であった（WPI vs. CAP；PFS（5 yr）＝64.2：84.5（%），p＝0.058 OS（5 yr）＝80.9：97.5（%），p＝0.019）[4]．しかしこの有意な結果はあくまでサブグループ解析としての解釈が必要であろう．その他JGOGでは，現在，術後高再発リスク症例を対象とし，AP（ADM＋CDDP），DP（DTX＋CDDP），TC（PTX＋CBDCA）の3療法のランダム化第III相試験が進行中であり，その結果が待たれるところである．

先に挙げたJGOG 2033の結果も，術後リスクがIntermediateな症例における術後補助療法を決定づけるものではなかったが，2007年のASCO（American Society of Clinical Oncology）において発表されたNSGO-EC-9501/EORTC 55991において，（主に）Intermediateリスクにおける放射線併用化学療法の有用性について検討されている[5]．対象はSurgical stage I・II期，腹水細胞診のみ陽性IIIA期，骨盤リンパ節のみ陽性IIIC期の患者372名で，放射線（44 Gy以上）単独群と放射線治療の前後に化学療法を行う群に振り分け比較検討された．結果はOSでは有意差は出なかった（HR＝0.65；CI 0.4～1.06，p＝0.08）が，Primary endpointであるPFSは有意な結果（HR＝0.62；CI 0.4～0.97，p＝0.03）であった．しかしながら，この結果ではIntermediateリスクに対しての術後放射線化学療法の意義が確立したとは言えないであろう．というのも，このStudyには，①化学療法のレジメが定まっていない（APでもTCやTAP，DTX/Epirubicin/CBDCAいずれでもよい）ことや，②手術や放射線治療が各施設でスタンダード化されていないこと，③計4コースの化療が70％しか完遂できていない（そのうち42％は患者側の拒否にて）ことなどいくつかの問題点が挙げられており，やはり**表2**に示したように，Intermediate症例に対しての術後補助療法は未だcontroversialの域を脱してはいない．

表3 単剤化学療法の成績

Drug	n	Response Rate（%）
CDDP	63	21
CBDCA	82	28
Epirubicin	27	26
ADM	161	26
5-FU	34	21
Paclitaxel	47	36
Docetaxel（tri-weekly）[9]	32	31
Docetaxel（weekly）[10]	33	21

3．進行（Stage IVb）・再発子宮体がんに対する化学療法

Stage IVb・再発子宮体がんに対する化学療法の目的は，治癒ではなく，あくまで延命や症状緩和のための姑息的手段（palliative therapy）の域を出ない．現時点での化学療法の奏効率は約20～60％であり，生存期間の中央値は約7～12カ月である．

1 単剤化学療法

子宮体がんに対する単剤での化学療法で，有効と考えられるagentの奏効率を**表3**に示した[6,9,10]．中でもタキサン系薬剤であるPaclitaxel（PTX）は最も良好な成績である．Ballらの報告したGOGで行われた第II相試験の結果では，進行・再発子宮体がん（前化学療法歴なし）28例に対し，PTX単剤を250 mg/m²を3週毎に投与した結果，奏効率36％（CR 4例，PR 6例）であった[7]．Lissoniらは前化学療法歴のある患者を対象としているが（n＝19），175 mg/m²を3週毎の投与量で奏効率37％（CR 2例，PR 5例）と，Ballらの報告と同程度の成績を報告している[8]．

PTXと同じくタキサン系薬剤であるDocetaxel（DTX）について，本邦での多施設試験（第II相）の報告がKatsumataらによりされているが[9]，前化学療法歴がないもしくは1レジメ以内の患者33例に対し，DTX単剤70 mg/m²を3週毎に

