,29].

We observed a markedly reduced incidence of NRM after transplantation from a related donor, which improved the outcome of patients who received allo-HCT in CR1 from a related donor. Among 134 patients who had a suitable related donor, 40% did not undergo allo-HCT during CR1. Unfortunately, the exact reason was not available from our retrospectively collected database. Possible reasons include disease relapse before the anticipated timing for allo-HCT, or failure to receive appropriate therapy because of being too ill. However, an analysis with a landmark extended to 5 months still proved that OS in the HCT group was significantly better compared to that in the CTx group among those who had a related donor.

In contrast to the favorable outcome in the setting of allo-HCT from a related donor, the outcome of allo-HCT from an alternative donor in CR1 was not significantly superior to that of chemotherapy alone. In addition to the significantly higher NRM after alternative

donor transplant, the incidence of relapse was not reduced in the alternative donor transplant compared to that in related donor transplant despite our expectation that a graft-versus-leukemia (GVL) effect would be more potent after allo-HCT from alternative donors. Several reports have indicated that the outcomes of allo-HCT from HLA allele-matched unrelated donors are comparable to those from related donors [14,27]. One possible explanation for this disparity is that patients who received allo-HCT from an alternative donor in our database were significantly more likely to have high-risk AML than those who received allo-HCT from a related donor. Second, HLA typing was predominantly performed serologically in the period of our study. About a third of the patient/donor pairs who are considered to be matched unrelated pairs by a serologic examination have been reported to have an allele-mismatch [30]. In addition, voluntary unrelated donors consisted only of BM donors because peripheral blood harvest is not yet allowed in our country, and unrelated CB accounted for one-third of the alternative donors in our study. Although allo-HCT from an alternative donor was not shown to have a benefit in elderly patients in our study, we may expect a better outcome with a smooth access to an allele-matched unrelated donor.

Whereas prior reports that have compared allo-HCT and chemotherapy in elderly patients targeted only allo-HCT with RIC [19,20], one-third of the HCT group patients in our study received an MA conditioning regimen. However, except for patient age, there were no significant differences in the disease risks between the MA and RIC groups, and OS was similar between the two groups. As has been previously pointed out, there were no significant differences in OS among different RIC regimens [31].

Because our database consists of retrospectively collected clinical data, this cohort of patients may have several inherent selection biases. Although we performed a landmark analysis to eliminate the biases by the patients who did not have a chance to receive allo-HCT in CR1 because of earlier relapse or comorbidity, patients in the HCT group may still have had favorable features that enabled them to successfully reach the point of allo-HCT in CR1. Furthermore, our database did not provide detailed information on consolidation chemotherapy after achievement of CR1 or the reasons why patients did not undergo allo-HCT such as the presence of comorbid conditions. Although the number of the elderly patients who received autologous HCT in CR1 was small, the exclusion of these patients may have made the non-HCT group have even more inherent selection bias, Nevertheless, the results drawn from our database, which includes 850 patients in the CTx group and 150 patients in the HCT group, may allow us to suggest optimal strategies for elderly patients with AML especially stratified by cytogenetic subgroups.

In conclusion, our study indicated that elderly patients with AML who underwent allo-HCT in CR1 had improved outcomes compared to those who were treated with conventional chemotherapy alone, and also revealed that intermediate-risk AML patients had an improved OS when they underwent allo-HCT in CR1. Because OS was better in elderly patients when they have a matched related donor and successfully undergo allo-HCT in CR1, they should be encouraged to seek the opportunity of allo-HCT in CR1 by performing HLA typing and donor search in the early period after achievement of CR1. Novel strategies to reduce the risk of relapse and better access to allele-matched unrelated donors should further improve the prognosis of elderly patients with AML.

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AUTHORSHIP STATEMENT

Contribution: S.K. designed the study, prepared the data file, performed the analysis, interpreted data, and wrote the manuscript; T.Yamaguchi was primarily responsible for designing the study, data analysis and interpretation of the data; N. Uchida., S.M., K.U., M.W., T. Yamashita., H.K., J. Tomiyama., Y. Nawa., S.Y., J. Takeuchi., K.Y., F.S., N. Uoshima., T. Yano., Y. Nannya, and Y.M. obtained the patients' data and interpreted data; I.M. reviewed the cytogenetic reports and interpreted data; Y.T. interpreted data and helped to write the paper; T.F. was primarily responsible for the entire paper as an accurate and verifiable report.

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APPENDIX: PARTICIPATING CENTERS

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