輸血後鉄過剰症とその治療

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【要　旨】
ヒトは鉄の積極的な排泄機構を有さず、そのため造血不全に対する治療として赤血球輸血が繰り返されると容易に鉄過剰に陥る。鉄過剰症に伴う臓器障害は患者のＱＯＬや予後に悪影響を及ぼすため、適切な鉄キレート療法が必要である。

◆キーワード
鉄過剰症
フェリチン
デフェラシロクス
造血不全
骨髄異形成症候群

輸血は貧血に対する治療の一つとして広く実施されている。中でも造血不全と言われる一群の疾患に対しては、原疾患が難治性のこともあり、長期にわたり実施されることが多い。国内では稀であるが、サラセミアなど幼少時より輸血依存となる疾患などを含め、長期の輸血実施例において輸血に伴う鉄過剰が生じ、これが患者予後を左右する問題となることが知られている。

鉄過剰に対しては、鉄キレート剤を用いた治療を実施する必要があるが、最近、経口鉄キレート剤が国内で使用可能となった。厚生労働省による特発性造血障害に関する調査研究班では「輸血後鉄過剰症の診療ガイド」[1]を作成した。本稿では輸血後鉄過剰症とその治療について、このガイドラインに沿って概説する。全体のまとめを表1に示す。

1．ヒトの鉄代謝

ヒトの体内には、おおよそ４００mgの鉄が存在し、その55％程度がヘモグロビンとして赤血球に分布する。25％程度は肝臓に、15％程度はマクロファージ（網内系）で貯蔵鉄として保持されている。その他、筋肉のミオグロビンや酵素の一部として5～10％が利用されている。鉄の摂取・排出を見てみると、1日当たり1～2mgが消化管より吸収され、同量が皮膚や粘膜の剝奪とともに失われており、外部との移動が大変少ない。

赤血球の体内寿命はおおよそ120日であり、網内系のマクロファージによって貪食・破壊される。これによって、20～25mg／日の鉄がマクロファージに取り込まれるが、この鉄はマクロファージから骨髄に移され、そこでほぼ全量が赤血球造血に利用される。このように、ヒトは積極的な鉄排出系を持たず、鉄代謝は基本的には半閉鎖系として再利用を中心としたサイクルを続けている。

鉄は消化管（小腸）から吸収されるが、フリー鉄の吸収には粘膜上皮のDcytb，ＤＭＴ１経路が利用され、ヘム鉄はＨＣＰ１を通じ

表1　輸血後鉄過剰症の診療ガイド（骨子）

対象患者	様々な原因による骨髄不全で輸血依存となり，かつ1年以上の余命が期待できる例
輸血後鉄過剰症診断基準	・総赤血球輸血量20単位（小児の場合，ヒト赤血球濃厚液50mℓ／体重kg）以上 および ・血清フェリチン値500ng／mℓ以上
鉄キレート療法開始基準	輸血後鉄過剰症において，下記の1と2を考慮して鉄キレート療法を開始する 1. 総赤血球輸血量40単位（小児の場合，ヒト赤血球濃厚液100mℓ／体重kg）以上 2. 連続する2回の測定で（2カ月間以上にわたって）血清フェリチン値＞1,000ng／mℓ
鉄キレート療法開始基準の解説	下記のような場合は、鉄キレート療法の開始に当たり，総輸血量および血清フェリチン値の両方を考慮し，総合的に判断する —慢性的な出血や溶血を伴う場合 —現在輸血を受けていない場合（造血幹細胞移植，薬物療法などが奏効した例） —輸血とは無関係に血清フェリチン値が慢性的に高値を示す合併症がある場合（例えば，スティル病，血球貪食症候群，悪性腫瘍など） なお，鉄キレート療法は，余命1年以上が期待できない患者に対しては推奨されない
維持基準	・鉄キレート剤により，血清フェリチン値を500～1,000ng／mℓに維持する

（文献[1]より）

て粘膜上皮に入る。また、粘膜から血液へはferroportinによって排出され、hephaestinにより三価鉄に酸化し、血液中でトランスフェリン（Tf）1分子が鉄2分子と結合して循環している。赤芽球表面にはTfに対する受容体TfR1が発現しており、この受容体を通じてTfとともに鉄を吸収する。赤芽球系細胞では分化の中期から後期にかけてTfR1が高発現し、ヘモグロビン合成との関係で合目的的である。利用されなかった鉄は貯蔵鉄としてフェリチンとなり、安全な形で体内に保持される。

鉄代謝は、体内の貯蔵鉄の調節・利用も含めて肝臓で合成される「ヘプシジン」による制御を受けている[2]。ヘプシジンはferroportinの抑制因子として働くことで、血漿中への鉄の放出を抑制している。炎症や体内の鉄過剰状態では、ヘプシジン産生が亢進することで、小腸粘膜からの鉄吸収を抑え、同時に網内系のマクロファージで処理された鉄の血漿中への放出を抑制することになる。

近年、赤血球成熟過程で分泌されるgrowth differentiation factor（GDF）15がヘプシジン発現を抑制することが報告され、赤血球造血と鉄代謝とのつながりを直接的に説明できるようになってきている。GDF15は赤血球無効造血時（骨髄異形成症候群の鉄芽球性貧血）に発現が亢進しており、同時にヘプシジンが抑制されていることが知られている。これによって、例えば骨髄異形成症候群では疾患そのものの特性によって鉄吸収が亢進し、鉄過剰状態となりやすいことが説明できる。

2．輸血による鉄過剰の機序

骨髄異形成症候群、再生不良性貧血に代表される造血不全の治療では、貧血への補充療法の一つとして赤血球輸血がある。原疾患、身体状況、生活内容などによってその頻度は様々であるが、貧血による臓器不全（心不全など）や生活の質を維持する目的で行われる。この赤血球に含まれるヘモグロビンは前記のように鉄を有し、血液2mℓに鉄1mgが含まれている。つまり400mℓの血液に由来する2単位（国内表示）の赤血球製剤は、およそ200mgの鉄を含んでおり、2単位の輸血によってほぼ100日分の鉄が体内に取り込まれることになる。造血不全を来す疾患の特性上、輸血は長期にわたって繰り返されることが多く、患者は輸血による鉄過剰状態に陥る。

体内の過剰な鉄は、まず肝臓や網内系細胞に貯蔵鉄として蓄えられる。細胞内の貯蔵鉄は、そのほとんどが前述のようにフェリチンタンパク質とともにあって毒性を

発揮しない。通常2～3％が、細胞内で鉄がタンパク質間を移動する際に自由鉄（labile iron pool：LIP）としてfreeで存在していると考えられているが、貯蔵鉄が過剰になると細胞内でＬＩＰが増加し、酸化反応の電子供与体として働くことになる。いわゆるフェントン反応が生じ、活性酸素種の中でも活性の高いヒドロキシラジカルが生成される。タンパク質、脂質、核酸が酸化反応の標的となり、細胞毒性へとつながる。

3．輸血後鉄過剰による臓器障害

輸血が頻回に行われると鉄キレート療法が実施されない限り鉄過剰が生じ、過剰鉄は網内系で対応できなくなると、全身の実質臓器に沈着を始める。例えば重症の鉄過剰患者で、皮膚がくすんだ色を呈してくるのは臨床的によく知られた所見である。鉄沈着によって障害を起こしてくる臓器としては、肝臓、膵臓、心臓、甲状腺、下垂体が中心となる。生理的な鉄貯蔵部位である肝臓では、過剰な鉄沈着によって肝細胞障害による機能異常から線維化、肝硬変へと進展する。膵臓では内分泌器官のβ細胞障害によって糖尿病が発症し、心臓においては心筋障害による心筋症、心不全や伝導系障害による不整脈、さらに甲状腺あるいは下垂体の機能低下などが様々な組み合わせで生じてくることになる。

特発性造血障害に関する調査研究班（小澤班）が２００５年に実施した全国調査によって国内の輸血後鉄過剰症の実態が明らかにされた[3]。全国43医療機関から集められた２９２例について解析がなされ、原疾患としては再生不良性貧血（30・8％）、骨髄異形成症候群（52・1％）が全体の80％を占めていた。そのほかは赤芽球癆（5・1％）、骨髄線維症（4・5％）などである。

生涯輸血量と血清フェリチン値は有意な相関を示し、輸血量がほぼ20単位で50％の患者が、40単位で75％の患者が異常フェリチン高値（１０００ng／mℓ超）を呈し、一部では５０００ng／mℓを超えていた。フェリチン高値は肝酵素ＡＳＴ、ＡＬＴ上昇と有意な相関があり、フェリチン値が１０００ng／mℓを超えるとＡＳＴ、ＡＬＴ上昇がそれぞれ31％、22％に出現し、フェリチン値の上昇とともに肝機能異常の割合が増加した。心機能においても、検査を行ったうちの21・9％に異常が見られ、やはりフェリチン値と弱い相関が認められた。さらに、空腹時血糖値の上昇が輸血総量と関連していた。

このように、国内でも輸血後鉄過剰と肝臓、心臓、膵臓機能異常の関連が明らかとなった。さらに調査されたうち、死亡例の死因について検討すると、心不全、肝不全がそれぞれ24％、6・7％に認められ、また血清フェリチン値が１０００ng／mℓを超える例は、それ未満の患者より死亡率が高く、輸血による鉄過剰が患者予後に関与することが示唆されていた。

国外からの報告でも、輸血による鉄過剰は臓器障害を引き起こし、鉄過剰に伴って生存期間が短縮することも明らかとなっている。長期の繰り返す輸血は鉄過剰という大きな問題を引き起こす。