		RR	PFS (mo.)	OS (mo.)
GOG 48 (1994)	ADM	22 %	3.2	6.7
	ADM/CPA	30 %	3.9	7.3
GOG 107 (2004)	ADM	25 %	3.8	9.2
	ADM/CDDP	42 %	5.7	9.0
EORTC (2003)	ADM	17 %	7.0	7.0
	ADM/CDDP	43 %	8.0	9.0
GOG 163 (2004)	ADM/CDDP	40 %	7.2	12.6
	ADM/PTX +G-CSF	43 %	6.0	13.6
GOG 177 (2004)	ADM/CDDP	34 %	5.3	12.3
	TAP (AP+PTX) +G-CSF	57 %	8.3	15.3

図2　進行子宮体がんに対するランダム化比較試験

投与し，奏効率31％，TTP (time to progression) 3.9カ月であった．しかし，有害事象としてG3・4の好中球減少の出現が94％と高いことが問題として挙げられた．一方Gunthertらは，DTXを35 mg/m²毎週投与を6週1サイクルとし2週休薬後，繰り返すレジメの第II相試験の結果，奏効率は21％だったものの，有害事象としてG3・4血液毒性が33例中1例も認めなかったと報告している[10]．

2 併用化学療法

併用化学療法の基本的な考え方は単独で有効とされ，異なる機序の化学療法剤を組み合わせ，その相乗効果によってより高い抗腫瘍効果を得ようとするものである．**図2**に，進行子宮体がんに対する併用化学療法の開発の歴史とも言えるGOGの第III相試験の結果を並べる．まず，GOG 48においてADM単剤 (60 mg/m²) とCPAとADMの併用療法 (CA療法；CPA 500 mg/m²+ADM 60 mg/m²) の比較の結果，奏効率では有意差は認めなかったが，生存期間でわずかCA療法が優れていた[11]．その後，ADM単剤 (60 mg/m²) とCDDPとADMの併用療法 (AP療法；ADM 60 mg/m²+CDDP 50 mg/m²) の比較がGOG 107で行われた．結果，奏効率では25％：42％とAP療法が優れており，PFSでも3.8カ月：5.7カ月とAP療法が有意に優れていた[12]．GOG 107では，生存期間において有意差を認めなかったが，EORTC (European Organization for Research and Treatment of Cancer) で行われたtrialにおいては，AP療法群がADM単剤と比較し良好な奏効率 (43％：17％) とOS (9カ月：7カ月) を示し[13]，以後AP療法が進行・再発子宮体がんの標準療法として位置付けられている．

また，前述した単剤でのタキサン系薬剤の有用性から，現在PTXを中心とした併用化学療法の開発が進められている．まずRCTとして，GOG 163においてAT療法 (ADM 60 mg/m²+PTX 150 mg/m²) とAP療法 (ADM 60 mg/m²+CDDP 80mg/m²) が比較された．317例が登録され，奏効率AT 43％，AP 40％，PFS (progression free survival) AT 6.0カ月，AP 7.2カ月，OS (overall survival) AT 13.6カ月，AP 12.6カ月であり，いずれも有意差がなくAT療法はAP療法に優る結果ではなかった[14]．GOGはこの結果を受けて，ADM，PTXにCDDPを加えた3剤併用 (TAP) 療法とAP療法の比較試験を行った (GOG 177)[15]．AP療法 (ADM 60 mg/m²+CDDP 50 mg/m²) 7コースに対し，TAP療法 (PTX 160 mg/m² 3 hr 投与+ADM 45 mg/

表4 進行・再発子宮体がんに対するMPA療法—GOG 81

		Response		MST (mo.)
		No.	%	
Grade	1	22/59	37	18.8
	2	26/113	23	7.5
	3	12/127	9	6.9
ER	<10	4/55	7	6.7
	≥10	20/77	26	8.3
PgR	<50	7/86	8	6.8
	≥50	17/46	37	12.1