4．輸血による鉄過剰の診断

体内の総鉄量は、肝臓の生検標本における鉄量と強く相関することが知られており、これが体内鉄量の評価方法のゴールドスタンダードであるが、一般的に実施できる方法ではない。特に、造血不全患者では血小板減少を伴うこともしばしばあり、生検そのものの危険性も大きくなる。ＭＲＩによる肝臓の貯蔵鉄を評価する方法もあるが、測定可能な機種が限られていることもあって国内では普及していない。

そこで、より簡便なマーカーとして血清フェリチンが用いられている。これは、鉄調節のメカニズムとして体内の鉄量が増えるとフェリチン合成が亢進することを利用したもので、血清フェリチン値は間接的にではあるが体内貯蔵鉄量を反映している。ただし、血清フェリチン値は炎症、膠原病、腫瘍、スティル病、血球貪食症候群、肝疾患など鉄代謝以外の機序でも変動するため、その解釈には注意が必要である。鉄過剰を判定する

際には、これらの疾患を除外するとともに、少なくとも2回の測定による評価が求められる。

出血がなければ輸血量が体内鉄量に強く関連するため、「輸血後鉄過剰症の診療ガイド」では①総赤血球輸血量20単位以上、②血清フェリチン値500ng／mℓ以上の2項目を満たす際に輸血後鉄過剰症と診断することになっている。さらに、鉄過剰の重症度は血清フェリチン値と臓器機能異常の有無によって細分化され、その後のマネージメントに生かされることになっている。血清フェリチン値は500ng／mℓ超、1000ng／mℓ超、2500ng／mℓ超、5000ng／mℓ超によってそれぞれステージ1～4に分け、臓器障害は①心臓：左室拍出量50％未満、②肝機能障害：肝酵素異常、肝線維化、肝硬変の所見、③膵内分泌機能障害：耐糖能低下の所見、によって評価し、いずれかに当てはまる時には臓器障害ありとして「B」と表記し、当てはまらない時には「A」として血清フェリチン値によるステージに併記する。

5. 輸血後鉄過剰症の治療

輸血後鉄過剰症の治療目的は、鉄過剰に伴う進行性かつ不可逆的な臓器障害のリスクを軽減し、患者のQOLと予後を改善することである。したがって、鉄過剰が存在すればすぐに治療の対象となるわけではなく、臓器障害に対するリスクの評価や治療がQOLや予後にどのような影響を与えるかについても考慮した上で治療の実施を決定する必要がある。診療ガイドでは鉄過剰に対する治療開始基準として、鉄過剰状態にあって臓器障害が惹起される可能性があるものとされており、①総赤血球輸血量40単位以上、②連続する2回の測定で血清フェリチン値1000ng／mℓ超の場合が推奨されている。

また、鉄過剰による臓器障害は一般に急速進行性ではないため、患者余命が1年以上と考えられる例が治療の対象となる。さらに、原疾患の改善によって輸血非依存となっている例や、今後どういった治療を受けるのか（例えば造血幹細胞移植など）など、個々の状況によっても判断する必要がある。

治療は体内の鉄を除去するいわゆる鉄キレート療法となるが、最も簡単な瀉血は造血不全に対しては適応がない。そこで、薬物によるキレートが実施されることになる。

(1)対象疾患

鉄キレート療法の対象となるのは鉄過剰となった例で、前記の治療開始基準を満たし、赤血球輸血依存（月2単位以上の輸血を6カ月以上継続）の患者で1年以上の余命が期待できる例となる。疾患として最も多いのは骨髄異形成症候群と思われるが、それ以外の骨髄不全症候群として、再生不良性貧血とその類縁疾患（慢性赤芽球癆など）、原発性骨髄線維症、二次性骨髄不全（がん化学療法に続発するものなど）がある。

(2)治　療

治療薬として国内で使用可能なのはデフェロキサミン、デフェラシロクスの2剤である。特発性造血障害に関する調査研究班の全国調査では、全体の43・2％（29例中126例）にデフェロキサミンによる鉄キレート療法が実施されていた。本剤は血中半減期が短いため、臨床的に十分な効果を得るために持続点滴または持続皮下注による投与が必要である。しかし、投与例の57・8％はデフェロキサミンの間欠的投与、25・8％は輸血実施時の投与であった。連日投与または持続投与がなされていたのは、わずか8・7％（126例中11例）にすぎなかったが、そうした例では確かに血清フェリチン値の低下と肝機能の改善、血糖の低下が得られ、除鉄による臓器機能の回復が示唆された。デフェロキサミンは輸血後鉄過剰症に対して有効な薬剤であるが、臨床的に十分な投与という点ではコンプライアンスが低い薬剤と考えられる。

デフェラシロクスはFe^{3+}に対して強い親和性を示し、経口での投与が可能な薬剤である。血中半減期が8～16時間と長いため1日1回の投与で十分な有効血中濃度が維持され、良好なコンプライアンスが期待できる。鉄と錯体を形成

して胆汁中に排泄され、糞便とともに体外に排出されることになる。

デフェラシロクスの初期投与量は20mg／kgであり、薬剤を100mℓ以上の水に懸濁した後、空腹時に内服する。内服後も30分程度は食物を取らないよう指導が必要である。薬剤の投与量は患者体重によるが、同時に輸血量によっても調節が必要である。すなわち、月に4～8単位の赤血球輸血を受けている場合には20mg／kg投与によって血清フェリチン値の減少が期待できるが、月に8単位を超える赤血球輸血が実施されている例では30mg／kgのデフェラシロクスが投与されないと除鉄は十分ではないと考えられる。

(3)治療の目標とモニタリング

鉄キレート療法の目標は、鉄過剰による臓器障害の予防とそれによるQOL改善である。したがって鉄キレート療法中は、除鉄効果の確認と有害事象に関するモニタリングが必要となる。デフェラシロクスの有害事象としては服用に伴う胃腸障害、腎機能障害、肝機能障害、水晶体混濁・視神経炎、難聴、皮疹が知られている。服用に伴う胃腸障害は腹痛、悪心、下痢で一般には軽度で、内服を継続できる例が多い。腎機能障害ではクレアチニンの上昇が多いが、持続的に上昇するものではなく、休薬に伴って回復が見られる。しかし、投薬中は定期的な肝・腎機能の確認とともに、半年に一度は、眼科的・耳鼻科的診察によるフォローアップが必要とされている。クレアチニンの上昇や肝酵素の上昇が見られる場合には、減量や休薬が必要である。こうした有害事象については、薬剤の添付文書に則ったモニタリングを実施する。例えば、クレアチニンが治療前値（平均）の33％を超えて増加する場合には、デフェラシロクスの減量（10mg／kg）が推奨されている。

除鉄効果のモニタリングには、血清フェリチン値を用いる。これを毎月測定し、治療開始後3～6カ月を経過しても血清フェリチン値の増加傾向が見られる場合には、効果不十分としてデフェラシロクスの増量を考慮する。治療の目標は血清フェリチン値を500～1000ng／mℓに維持することで、500ng／mℓ以下となった場合には休薬する。輸血が継続されると血清フェリチン値は再び上昇に転ずるが、1000ng／mℓを超えた時点でデフェラシロクスを再開するとよい。除鉄効果と同時に臓器障害やその回復を見るために心エコー検査、肝機能検査、耐糖能検査（グリコアルブミン、血糖など）を定期的に実施する。除鉄効果とともにこうした検査によって臓器機能の回復や、輸血依存であっても臓器障害がない状態に維持されることを確認できる。

小児においては、鉄過剰に伴う成長障害を早期に発見するために体重、身長、二次性徴の定期的なモニタリングも必要となる。

(4)治療による効果

鉄キレート療法による肝機能障害（肝酵素異常）の改善や生存期間の延長が示唆されている。国内には少ないが、サラセミアにおいては早期の除鉄療法によって予後が著明に改善することが示されており[4]、鉄過剰による臓器障害が生ずる前の鉄キレート療法開始が推奨されている。また、骨髄異形成症候群など造血不全に対しても鉄キレート療法が予後に対する有意な因子として挙げられるなど、その有用性が指摘されている。

一方で、最近、比較的予後の短いhigh-risk骨髄異形成症候群に対してもデフェラシロクスの投与が増えていることから、前向き比較試験によるデフェラシロクスの有用性確認が必要であるとの指摘もあり[5]、特に骨髄異形成症候群の場合、治療の適用が再び問われている。国内においては、前述の診療ガイドに則った輸血後鉄過剰症の診断・治療が勧められる。

□■□文　献□■□

1) 特発性造血障害に関する調査研究班（班長：小澤敬也）：輸血後鉄過剰症の診療ガイド，厚生労働科学研究費補助金難治性疾患克服研究事業，平成20年度．＜http://www.jichi.ac.jp/zoketsushogaihan/tetsufinal.pdf＞ 2) Nemeth E, et al : Annu Rev Nutr 26 : 323, 2006. 3) Takatoku M, et al : Eur J Haematol 78 : 487, 2007. 4) Brittenham GM, et al : N Engl J Med 331 : 567, 1994. 5) Tefferi A, et al : Leukemia 23 : 1373, 2009.

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LR-3704; No. of Pages 7

Leukemia Research xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

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

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ARTICLE INFO

Article history:
Received 3 August 2009
Received in revised form
11 November 2009
Accepted 18 November 2009
Available online xxx

Keywords:
Myelodysplastic syndromes
Refractory anemia
Myelodysplastic syndrome-unclassified
WHO classification
FAB classification
Prognosis

ABSTRACT

We reported the different clinical features between Japanese and German refractory anemia (RA) patients in FAB classification. We re-analyzed the clinical features by WHO classification revised in 2008. The frequencies of refractory cytopenia with unilineage dysplasia (RCUD) and myelodysplastic syndrome-unclassified (MDS-U) with pancytopenia in Japanese patients were higher than in German patients ($p < 0.001$). Refractory cytopenia with multilineage dysplasia patients showed the most unfavorable prognosis in both countries. The higher frequencies of MDS-U with pancytopenia and RCUD in Japanese patients may influence the different clinical characteristics between Japanese and German FAB-RA patients.