m^2+CDDP 50 mg/m^2) 7コースを比較したところ，奏効率（AP 34％，TAP 57％），PFS（AP 5.3カ月，TAP 8.3カ月），OS（AP 12.3カ月，TAP 15.3カ月）と有意にTAP療法群が優っていた．しかしながら，G2以上の神経毒性がAP療法群で5％であったのに対し，TAP療法群では40％と有意に多く，その原因としてPTXの投与法の問題（3 hr投与が行われたこと），CDDPの総投与量の差の問題（G-CSF使用基準が両群間で違ったことから，AP群がTAP群と比較しCDDPの総投与量が低かった）等が挙げられている．しかしながら，この結果によりPTXを含む併用化学療法の有用性についてはある程度の根拠ができたと考えられ，その上で安全に施行できるレジメの模索として，引き続いて現在GOGではTAP療法群とTC療法（CBDCA（AUC5）＋PTX 160 mg/m^2 3 hr投与）のRCT（GOG 209）が進行中である．また，本邦においてもタキサン系薬剤とプラチナ系薬剤の併用療法の有効性の検討として，DP（DTX＋CDDP），DC（DTX＋CBDCA），TC（CBDCA＋PTX）の3群を比較したRCT（JGOG 2041）の症例集積が終了し，結果が待たれるところである．

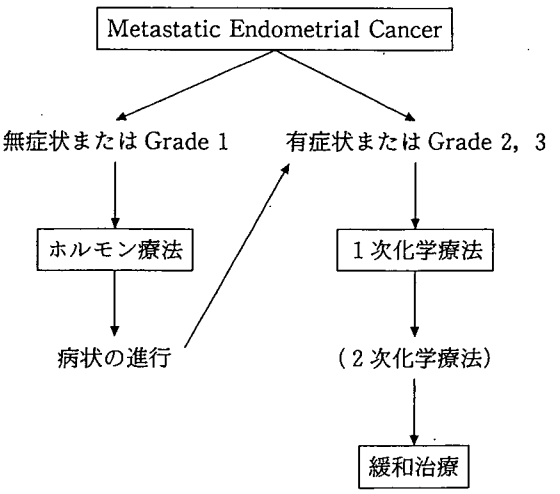

図3 進行（Stage IVB）・再発子宮体がんの治療
NCCNガイドライン http://www.nccn.org/

4．内分泌療法

子宮体がんに対してのプロゲステロン製剤による治療はかなり歴史のあるもので，1984年のKauppilaらのreviewでは異なる複数のtrialにおいてMedroxyprogesterone Acetete（MPA）も含めたプロゲステロン製剤治療を受けた1068名の進行・再発子宮体がん患者に対する奏効率は34％であった[16]．しかしながら，その後の治療効果判定が確立していく中で行われた臨床試験においては，奏効率11～16％と結果は満足できるものではなかった[17,18]．1999年Thigpenらに報告されたGOG 81において，進行・再発子宮体がん患者299名がMPA 200 mg/日投与群と1000 mg/日投与群に分けられ比較された[19]．200 mg投与群で奏効率が25％であったのに対し1000 mg投与群では15％であり，PFS 3.2カ月と2.5カ月，OS 11.1カ月，7カ月といずれも200 mg投与群が成績良好であった．また，この試験の中でGrade，ERレベル，PgRレベルがMPAの奏効率や予後に重要な影響を与えていることが認め

られた（表4）．この結果から，MPA療法は，ホルモンレセプター（特にPgR）陽性で，加えてHE染色での悪性度（Grade）が低い症例を選択して投与することが有用であり，またその初期投与量は200 mg/日が望ましいことが示された．現在，NCCNのガイドライン（Webを引用；http://www.nccn.org/）においてホルモン療法は，症状を伴わないGrade 1の症例に対し1st lineとして位置付けられている（図3）．

子宮体がんにおけるプロゲステロン製剤の活性は，腫瘍組織内でしばしば起こるPgRのdown-regulationによって制限される．一方，Tamoxifen（TAM）は腫瘍組織内のPgRを増加させる作用があるとされるため，プロゲステロン製剤との併用療法についての臨床試験がGOGにおいて第II相試験として行われた[20]．対象として61名の進行・再発子宮体がん患者が登録され，TAM 40 mg/日内服とMPA 200 mg/日内服を1週間交替で続けられた．結果は奏効率33％，PFS 3カ月，OS 13カ月であった．一見結果として比較的良好に見えるが，前述のGOG 81と比べPFSはほとんど変わらない点から，少なくともTAM併用がそのPgR増加作用によりプロゲステロン製剤の有効期間を延ばすには至らないのではと疑問が出てくる．しかしながら，これはあくまで第II相試験の結果であり，結論を得るには第III相試験での評価が必要であろう．

5．分子標的治療

近年，分子細胞生物学の進歩により，がん細胞の浸潤・増殖・転移などに関係する因子（target）の研究が進み，その因子に直接，作用することを目指した分子標的治療薬が様々な癌種で臨床応用され，その効果が証明されているが，子宮体がんにおいてはまだその段階までは至らず，有用と思われる候補を見つけようとしている段階と言える．その候補をいくつかを挙げてみる．

1 mTOR（mammalian target of rapamycin）阻害剤

腫瘍増殖においてPI3K-AKT-mTORシグナル経路はRAS-RAF-MARK-ERK経路と同様，非常に重要である．腫瘍細胞中のPTEN機能の消失は，mTOR経路の下流因子の活性化を促し，PTEN機能の低下の原因と考えられるPTEN遺伝子変異は，悪性神経膠腫や前立腺がん，そして子宮体がん等に見られる．子宮体がんにおけるPTEN機能消失は，遺伝子変異やその他の要因により割合早い段階で36～83％に認められると言われている．最近の研究では子宮体がん61検体において，66％がPTEN発現低下を示していたと報告されている[21]．Terakawaらは，98例の進行子宮体がん患者で，PTEN発現陽性患者が陰性患者と比較し，明らかに生存率が良かったと報告している[22]．このようにPTEN機能消失が子宮体がんにおいて高頻度に見られていることから，mTOR経路阻害剤による腫瘍抑制効果が期待され，Rapamycinアナログである CCI779（Temsirolimus）やRAD-001（Everolimus），AP23573（ARIAD）等の臨床試験が現在進められている[23]．この中で2007年ASCOにおいて，AP23573単剤投与の第II相試験の結果が途中報告されている．対象はほとんどが前治療歴のある進行子宮体がん患者で，その27名中の33％がCBRs（Clinical Benefit Response：CR or PR or long SD）を得たとしている[24]．毒性は倦怠感・貧血・口唇痛・嘔気等で，今のところ大きな問題はないようである．今後これらの第II相試験が積み重ねられ，その結果を踏まえて第III相試験が組まれていくものと考えられる．

2 EGFR（epidermal growth factor receptor）阻害剤

EGFRは正常子宮体内膜にも発現するが，子宮体がんにおいて過剰発現をし，進行度や予後との関連も指摘されている．EGFRチロシンキナーゼ阻害薬であるGefitinibやLapatinib，Erlotinib

等の小規模第II相試験が進められているが，まだその有用性は示されていない[23]．

ま と め

子宮体がんの化学療法を簡単ではあるがまとめさせていただいた．今後，術後療法も含めた併用化学療法の中でのタキサンの役割がevidenceとして確立することと予想するが，その後の分子標的薬やホルモン療法をからめた新たな領域の開拓と更なる進歩が期待される．

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Support Care Cancer (2007) 15: 287–291
DOI 10.1007/s00520-006-0126-6

ORIGINAL ARTICLE

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The outpatient management of low-risk febrile patients with neutropenia: risk assessment over the telephone

Received: 10 February 2006
Accepted: 5 July 2006
Published online: 29 August 2006