1. Introduction

Myelodysplastic syndromes (MDS) are acquired clonal stem cell disorders characterized by ineffective hematopoiesis with myelodysplasia [1] and are associated with a high risk of progression to acute leukemias [2]. MDS are very heterogeneous in terms of their morphology, clinical features, and survival [3]. There are several reports indicating possible differences in clinical features between Western MDS types and Eastern MDS types [4–9]. The median age of MDS patients in Korea and Thailand were reported to be 57 [8] and 56 [7], respectively. On the other hand, large MDS studies from Western countries showed a median or mean age of 68–73 years [10–13]. We have reported that the clinical features of refractory anemia with excess of blasts (RAEB) or RAEB in transformation (RAEB-t) according to the French–American–British (FAB) classification [14] seemed to be similar between Japanese and Western patients [15]. However, previous reports [5,15] indicated that Japanese MDS patients have a lower frequency of refractory anemia with ringed sideroblasts (RARS) according to the FAB classification and a higher frequency of refractory anemia according to the FAB classification (FAB-RA) than the Western International Prognostic Scoring System (IPSS) study [10], and we reported that the clinical and laboratory features of Japanese FAB-RA patients apparently differ from those of German patients after a precise morphologic consensus (FAB classification: concordance rate, 98.4%; κ, 0.94; $p < 0.001$; prior World Health Organization (WHO) classification (WHO classification 2001) [16]: concordance rate, 83.8%; κ, 0.73; $p < 0.001$) [17]. That was the first comparison report between Western and Eastern FAB-RA patients after confirming morphological consensus. Japanese FAB-RA patients were younger, showed more severe cytopenia(s), a lower frequency of abnormal karyotypes, a lower frequency of MDS with isolated del(5q) (5q-syndrome), and a more favorable prognosis in terms of the overall survival (OS) and leukemia free survival (LFS) in our previous study.

MDS subtypes in the WHO classification 2001 [16] was revised in 2008 (WHO classification 2008) [18]. Refractory anemia (RA), refractory neutropenia (RN), and refractory thrombocytopenia (RT) were combined into refractory cytopenia with unilineage dysplasia

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0145-2126/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.leukres.2009.11.015

(RCUD) in the WHO classification 2008. The diagnosis of MDS-unclassified (MDS-U) according to the WHO classification 2008 can be made in the following instances:

1. Patients with the findings of RCUD or refractory cytopenia with multilineage dysplasia (RCMD) but with 1% blasts in the peripheral blood (PB) (PB blasts type).
2. Cases of RCUD which are associated with pancytopenia (RCUD/pancytopenia type).
3. Patients with cytopenia(s) with 1% or fewer blasts in the PB and fewer than 5% in the bone marrow (BM), unequivocal dysplasia in <10% of the cells in one or more myeloid lineages, and who have cytogenetic abnormalities (cytogenetic abnormalities type).

MDS-U (PB blasts type) is classified as RAEB according to the FAB classification because of 1% blasts in the PB. MDS-U (cytogenetic abnormalities type) is not diagnosed as MDS according to the FAB classification because of unequivocal dysplasia. Thus, FAB-RA patients are classified as RCUD, RCMD, MDS with isolated del(5q) (5q- syndrome) or MDS-U (RCUD/pancytopenia type) according to the WHO classification 2008. In the present study, we re-analyzed in detail the clinical features of Japanese and German FAB-RA patients by using revised MDS subtypes in the WHO classification 2008.

2. Patients and methods

The dataset of consecutive patients with primary FAB-RA of our previous study [17] (total 728 consecutive patients: Japan, 131 cases; Germany, 597 cases) were used for the present retrospective analysis. Japanese patients of this dataset were diagnosed at the Saitama Medical University Hospital, Nagasaki University Hospital or affiliated hospitals between April 1976 and January 1997. German patients were diagnosed at the Department of Hematology, Oncology and Clinical Immunology of the Heinrich-Heine University between January 1973 and December 2002. Patients who had previously been treated with anti-neoplastic drugs or ionizing radiation were excluded from the study. Patients without the available necessary data for the WHO classification 2008 were excluded from the present study. Cytogenetic analyses were performed with a trypsin-Giemsa banding technique on BM cells from aspirates. Ordinarily 20–30 metaphases were examined. Cytogenetic aberrations were grouped according to the IPSS publication [10]. Thresholds for cytopenia(s) were defined as those of the IPSS (hemoglobin (Hb) <10.0 g/dL, absolute neutrophil count (ANC) $<1.8 \times 10^9$/L, and platelet $<100 \times 10^9$/L). Criteria for dysplasia were defined as those of a previous German report [19]. Hypoplastic BM was defined as <30% cellular in patients <60 years old, or <20% cellular in patients ≥60 years old [20]. If hypoplastic BM and certain dysplasia more than 10% in one or more of major myeloid cell lines were present, a diagnosis of hypoplastic MDS was made. Patients were reclassified according to the definition of WHO classification 2008 for MDS subtyping by using PB and BM findings, morphologic findings, and cytogenetic findings of the previous dataset [17]. Comparisons of the clinical features at the time of diagnosis and OS and LFS were analyzed by using the dataset of our previous study [17]. OS was measured from the date of diagnosis until death due to any cause, the date of stem cell transplantation, or until the last patient contact. LFS was measured from the date of diagnosis until the date of diagnosis of acute leukemia. This study was approved by the Institutional Review Board of Saitama International Medical Center, Saitama Medical University, Saitama, Japan.

2.1. Statistical methods

The chi-square test and the nonparametric Mann–Whitney test were used to compare the proportions of patients and continuous data, respectively. The Kaplan–Meier method was used to generate the estimate of cumulative probabilities of OS and LFS. The difference in the cumulative probabilities within subcategories of patients was compared using a two-sided log-rank test. A two-sided p value of <0.05 was considered to be statistically significant. All statistical analyses were performed with the use of StatView (version 5.0, SAS Institute, Cary, NC).

3. Results

3.1. Comparison of frequencies of subtypes according to the WHO classification 2008 between Japanese and German FAB-RA patients

A total of 295 patients (Japan, 102 cases; Germany, 193 cases) could be classified according to the WHO classification 2008. A total of 433 patients (Japan, 29 cases; Germany, 404 cases) could not be classified according to the WHO classification 2008 due to a deficit of either cytogenetic data or adequate peripheral blood data, and 427 patients presented without available cytogenetic findings (Japan, 29 cases; Germany, 398 cases). There were 6 patients (Germany, 6 cases) without any data of peripheral blood.

MDS-U (PB blasts type) is classified as RAEB according to the FAB classification. MDS-U (cytogenetic abnormalities type) is not diagnosed as MDS according to the FAB classification due to unequivocal dysplasia. Therefore, patients with MDS-U (PB blasts type) or with MDS-U (cytogenetic abnormalities type) were not included in the previous dataset. Because the previous dataset used in the present study was that of FAB-RA patients, dysplasia existed in at least one lineage and the frequency of blasts in PB was <1% in all patients. Therefore, all MDS-U patients in the present study were diagnosed as RCUD/pancytopenia type. Most Japanese FAB-RA patients were classified as RCUD, RCMD, or MDS-U (RCUD/pancytopenia type) according to the WHO classification 2008 (Table 1A). Most German FAB-RA patients were classified as RCUD, RCMD, or 5q- syndrome (Table 1B). The frequency of RCUD in Japanese FAB-RA patients (45%) was significantly higher than that in German FAB-RA patients (19%) ($p < 0.001$). The frequency of patients with bicytopenia in Japanese RCUD patients was 59%, but that in the German RCUD patients was only 19%. Among 46 Japanese RCUD patients, number of patients with single cytopenia was 17 cases (37%) including 2 RA, 4 RN and 11 RT cases. Among 37 German RCUD patients, number of patients with single cytopenia was 22 cases (59%) including 7 RA, 11 RN and 4 RT cases. Frequency of RT was 2% of German FAB-RA patients. The frequency of RT of Japanese FAB-RA patients (11%) was higher than that of German FAB-RA patients. The frequency of MDS-U in Japanese FAB-RA patients (29%) was significantly higher than that in German FAB-RA patients (3%) ($p < 0.001$). The frequency of RCMD in Japanese FAB-RA patients (25%) was significantly lower than in German FAB-RA patients (58%) ($p < 0.001$). The frequency of 5q- syndrome in Japanese FAB-RA patients (3%) was significantly lower than in German FAB-RA patients (20%) ($p < 0.001$) (Table 1C).

3.2. Comparison of clinical and laboratory features at the time of diagnosis between Japanese and German patients could be classified according to the WHO classification 2008

The age of patients in RCUD, MDS-U and RCMD subtypes did not differ between the two countries. The MDS-U (RCUD/pancytopenia type) subtype was younger than other subgroups in Japanese patients. The gender ratios in the RCUD

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Table 1
Laboratory features at the time of diagnosis in FAB-RA patients who could be classified according to the WHO classification 2008.