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Abstract *Objective:* The purpose of this retrospective study is to evaluate the feasibility of the risk assessment over the telephone in the outpatient management of low-risk febrile patients with neutropenia. *Materials and methods:* Febrile patients with neutropenia were eligible for outpatient management with oral ciprofloxacin if they demonstrated the following characteristics: resolution of neutropenia expected in <10 days, good performance status, controlled cancer, no symptoms or signs suggesting systemic infection other than fever, and no comorbidity requiring hospitalization. Eligible patients received oral ciprofloxacin (400 mg, three times daily) and were monitored as far as possible by telephone. Risk assessment concerning general condition was carried out over the telephone. *Results:* Of the 60 consecutive patients who received neoadjuvant chemotherapy as a phase II trial of docetaxel (60 mg/m^2) and doxorubicin (50 mg/m^2) for primary breast cancer, 30 low-risk febrile patients received oral ciprofloxacin. Twenty-seven of these patients (90%) recovered uneventfully without hospitalization and the use of granulocyte colony-stimulating factor. Treatment was considered to have failed in the remaining three (10%) on the account of the need to modify or change their regimens. *Conclusions:* For carefully selected low-risk febrile patients with neutropenia, risk assessment over the telephone may be convenient, and close daily medical scrutiny may be not routinely required in the outpatient.

Keywords Low-risk · Febrile patients with neutropenia · Outpatient therapy · Oral ciprofloxacin · Risk assessment

Introduction

Febrile neutropenia is the first manifestation of life-threatening bacterial infection accompanying cancer chemotherapy. Its standard management includes prompt administration of empirical, broad-spectrum, parenteral antibiotics; this substantially reduces morbidity and mortality. However, antibiotic therapy is generally administered in a hospital setting and leads to prolonged hospitalization and increased cost. Recent studies suggest that febrile patients with neutropenia can be stratified into low-risk and high-risk groups, primarily according to the expected duration of neutropenia and the presence or absence of underlying conditions [1, 2]. Low-risk patients do not need to be hospitalized and can be safely treated with oral antibiotics in an outpatient or domestic setting [3–7].

Factors indicating low-risk are: controlled cancer, no comorbid complications, resolution of neutropenia expected in <10 days, and no documented infection. These factors are considered to serve as guidelines for selecting patients for outpatient therapy [1]. Outpatient therapy has several advantages including lower cost and improved quality of life. On the other hand, its most important disadvantage is thought to be the risk of serious complications such as septic shock. In previous studies,

low-risk febrile patients undergoing oral treatment were followed up every other day in the outpatient clinic [7].

The combination of docetaxel and doxorubicin is among the most effective chemotherapies for the treatment of breast cancer. In a phase I/II study by a French group [8, 9], 42 patients with metastatic breast cancer received this combination as first-line therapy, and a 3-week schedule of doxorubicin 50 mg/m^2 plus docetaxel 75 mg/m^2 was recommended. Leukopenia with subsequent infection was the dose-limiting toxicity, and grade 4 neutropenia occurred in 93% of the patients not receiving granulocyte colony-stimulating factor (GCSF). That study also showed that grade 4 neutropenia lasted not more than 10 days without GCSF, and febrile neutropenia occurred in 40% of the patients with neutropenia. After this trial, GCSF (5 μg/kg) had routinely been given prophylactically in this regimen from day 2 or 3 until a postnadir neutrophil count was obtained [10]. The duration of neutropenia is one of the principal risk factors for the occurrence of infectious complications. Breast cancer patients who receive this regimen in a neoadjuvant setting, namely, those with controlled cancer and good performance status (PS), are the population most likely to be low-risk febrile patients with neutropenia.

We hypothesized that carefully selected low-risk febrile patient with neutropenia, such as the one with primary breast cancer receiving neoadjuvant chemotherapy, can be treated safely as outpatients without daily follow-up. This study was conducted to test this hypothesis.

Materials and methods

Patients were the ones who had primary breast cancer (stages II and III, tumor size >3 cm), who received neoadjuvant chemotherapy as a phase II trial of docetaxel 60 mg/m^2 and doxorubicin 50 mg/m^2 at the National Cancer Center Hospital from 1998 to 2000.

The records of febrile patients with neutropenia, who received neoadjuvant chemotherapy for primary breast cancer, were retrospectively reviewed.

In accord with previous studies using this regimen, febrile neutropenia was defined as a single oral or axillary temperature of greater than 38°C occurring between 8 and 14 days after the start of chemotherapy.

We defined low-risk patients as those in whom the duration of neutropenia (absolute neutrophil count <500 cells/ml) was expected to be brief (less than 10 days) and who had no other serious medical conditions, Eastern Cooperative Oncology Group performance status of 0 to 1, the ability to take oral medication, controlled cancer, no symptoms or signs suggesting systemic infection other than fever, and no comorbidity requiring hospitalization. Comorbidity was defined, following the definition of Talcott et al. [2], as another medical condition that independently required inpatient observation.

Exclusion criteria were evidence of hypotension, dehydration requiring intravenous fluid administration, allergy to ciprofloxacin and ceftazidime, severe mucositis that prevented adequate oral hydration, severe gastrointestinal symptoms (nausea, vomiting, and diarrhea), and respiratory distress or other evidence of pneumonia.

Patients who were considered low risk whose temperature exceeded 38°C were given oral ciprofloxacin (400 mg, three times daily). Oral antibiotic therapy was maintained for 5 days, decreasing the fever to below 37°C within 3 days.

Patients were told to report to the hospital if there was no improvement after 3 days of oral antibiotic therapy, or they developed any new signs and symptoms. Outpatients were instructed to maintain close telephone contact. Risk assessment over the telephone was concerned with general condition, namely, PS, oral intake, dehydration, and presence or absence of symptoms.

Figure 1 provides a flow diagram of the patients in this study. The use of GCSF was avoided as much as possible while patients were low risk, but it was immediately administered if a patient was considered to have become high risk, for example, because of low PS or dehydration.

Results

Characteristics of the patients

Of the 60 consecutive patients who received neoadjuvant chemotherapy as a phase II trial of docetaxel and doxorubicin for primary breast cancer at the National Cancer Center Hospital from 1998 to 2000, 35 developed febrile neutropenia during the first cycle. Thirty-one of these patients received first-cycle chemotherapy in the hospital and were discharged immediately thereafter. For the other four patients, chemotherapy was started in the outpatient clinic.

Of the 35 patients, 30, classified as low risk, received oral ciprofloxacin, whereas the others received parenteral

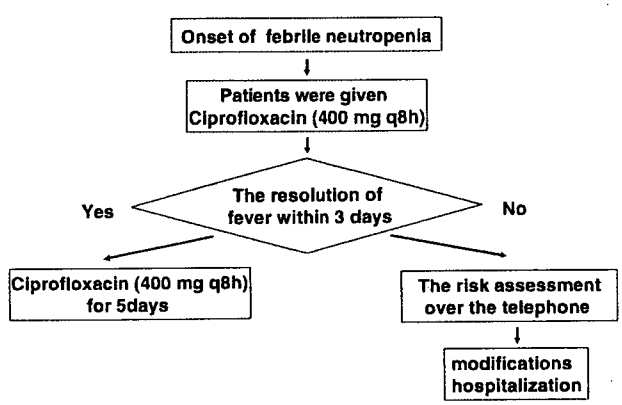

Fig. 1 Flow diagram of patients in this study

antibiotics (ceftazidime or ceftazidime plus amikacin). Of the 30 low-risk patients, 10 were PS 0 and 20 were PS 1 when febrile neutropenia occurred. Their median age was 50.5 years (range 32–67).

Outcome

Treatment outcomes of the 30 febrile patients with neutropenia were divided into success and failure based on previous studies [4, 5]. Our definition of success was resolution of the fever without development of any serious medical condition, no need for modification of treatment such as administration of GCSF, or for antifungal or antiviral agents, or a change of regimen. The need for hospitalization or intravenous supportive therapy for severe mucositis or gastrointestinal symptoms (nausea, vomiting, and diarrhea) was also considered to represent failure. According to these criteria, antibiotic therapy was considered successful in 27 (90%) of the patients and unsuccessful in 3 (10%) of them (Table 1). Records of the duration of fever were available for 22 of the 27 patients who were successfully treated. By day 3 of antibiotic therapy, the fever had disappeared in 16 patients, whereas it persisted for longer than 4 days in the remaining 6. Three cases were considered as treatment failures because one required additional treatment with GCSF and two had their treatment regimen changed to parenteral administration (1 ceftazidime and 1 ceftriaxone sodium). The reasons for this alteration in regimen were mainly gastrointestinal symptoms (including appetite loss, nausea, and vomiting) rather than documented infection or breakthrough bacteremias (Table 2).