	RCUD	MDS-U	RCMD	5q- synd
(A) Japanese patients, $n = 102$				
Patients = n (%)	46(45)	28(29)	25(25)	3(3)
Gender (male/female)	28/18	12/16	11/14	2/1
Age (years)	57(16–86)	51(15–82)	63(16–88)	60(59–74)
Neutrophils ($\times 10^9$/L)	1.89 (0.44–4.69)	1.10 (0.26–1.77)	1.28 (0.05–10.24)	0.73 (0.50–2.54)
Hemoglobin (g/dL)	10.2 (3.0–14.3)	6.9 (4.2–9.1)	8.2 (2.9–14.0)	6.3 (4.6–10.8)
Platelets ($\times 10^9$/L)	41(4–246)	29(7–98)	50(13–390)	207(134–212)
Abnormal karyotype = n (%)	12(26)	6(21)	9(36)	3(100)
Hypoplastic bone marrow = n (%)	3(7)	3(11)	0(0)	0(0)
(B) German patients, $n = 193$				
Patients = n (%)	37(19)	6(3)	111(58)	39(20)
Gender (male/female)	20/17	1/5	80/31	14/25
Age (years)	62(20–80)	56(19–59)	63(15–86)	62(32–78)
Neutrophils ($\times 10^9$/L)	1.92 (0.36–8.72)	1.41 (0.48–1.50)	1.60 (0.21–19.40)	1.95 (0.61–6.78)
Hemoglobin (g/dL)	11.0 (5.2–15.4)	9.4 (5.5–9.8)	9.2 (5.1–16.9)	8.7 (3.0–12.2)
Platelets ($\times 10^9$/L)	128(2–840)	33(10–90)	102(9–999)	250(28–1540)
Abnormal karyotype = n (%)	12(32)	3(50)	47(42)	39(100)
Hypoplastic bone marrow = n (%)	3(8)	2(33)	13(12)	5(13)
	Japan vs Germany			
(C) Comparison between Japanese and German patients				
(1) RCUD patients				
Frequency	$p < 0.001$			
Gender (male/female)	$p = 0.532$			
Age (years)	$p = 0.150$			
Neutrophils ($\times 10^9$/L)	$p = 0.466$			
Hemoglobin (g/dL)	$p = 0.087$			
Platelets ($\times 10^9$/L)	$p < 0.001$			
Abnormal karyotype (%)	$p = 0.526$			
Hypoplastic bone marrow (%)	$p = 0.782$			
(2) MDS-U patients				
Frequency	$p < 0.001$			
Gender (male/female)	$p = 0.239$			
Age (years)	$p = 0.557$			
Neutrophils ($\times 10^9$/L)	$p = 0.821$			
Hemoglobin (g/dL)	$p = 0.036$			
Platelets ($\times 10^9$/L)	$p = 0.752$			
Abnormal karyotype (%)	$p = 0.150$			
Hypoplastic bone marrow (%)	$p = 0.156$			
(3) RCMD patients				
Frequency	$p < 0.001$			
Gender (male/female)	$p = 0.007$			
Age (years)	$p = 0.401$			
Neutrophils ($\times 10^9$/L)	$p = 0.494$			
Hemoglobin (g/dL)	$p = 0.016$			
Platelets ($\times 10^9$/L)	$p = 0.030$			
Abnormal karyotype (%)	$p = 0.561$			
Hypoplastic bone marrow (%)	$p = 0.072$			
(4) 5q- synd patients				
Frequency	$p < 0.001$			
Gender (male/female)	$p = 0.290$			
Age (years)	$p = 0.920$			
Neutrophils ($\times 10^9$/L)	$p = 0.144$			
Hemoglobin (g/dL)	$p = 0.370$			
Platelets ($\times 10^9$/L)	$p = 0.188$			
Abnormal karyotype (%)	N/A			
Hypoplastic bone marrow (%)	$p = 0.509$			

Values for presentation characteristics are given as median and range where applicable. N/A, not applicable; RCUD, refractory cytopenia with unilineage dysplasia; MDS-U, MDS-unclassified; RCMD, refractory cytopenia with multilineage dysplasia; 5q- synd, MDS with isolated del(5q).

and MDS-U subtypes were not significantly different between the two countries. The frequency of male patients in Japanese RCMD subgroup was significantly lower than that in German RCMD subtype. Japanese patients had significantly lower platelet counts than German patients in both the RCUD and RCMD subtypes. Japanese MDS-U (RCUD/pancytopenia type) and RCMD patients showed significantly lower Hb concentrations than German MDS-U (RCUD/pancytopenia type) and RCMD patients. Japanese RCUD patients showed a tendency towards lower Hb concentrations than German RCUD patients. The ANC did not differ significantly between the two countries in RCUD, MDS-U (RCUD/pancytopenia type), and RCMD patients (Table 1). The frequency of cytogenetic abnormalities in the Japanese FAB-RA patients was significantly lower than in German patients ($p < 0.001$) (Tables 1 and 2). The frequencies of cytogenetic abnormalities in the RCUD, MDS-U (RCUD/pancytopenia type), and RCMD subtypes were not significantly different between the two countries (RCUD, $p = 0.526$; RCMD, $p = 0.561$; MDS-U (RCUD/pancytopenia type), $p = 0.150$). The frequency of isolated del(5q) in Japanese FAB-RA patients was significantly lower than in German patients

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Table 2
Cytogenetic findings at the time of diagnosis in FAB-RA patients who could be classified according to the WHO classification 2008.

	RCUD	MDS-U	RCMD	5q- synd	Total
(A) Japanese patients, $n=102$					
Patients = n	46	28	25	3	102
Good	37(80.4%)	23(82.1%)	16(64.0%)	3(100%)	79(77.5%)
Normal	34(73.9%)	22(78.6%)	16(64.0%)	0(0%)	70(68.6%)
−Y	0	1	0	0	1
del(5q)	0	0	0	3	3
del(20q)	3	0	0	0	3
Intermediate	8(17.4%)	3(10.7%)	4(16.0%)	0	15(14.7%)
Poor	1(0.2%)	2(7.2%)	5(20.0%)	0	8(7.8%)
Complex (≥3 abnormalities)	0	1	4	0	5
Chromosome 7 anomalies	1	1	1	0	3
(B) German patients, $n=193$					
Patients = n	37	6	111	39	193
Good	27(73.0%)	3(50.0%)	72(64.9%)	39(100%)	141(73.1%)
Normal	25(67.6%)	3(50.0%)	64(57.7%)	0(0%)	92(47.7%)
−Y	2	0	2	0	4
del(5q)	0	0	0	39	39
del(20q)	0	0	6	0	6
Intermediate	4(10.8%)	2(33.3%)	23(20.7%)	0	29(15.0%)
Poor	6(16.2%)	1(16.7%)	16(14.4%)	0	23(11.9%)
Complex (≥3 abnormalities)	5	0	9	0	14
Chromosome 7 anomalies	1	1	7	0	9

Good indicates normal, −Y, del(5q), del(20q); poor, complex (≥3 abnormalities) or chromosome 7 anomalies; intermediate, other abnormalities not listed in good and poor subgroups.

($p<0.001$) (Table 2). The most frequent cytogenetic aberration in the intermediate cytogenetic risk according to the IPSS publication was trisomy 8 (4 German RCMD cases, 3 Japanese RCUD cases, 1 Japanese MDS-U case). The frequencies of hypoplastic BM were not significantly different between the two countries in the RCUD and MDS-U (RCUD/pancytopenia type) subtypes. In the RCMD subtype, there were no Japanese patients presenting with findings concordant with hypoplastic BM. However, the frequency of German RCMD patients with hypoplastic BM was 12% (Table 1).

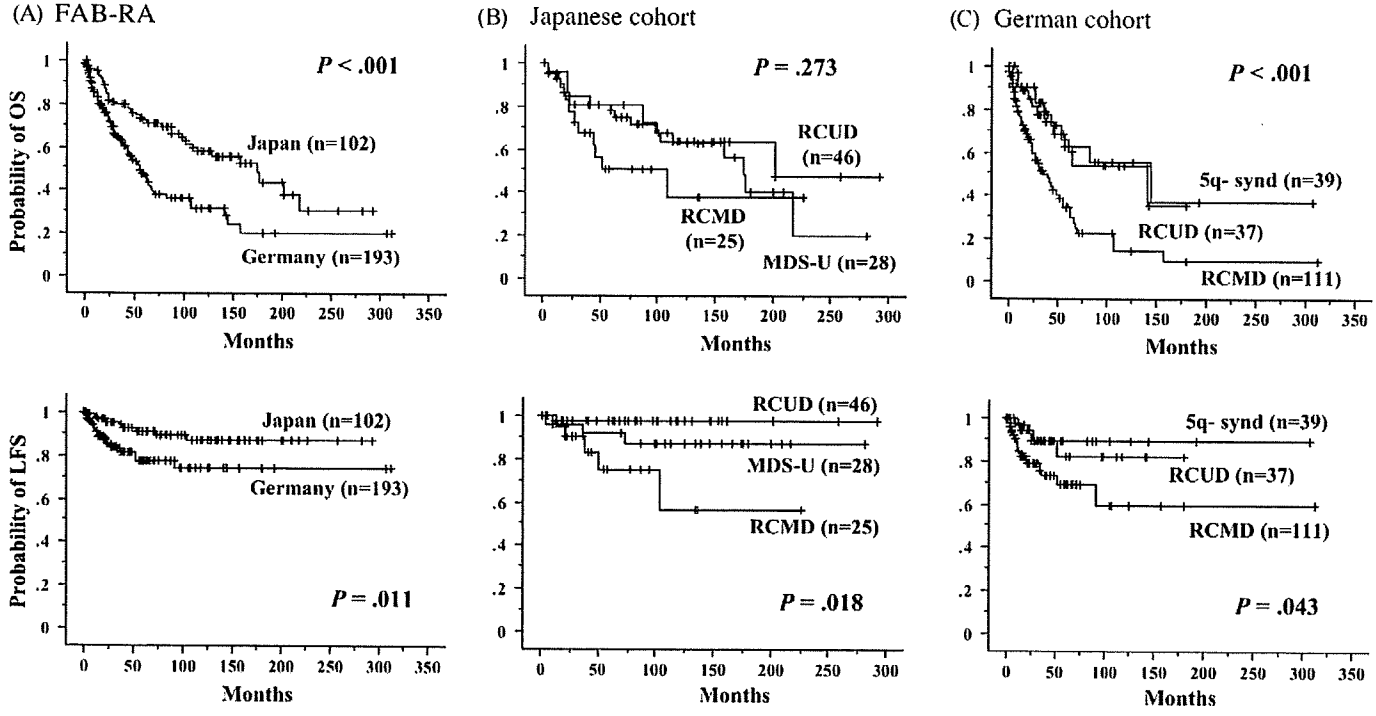

Fig. 1. Cumulative overall survival and leukemia free survival of FAB-RA patients who could be classified according to the WHO classification 2008. (Top) Overall survival (OS). (Bottom) Leukemia free survival (LFS). (A) In FAB-RA patients who could be classified according to the WHO classification 2008, Japanese patients had a more favorable OS than German patients ($p<0.001$). Japanese patients had a more favorable LFS than German patients ($p=0.011$). (B) In Japanese FAB-RA patients who could be classified according to the WHO classification 2008, RCMD patients showed the least favorable OS and LFS compared with the other subtypes excluding a rare subtype (5q- syndrome subtype). RCUD patients showed more favorable OS and LFS than RCMD patients (OS, $p=0.128$; LFS, $p=0.004$). MDS-U (RCUD/pancytopenia type) patients tended to show more favorable OS and LFS than RCMD patients (OS, $p=0.218$; LFS, $p=0.137$). (C) In German FAB-RA patients who could be classified according to the WHO classification 2008, RCMD patients showed the least favorable OS and LFS compared with the other subtypes excluding a rare subtype (MDS-U (RCUD/pancytopenia type) subtype). RCUD patients showed more favorable OS and LFS than RCMD patients (OS, $p=0.003$; LFS, $p=0.075$). 5q- syndrome patients showed more favorable OS and LFS than RCMD patients (OS, $p=0.002$; LFS, $p=0.043$).

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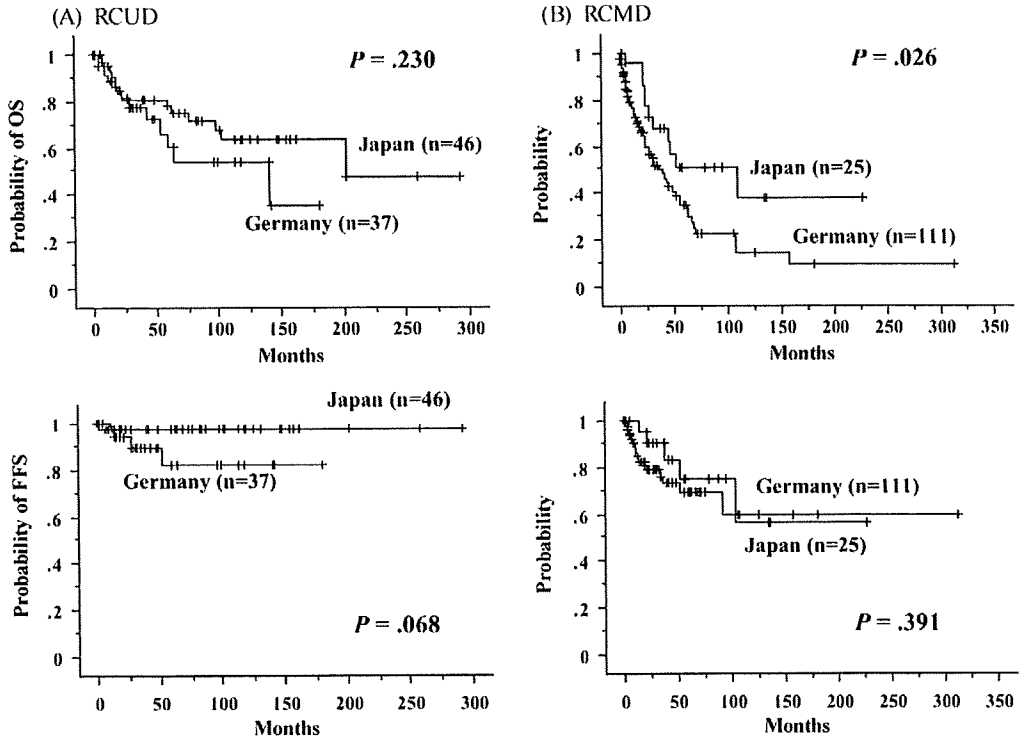

Fig. 2. Comparison of cumulative overall survival and leukemia free survival of RCUD and RCMD between Japanese and German patients. (Top) Overall survival (OS). (Bottom) Leukemia free survival (LFS). (A) The OS of RCUD patients was not significantly different between the two countries ($p = 0.230$). Japanese RCUD patients tended to show a more favorable LFS than German RCUD patients ($p = 0.068$). (B) Japanese RCMD patients showed a more favorable OS than German RCMD patients ($p = 0.026$). The LFS of RCMD patients was not significantly different between the two countries ($p = 0.391$).

3.3. Prognosis

Follow-up periods ranged from 1 to 292 months (median, 78 months) in Japanese FAB-RA patients who could be classified according to the WHO classification 2008. Follow-up periods in German patients ranged from 0 to 313 months (median, 23 months). During the follow-up period, 9 Japanese patients and 27 German patients progressed to acute myeloid leukemia (AML). Forty Japanese patients (9 AML, 15 infection, 7 bleeding, 1 heart failure, 2 others (non-hematological causes), 6 unknown) and 81 German patients (24 AML, 16 infection, 7 bleeding, 2 heart failure, 5 others (non-hematological cause), 27 unknown) died.

For the OS, Japanese FAB-RA patients who could be classified according to the WHO classification 2008 had a more favorable prognosis than German FAB-RA patients (OS median survival: Japan, 117 months; Germany, 55 months; $p < 0.001$). In LFS, Japanese FAB-RA patients who could be classified according to the WHO classification 2008 had a more favorable prognosis than German FAB-RA patients (10% LFS: Japan, 74 months; Germany, 14 months; $p = 0.011$) (Fig. 1A). RCMD patients showed the least favorable OS and LFS compared with the other subtypes excluding rare subtypes (Japan, 5q -syndrome subgroup; Germany, MDS-U (RCUD/pancytopenia type) subgroup) in both countries (Fig. 1B and C). The OS of RCUD patients was not significantly different between the two countries (OS median survival: Japan, 202 months; Germany, 141 months; $p = 0.230$). Japanese RCUD patients tended to show a more favorable LFS than German RCUD patients (LFS median survival: Japan, more than 292 months; Germany, 27 months; $p = 0.068$) (Fig. 2A). Japanese RCMD patients showed a more favorable OS than German RCMD patients (OS median survival: Japan, 109 months; Germany, 36 months; $p = 0.026$). The LFS of RCMD patients was not significantly different between the two countries (10% LFS: Japan, 38 months; Germany, 10 months; $p = 0.391$) (Fig. 2B). Follow-up periods ranged from 1 to 282 months (median, 114 months) in Japanese MDS-U (pancytopenia type) patients. In contrast, follow-up periods ranged from 15 to 46 months (median, 31 months) in German MDS-U (RCUD/pancytopenia type) patients. In addition, there were only 6 German MDS-U (RCUD/pancytopenia type) patients. Because of the short follow-up periods and the small number of German patients, the comparison of OS and LFS between the two countries was not adequate in the MDS-U (RCUD/pancytopenia type) subgroup. For the same reasons as for the MDS-U (RCUD/pancytopenia type) subtype, the comparison of OS and LFS between the two countries was not adequate in the 5q- syndrome subtype.

4. Discussion

There was no centralized pathology review in this study. However, we previously reported that morphologic diagnosis between the German and Japanese hematologists was in line [17]. Morphologic diagnosis of this study was performed by the same Japanese and German hematologists. Therefore, we believe that there may be extremely little differences between the interpretations of pathologists in Germany versus Japan.

Concerning the frequencies of subtypes of the WHO classification 2008, Japanese FAB-RA patients differed from German patients. The frequency of RCUD in Japanese FAB-RA patients was higher than in German patients. The frequency of RCMD in Japanese FAB-RA patients was lower than in German patients. The frequency of RT of Japanese FAB-RA patients was higher than that of German patients. The frequency of 5q- syndrome in Japanese FAB-RA patients was lower than in German patients. Morel et al. [21] and Greenberg et al. [10] reported that the frequencies of isolated del(5q) in patients with all MDS subtypes were 4.7% and 5.9%, respectively. Several reports have already indicated that MDS with isolated del(5q) is rare in Japanese patients. Toyama et al. [5] and Matsushima et al. [6] (Toyama

Please cite this article in press as: Matsuda A, 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. Leuk Res (2009), doi:10.1016/j.leukres.2009.11.015

et al., 2.0%; Matsushima et al., 1.5%) reported that Japanese MDS patients had a lower frequency of isolated del(5q) than patients in Western reports. Most interestingly, the frequency of MDS-U (RCUD/pancytopenia type) in Japanese FAB-RA patients was significantly higher than in German FAB-RA patients. It is suggested here that the frequencies of each MDS subtype cannot be solely judged by the results of the present study. However, in the previous consecutive dataset [17] of the present study including the patients classified according to the WHO classification 2008, the frequency of Japanese FAB-RA patients with pancytopenia (35.1%) was significantly higher than in German patients (13.1%) ($p < 0.001$). Therefore, it is very likely that the frequency of the MDS-U (RCUD/pancytopenia type) subtype in Japanese patients is higher than that in German patients. We believe that the different frequencies of RCUD and MDS-U (RCUD/pancytopenia type) between two countries are noticeable and important for discussing the differences in clinical features between these two countries.

Japanese FAB-RA patients were younger than German FAB-RA patients in our previous study [17]. In contrast, the age of Japanese patients was not significantly different from that of German patients in the RCUD, MDS-U and RCMD subgroups in the present study. However, the comparison of age in the present study is problematic. Cytogenetic findings are necessary for a diagnosis according to the WHO classification 2008. Therefore, patients in the previous data set without available cytogenetic data were excluded from the present study. In German patients with advanced age, the frequency of patients where cytogenetic examinations were performed was low. In German patients, the age of patients without available cytogenetic data (median, 74 years) was significantly higher than in patients with available cytogenetic data (median, 63 years) ($p < 0.001$). In contrast, the age of Japanese patients without available cytogenetic data (median, 60 years) was not significantly different from Japanese patients with available cytogenetic data (median, 56 years) ($p = 0.542$). The age of German patients without available cytogenetic data (median, 74 years) was significantly higher than that of Japanese patients without available cytogenetic data (median, 60 years) ($p < 0.001$). Therefore, it was considered that the age of German patients in the present study was not representative. MDS-U (RCUD/pancytopenia type) patients (median, 51 years) tended to be younger than FAB-RA patients excluding the MDS-U (RCUD/pancytopenia type) subtype (median, 58 years) in Japanese patients. The German MDS-U (RCUD/pancytopenia type) patients also tended to be younger than other subtypes.

We previously reported that Japanese FAB-RA patients showed more severe cytopenia(s) [17]. The MDS-U (RCUD/pancytopenia type) subtype showed more severe cytopenia(s) in the present study. The frequency of MDS-U (RCUD/pancytopenia type) in Japanese patients was higher than that in German patients. The high frequency of the MDS-U (RCUD/pancytopenia type) subtype in Japanese patients may largely influence the unique characteristics (younger age and more severe cytopenia(s)) of the Japanese FAB-RA patients that were clarified by our previous report [17].

We reported that the frequency of cytogenetic abnormalities in Japanese FAB-RA patients were lower than in German patients in previous study [17]. The cause of this finding was the low frequency of 5q- syndrome in Japanese FAB-RA patients.

We reported that Japanese FAB-RA patients presented with a favorable overall OS and LFS in previous study [17]. The OS and LFS of Japanese and German FAB-RA patients who could be classified according to the WHO classification 2008 in the present study were similar to our previous report. Several guidelines [22–24] have been published in Western countries. To adapt these Western guidelines to Asian patients, some modifications may be required, taking into account ethnic differences. Nevertheless, no difference was found in LFS between Japanese and German RCMD patients, Japanese RCMD patients showed a more favorable OS than German RCMD patients. It was reported that transfusion dependency was an adverse prognostic factor in MDS patients [3]. Most Japanese patients with Hb concentrations lower than 7.0 g/dL had received red cell transfusion. In contrast, most German patients with Hb concentrations lower than 9.0 g/dL had received red cell transfusion. This difference in threshold for the induction of transfusion between the two countries may influence the different OS between the two countries. The frequency of German patients with Hb concentrations lower than 9.0 g/dL (41%) was higher than that of Japanese RCMD patients with Hb concentrations lower than 7.0 g/dL (28%). In fact, RCMD patients with Hb concentrations lower than 9.0 g/dL tended to show a more unfavorable OS than RCMD patients with Hb concentrations of 9.0 g/dL or more in German patients (OS median survival: Hb lower than 9.0 g/dL, 30 months; Hb at least 9.0 g/dL, 48 months; $p = 0.054$).

Reports of several Eastern countries showed consistently unique characteristics of Eastern MDS, like young age, and a low frequency of RARS and 5q- syndrome [5,8,9,15] and the absence of a prognostic impact of cytopenia [7,8,17], although environmental factors differ between the countries. Therefore, we consider that there are genetic differences between East and West, rather than environmental factors.

In conclusion, the frequency of RCUD and MDS-U (RCUD/pancytopenia type) in Japanese patients was higher than in German patients. In particular, MDS-U (RCUD/pancytopenia type) patients occupied approximately 30% among Japanese FAB-RA patients, but MDS-U was rare (3%) in German patients. Concerning the age at the time of diagnosis, the MDS-U (RCUD/pancytopenia type) subtype was apparently younger than other subgroups in Japanese patients. The cytopenia(s) of the MDS-U (RCUD/pancytopenia type) subtype were more severe than in the RCUD and RCMD subtypes in Japanese patients. RCMD patients showed the less favorable OS and LFS than the other subtypes in both countries. The frequency of RCMD in Japanese patients was lower than that in German patients. We believe that the different frequencies of MDS subtypes according to the WHO classification 2008 between Japanese and German FAB-RA patients underlie the different clinical characteristics of FAB-RA patients between the two countries.

Conflict of interest statement

The authors reported no potential conflict of interest.

Acknowledgements

Contributors. A.M. designed the research, performed morphological analyses, collected data, analyzed data and wrote the manuscript. U.G. and I.J. designed the research, performed morphological analyses, collected data and analyzed data. M.T. designed the research, performed morphological analyses and analyzed data. M.I. collected data, performed morphological analyses and analyzed data. M.B. designed the research and analyzed data. A.K., C.S. and N.G. performed morphological analyses and collected data. K.A., Y.M. and T.H. collected data.

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Please cite this article in press as: Matsuda A, 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. Leuk Res (2009), doi:10.1016/j.leukres.2009.11.015

Int J Hematol (2010) 91:97–103
DOI 10.1007/s12185-009-0473-4

ORIGINAL ARTICLE

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

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Received: 12 August 2009 / Revised: 2 December 2009 / Accepted: 14 December 2009 / Published online: 5 January 2010

Abstract A total of 120 patients with high-risk myelodysplastic syndrome (MDS) and AML progressed from MDS (MDS–AML) were registered in a randomized controlled study of the Japan Adult Leukemia Study Group (JALSG). Untreated adult patients with high-risk MDS and MDS–AML were randomly assigned to receive either idarubicin and cytosine arabinoside (IDR/Ara-C) (Group A) or low-dose cytosine arabinoside and aclarubicin (CA) (Group B). The remission rates were 64.7% for Group A (33 of 51 evaluable cases) and 43.9% for Group B (29 out of 66 evaluable cases). The 2-year overall survival rates and disease-free survival rates were 28.1 and 26.0% for Group A, and 32.1 and 24.8% for Group B, respectively. The duration of CR was 320.6 days for Group A and 378.7 days for Group B. There were 15 patients who lived longer than 1,000 days after diagnosis: 6 and 9 patients in Groups A and B, respectively. However, among patients enrolled in this trial, intensive chemotherapy did not produce better survival than low-dose chemotherapy. In conclusion, it is necessary to introduce the first line therapy excluding the chemotherapy that can prolong survival in patients with high-risk MDS and MDS–AML.

For the Japan Adult Leukemia Study Group.

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Keywords MDS · MDS–AML · JALSG MDS200 · Induction therapy · HSCT

1 Introduction

Myelodysplastic syndrome (MDS) is a group of disorders in which abnormalities occur at the level of hematopoietic stem cells [1], leading to disturbance in the production of blood cells characterized by ineffective hematopoiesis [2], decrease in the number of peripheral blood cells and morphological/functional abnormalities in blood cells [3]. Allogeneic hematopoietic cell transplantation (allo-HCT) is the most effective curative therapy for acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) [4]. However, for patients with high-risk MDS (those with refractory anemia with excess of blasts in transformation (RAEB)-t and some patients with RAEB) and patients with acute myeloid leukemia progressed from MDS (MDS–AML), chemotherapy aimed at remission is being used. The reasons for this are that MDS often affects elderly people [5], suitable donors are not always available at the time of disease onset, the necessity of pretransplant conditioning chemotherapy is controversial [6, 7] with a lack of sufficient evidence, and the optimal timing for transplantation varies widely depending on disease type [8].

On the other hand, reduced-intensity conditioning has extended the use of allo-HSCT to patients otherwise not eligible for this treatment due to older age or frailty [9]. However, allo-HSCT using traditional myeloablative preparative regimens is not easily tolerated by the elderly or frailer patient, and may lead to prohibitive treatment-related mortality rates. Most patients treated in the past were younger and devoid of comorbid clinical conditions. Novel reduced-intensity regimens have recently made allogeneic transplants applicable to the elderly, providing the benefit of the graft-versus-leukemia effect to a larger number of patients in need [10].

Low-dose chemotherapy, which has been used in clinical practice for 20 years, reduces the number of myeloblasts, improves pancytopenia and induces remission not only in MDS patients but also in some MDS–AML patients [11]. Common antineoplastic agents used in low-dose chemotherapy include cytosine arabinoside (Ara-C), aclarubicin (ACR), melphalan and etoposide. Nevertheless, despite improved Ara-C and regimens, the prognosis of AML in patients beyond 60 years of age remains dismal [4]. Low-dose antineoplastic drug therapy is still being used in some patients with MDS, which is common in elderly people, especially when the patient is at risk due to poor general condition or organ disorder [12].

The Japan Adult Leukemia Study Group (JALSG) previously conducted a pilot study for the treatment of high-risk MDS and MDS–AML to compare low-dose monotherapy with low-dose Ara-C plus granulocyte colony-stimulating factor (G-CSF) and multiple drug therapy with Ara-C plus Mitoxantrone plus VP-16. Later, JALSG conducted studies using a single protocol (JALSG MDS96) in 1996, in which remission induction and post-remission therapies using Ara-C and IDR in patients with high-risk MDS (RAEB-t) and in those with MDS–AML were performed, after which the efficacy and safety of these therapies were evaluated [13]. Furthermore, a randomized controlled study (JALSG MDS200) of intensive chemotherapy (IDR/Ara-C) or low-dose chemotherapy (CA) for high-risk MDS was also performed by JALSG.

Here, we present and analyze the results of the JALSG MDS200 study to assess and evaluate the validity of the MDS200 protocol for MDS treatment.

2 Patients and methods

2.1 Patient eligibility

A total of 120 patients were initially registered into the JALSG MDS200 study between June 2000 and March 2005. They were assigned into two groups, namely, Groups A and B (Table 1). Patients aged 15 years or more and diagnosed as having high-risk RAEB with high International Prognostic Scoring System score [14], RAEB-t or MDS-AML were eligible for this study. MDS–AML denotes secondary AML transformed from MDS.

Other eligibility criteria were as follows: patients with a performance status (PS) of 0–2 (ECOG); patients whose key organs other than the bone marrow retain intact function; patients who have not undergone any chemotherapy, except for pretreatment that does not affect the outcome of the main therapy; and patients who have given informed consent. Informed consent was obtained after carefully explaining the protocol and before registration.

2.2 Study protocol

The MDS200 protocol (Fig. 1) was designed based on the results of MDS96, and involved a dose-attenuation plan and allowed a wider range of chemotherapy. Patients were randomly assigned to either Group A or B.

In therapy A, the dose was adjusted according to a dose attenuation plan based on the presence of risk factors. The following 3 factors were regarded as risk factors: (1) Age ($\geq$60 years), (2) hypoplastic bone marrow and (3) PS $\geq$ 2. Patients with no risk factor received the standard dose, those with 1 risk factor received 80% of the dose and those with 2 or more risk factors received 60% of the dose (equivalent to the dose of MDS96). In therapy B, the use of

Table 1 Characteristics of patients

Group	A ($n = 53$)	B ($n = 67$)	P value (A vs. B)
Age (range)	63 (23–77)	61 (32–81)	0.505
Gender			
Male	37	52	0.332
Female	16	15	
Disease type			
HR-RAEB	4	11	0.269
RAEB-T	22	29	
MDS–AML	27	27	
Infection			
Presence	10	11	0.726
None	43	56	
Karyotype[a]			
Good	23 (44.2%) $n = 52$	21 (33.9%) $n = 62$	0.524
Int	11 (21.2%)	15 (24.2%)	
Poor	18 (34.6%)	26 (41.9%)	
PB (range)			
WBC (/μL)	2,500 (700–64,240)	2,720 (600–43,700)	0.665
Hb (g/dL)	8 (4.7–12.6)	7.9 (4.4–12.7) $n = 66$	0.562
Plt (/μL)	5.8 (0.2–31.4)	5.9 (0.5–36.7)	0.363
BM (range)			
Blast (%)	30 (4–95) $n = 51$	24.2 (1.9–96) $n = 66$	0.171
Biochemical data (range)			
LDH (IU/L)	296 (132–882)	303.5 (111–906) $n = 66$	0.998
CRP (mg/dL)	0.5 (0–20.2)	0.35 (0–11.7) $n = 66$	0.292

Patients who met all of the inclusion criteria and did not meet any of the stated exclusion criteria were included the study. The disease types were classified by FAB classification

Statistical analysis between Group A and Group B was done using χ^2 test or Mann–Whitney U-test

MDS myelodysplastic syndrome, *HR-RAEB* high risk-refractory anemia excess of blasts with high International Prognostic Scoring System Score, *RAEB-T* refractory anemia excess of blasts in transformation, *MDS–AML* MDS overt leukemia, *WBC* white blood cell, *Hb* hemoglobin, *Plt* platelet, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *PB* peripheral blood, *BM* bone marrow

[a] Shows IPSS risk

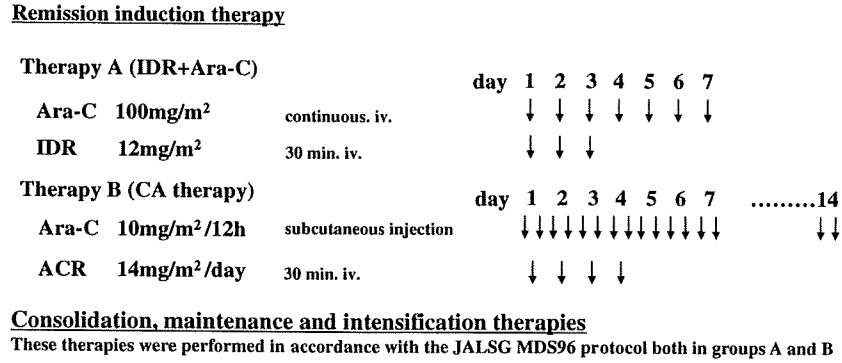

Fig. 1 Japan Adult Leukemia Study Group—myelodysplastic syndrome (JALSG MDS200 Protocol). In therapy A, the dose was adjusted according to a dose attenuation plan based on the presence of risk factors. The following 3 factors were regarded as risk factors: (1) Age (≥60 years), (2) hypoplastic bone marrow and (3) PS ≥ 2. Patients with no risk factor received the standard dose, those with 1 risk factor received 80% of the dose, and those with 2 or more risk factors received 60% of the dose (equivalent to the dose of MDS-96). In therapy B, the use of CAG therapy involving co-administration of G-CSF was allowed. *IDR* idarubicin, *Ara-C* cytosine arabinoside, *ACR* aclarubicin, *G-CSF* granulocyte colony-stimulating factor, *iv* intravenous injection, *min* minutes

CAG therapy involving the co-administration of granulocyte colony-stimulating factor (G-CSF) was allowed.

Untreated adult patients (≥15 years) with MDS (RAEB, RAEB-t or MDS–AML) were randomly assigned to receive either IDR/Ara-C (Group A) or CA (Group B) [15]. Complete remission (CR) rate, CR duration, overall survival (OS) rate and disease-/relapse-free survival (DFS/RFS) rate were compared between the two groups.

Consolidation therapy and maintenance therapy were performed in accordance with JALSG MDS96 [13].

2.3 Evaluation of response

Response to treatment was evaluated in accordance with JALSG criteria [13]. CR was considered achieved when the following conditions remained for at least 4 weeks. For the bone marrow: blasts accounting for ≤5% of all cells; absence of blasts with Auer body; and presence of normal erythroblasts, granulocytes and megakaryocytes. For peripheral blood: absence of blasts; neutrophils ≥ 1,000/ml; platelets ≥ 100,000/μL; and no evidence of extramedullary leukemia. CR duration was defined as the duration from the day when CR is achieved to the day of relapse or death, OS or DFS as the duration from the day of initiation of treatment to the day of death and DFS as the duration in which CR patients survived without relapse. Patients who were treated with HCST were not censored at the date of transplantation. All toxicity was graded using the World Health Organization criteria [16].

2.4 Statistical analysis

The primary endpoint of this study is DFS. Assuming a 1-year DFS rate of 60% in the Group A and 40% in the Group B, this design required the randomization of 200 patients. Eligible patients were randomized according to age, sex and disease type. Differences in background factors (e.g., age, gender and disease type) between Groups A and B were statistically analyzed using the χ^2 test or Mann–Whitney *U*-test. Probability of OS and DFS were estimated according to the method of Kaplan and Meier.

3 Results

3.1 Recruitment of patients and suspension of the study

The initially registered 120 patients were assigned into two groups, namely, Groups A and B. The clinical characteristics of the registered patients are shown in Table 1. The present protocol was originally planned to recruit 200 patients for Groups A and B within 3 years. However, the recruitment pace was slower than expected and thus the study period was extended from 3 years to 4.5 years. At the end of 2004, that is, after 4.5 years from the start of the study, the number of registered patients was only 113 in Groups A and B, which was 56.5% of the target number. At that point, the committee members discussed the progress of the MDS200 study and decided to suspend it at the end of March 2005. Since the final total number of patients did not reach the target number, we did not statistically compare DFS between Groups A and B, which was the primary endpoint of this study.

3.2 Characteristics of patients

There were no clear differences in the clinical characteristics of the patients between Groups A and B, such as FAB subtype, initial blood cell count, presence of infection, distribution in the karyotype group and biochemical data, as well as sex distribution (male/female ratio, 37/16 = 2.315 in Group A, and 52/15 = 3.467 in Group B).

3.3 Treatment outcome

The remission rates were 64.7% in Group A (33 out of 51 evaluable cases) and 43.9% in Group B (29 out of 66 evaluable cases). The 2-year overall survival (OS) rates were 28.1% in Group A and 32.1% in Group B, and the 2-year DFS rates were 26.0% in Group A and 24.8% in Group B. The mean duration of CR was 320.6 days (median: 213 days) in Group A and 378.7 days (median: 273 days) in Group B (Table 2). Reflecting the intensity of the remission induction chemotherapy, the period of WBC (<1,000/μL) after the therapy was longer in Group A than in Group B (19 days and 4 days, respectively). There were more grade 3 or 4 adverse events during the remission induction therapy in Group A (19 out of 53 evaluable patients) than in Group B (13 out of 67 evaluable patients). This difference was mostly attributable to infectious episodes (17 patients in Group A and 4 patients in Group B). In terms of bleeding episodes, 1 patient in Group A and 2 in Group B had grade 3/4 adverse events. The numbers of

Table 2 Treatment outcome (Group A vs. B)

	Group A (n = 53)	Group B (n = 67)
Remission rate (%)	64.7	43.9
Mean duration of remission (days)	320.6 (median: 213)	378.7 (median: 273)
2-Year survival rate (%)	28.1	32.1
2-Year disease-free survival rate (%)	26.0	24.8

The remission rates, 2-year overall survival (OS) rates and 2-year disease-free survival (DFS) rates are shown as percentages

early death in remission induction chemotherapy (death within 30 days) were 1 patient in Group A and 3 patients in Group B (Table 3). The cause of death in each group was infection or tumor progression. The completion rate of consolidation therapies were 37.3% in Group A (12 out of 33 evaluable cases), 37.9% in Group B (11 out of 29 evaluable cases). On the other hand, the maintenance therapies were completed 21.2% in Group A (7 out of 33 evaluable cases), and 15.2% in Group B (5 out of 33 evaluable cases). The numbers of dose attenuation in Group A were 30 patients of 100% dose, 21 patients of 80% or 60% dose and 2 patients of unknown.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) was performed in 11 out of 50 patients (22%) in Group A and 19 out of 66 patients (28.8%) in Group B. Among those who received allo-HSCT, the transplantation was performed during the first remission in 40%, 21% of patients in Groups A, B, respectively.

There were 15 patients who lived longer than 1,000 days after diagnosis: 6, 9 patients in Groups A, B, respectively. Regarding the transplantation among long-term survivors, 3 out of 6 patients were transplanted in Group A, 6 out of 9 in Group B. Comparing the achievement of CR among these patients in Groups A and B, all 6 patients in Group A achieved CR, but only 4 out of 9 patients in Group B achieved CR.

Table 3 Toxicity of the induction therapy

	A ($n = 53$) (range)	B ($n = 67$) (range)	P value (A vs. B)
Period of WBC <1,000 (day)	19 (0–44) $n = 49$	4 (0–50) $n = 63$	<0.0001
Toxicity (grade 3/4)			
Presence	19	13	0.427
Bleeding	2	1	ND
Infection	17	11	0.04
Others	2	2	ND
Early death (<30 days)	1	3	ND

Statistical analysis between Groups A and B was performed using the χ^2 test or Mann–Whitney U-test

ND not done

4 Discussion

In this MDS200 study, patients with high-risk MDS and AML transformed from MDS (MDS–AML) were treated with either intensive or low-dose remission induction therapy, followed by intensive post-remission therapy that was the same as in the JALSG MDS96 study [13].

Although we did not perform statistical comparison of DFS or OS between these two treatment groups due to the insufficient number of patients enrolled, the results suggest that there was no significant difference, that is, survival curves were superimposable (Figs. 2, 3). Intensive chemotherapy similar to that for AML can produce a CR rate of 64.7% for high-risk MDS and MDS–AML patients, whereas low-dose induction therapy can result in a CR rate of 43.9%. However, among the patients enrolled in this trial, the difference in CR rate did not lead to better survival as described above. In terms of adverse events, patients who received intensive treatment had more grade 3 or 4 adverse events, particularly infectious events with a longer period of leukopenia. There was no increase in the number of patients succumbing to early death (death within 30 days after the

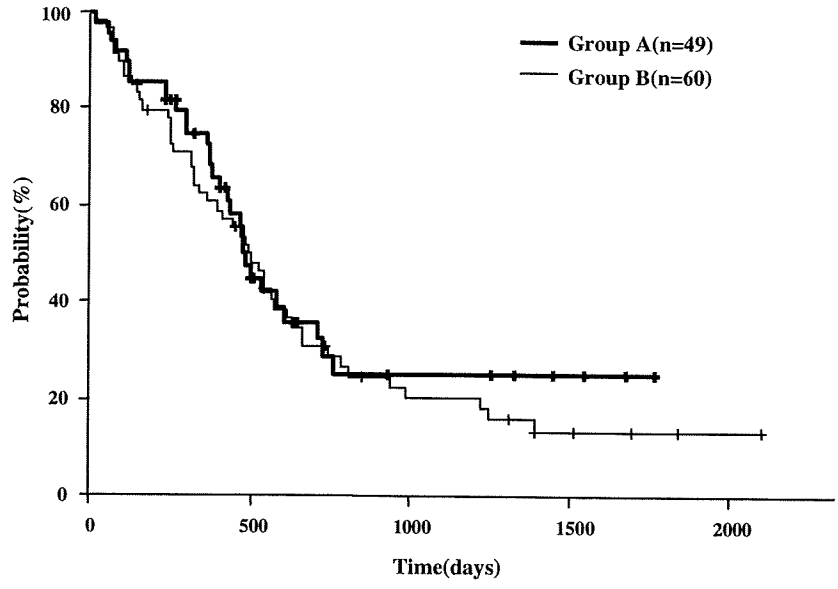

Fig. 2 Overall survival. Survival was calculated from the date of the start of treatment to the date of death due to any cause or to the date of the most recent follow-up. These data were not censored at the time of HSCT. All randomized patients were not included this data in each group. Due to this reason, some patients were not known to be CR or not, but known to be alive or not

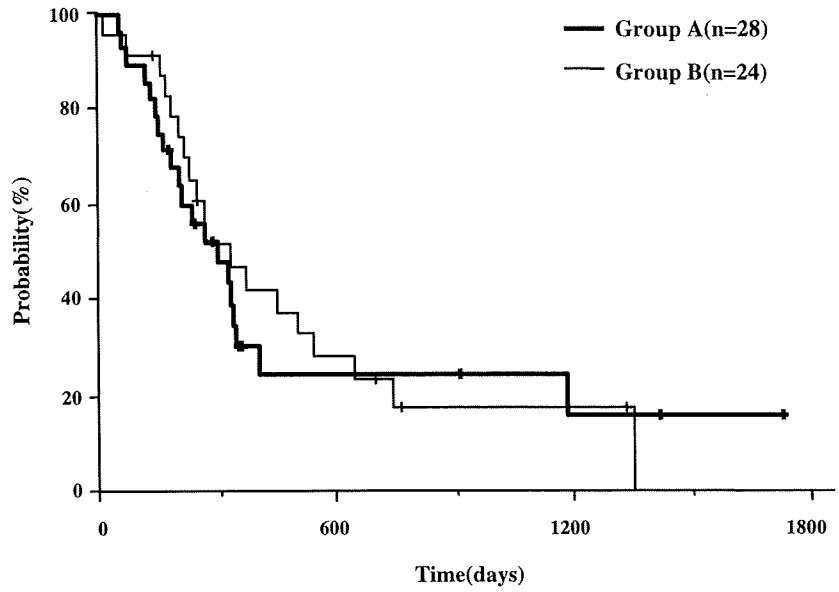

Fig. 3 Disease-/relapse-free survival. RFS was calculated from the date of achieving complete remission to the date of relapse, death or the most recent follow-up. These data were not censored at the time of HSCT. All randomized patients were not included this data in each group. Due to this reason, some patients were not known to be CR state or relapse, but known to be alive or not

start of treatment) in Group A, suggesting that intensive treatment produced higher CR rate, and higher toxicity resulted in a similar survival rate with low-dose induction therapy at least during the early phase of treatment.

There are several reasons that could explain why no difference in survival rate was observed regardless of the difference in CR rate. One could be the similar post-remission therapy between Groups A and B, as demonstrated by the almost similar DFS curves among the two groups. Another reason could be the disease status at the time of transplantation for patients in the two groups. In Group A, 60% of the transplantation was performed during the period other than that covering the first CR; this was 79% in Group B. Allo-HSCT has been shown to have the strongest antileukemia effect, and this was also found in the current study in which 6 out of 15 long-term survivors received allo-HSCT in Groups A and B. From the viewpoint of transplantation, intensive treatment merely selected cases that were suitable for transplantation, as observed in the case of transplantation for relapsed AML patients [17]. There are arguments against remission induction therapy for MDS patients in that it does not affect post-transplant prognosis [6, 18]. In the results of JSHCT, the chemotherapy before undergoing allo-SCT is not necessary in patients with MDS [6]. A group from the Institute of Medical Science of Tokyo University performed umbilical cord blood stem cell transplantation without remission induction therapy in high-risk MDS patients aged not more than 55 years and obtained favorable results with reduced time from diagnosis to transplantation [19]. It is important to perform clinical studies based on the concept that HCST should be performed immediately after diagnosis without remission induction, and determine the types of patients who would benefit from remission induction therapy prior to transplantation in terms of prognosis. In the present study, although suspended because of the insufficient number of patients enrolled, it appears that remission induction therapy with IDR and Ara-C did not produce better survival than that with low-dose chemotherapy despite higher CR rate. Therefore, it is suggested that CR rate is not a suitable surrogate marker for the evaluation of the outcome of chemotherapy for high-risk MDS and MDS–AML. In the latest reports, induction chemotherapy for patients with high-risk MDS and MDS–AML also provide no survival advantage [20, 21]. Considering the low survival rate of patients in this category, it is clearly necessary to introduce new strategies for the treatment of high-risk MDS and MDS–AML, such as molecular targeting agents and allo-HSCT with reduced-intensity conditioning regimens.

Acknowledgments We would like to thank the participating physicians in the Japan Adult Leukemia Study Group (JALSG) MDS200 study for their cooperation. This work was supported in part by grants-in-aid for Scientific Research from the Japanese Ministry of Education, Culture, Sport, Science, and Technology, and grants-in-aid for Cancer Research from the Japanese Ministry of Health, Labor, and Welfare.

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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

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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

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Published online: 07 January 2010