Discussions

Several recent studies provide evidence that with careful patient selection and appropriate antimicrobial regimens, outpatient therapy for low-risk febrile patients with neutropenia is safe and effective [13]. Outpatient antibiotic therapy has several advantages, including lower cost and improved quality of life. On the other hand, its most important disadvantage is thought to be the risk of serious complications such as septic shock, as outpatients cannot be monitored closely for secondary infections and adverse effects. In previous studies comparing outpatient oral and inpatient parenteral therapy in low-risk febrile patients with neutropenia, patients undergoing oral treatment were followed up every other day in the outpatient clinic [7]. But is close monitoring really necessary for all low-risk patients?

Between 70 and 80% of low-risk febrile patients with neutropenia had fever of unknown origin [5, 6]. The prognosis in low-risk patients with fever and neutropenia is generally good, particularly when the origin of the fever is unexplained. Patients with documented infections had higher rates of complications than patients with fever of unknown origin. At least 80% of low-risk patients seem to be in no need of follow-up every other day. In terms of quality of life, follow-up every other day is a serious problem for patients who live far away from their hospitals. Risk assessment over the telephone is convenient for such patients and may be useful for evaluating PS, particularly symptoms such as nausea and vomiting that limit oral intake.

In previous studies, patients were thought to need hospitalization when oral antibiotic therapy failed [7]. However, it is uncertain whether hospitalization can prevent rare events such as septic shock and death. Moreover, admission of low-risk patients may expose them to potential iatrogenic complications and drug-resistant nosocomial infections. Coagulase-negative staphylococci (CNS) that cause bacteremia in neutropenic patients are recognized as a major cause of nosocomial infection [12].

In outpatient therapy for low-risk febrile patients with neutropenia, quinolones, such as oral ofloxacin, have also been evaluated as monotherapy in limited studies [3, 7, 11]. They have broad-spectrum antibacterial activity, are particularly effective in treating Gram-negative bacteria, and are well tolerated, with few adverse effects.

In a study conducted in Pakistan, Malik et al. [3, 7] evaluated the efficacy of self-administered oral ofloxacin (400 mg, twice daily) as empirical therapy in low-risk febrile patients with neutropenia. At the University of Texas M.D. Anderson Cancer Center, two studies comparing outpatient oral (ciprofloxacin 750 mg q8h plus clindamycin 600 mg q8h) and parenteral regimens (aztreonam 2 g q8h plus clindamycin 600 mg q8h) in low-risk febrile patients with neutropenia demonstrated that oral antibiotic therapy was as effective as parenteral antibiotic therapy [14]. However, there have been few reports of the use of single-agent oral ciprofloxacin in low-risk febrile patients with neutropenia in the outpatient setting [15]. As ciprofloxacin has better antipseudomonal coverage, it has the advantage that it might prove more

Table 1 Treatment outcomes

Treatment outcomes	n=30
Success	27
Failure	3
Modification required	
Addition of antiviral agent	0
Addition of antifungal agent	0
Addition of GCSF	1
A change in regimen[a]	2

[a]Two had their treatment regimen changed to parenteral administration (1 ceftazidime and 1 ceftriaxone sodium). The reasons for this alteration in regimen were mainly gastrointestinal symptoms.

Table 2 Reasons for failure

Case	Age	PS	Reasons	Modification
1	67	1	Appetite loss, mucositis	Parenteral treatment
2	54	1	appetite loss abdominal pain	Parenteral treatment
3	48	1	appetite loss, nausea/vomiting	Addition of GCSF

effective than ofloxacin, although a comparative trial would be required to establish this.

One of the problems with the use of quinolone monotherapy for low-risk febrile patients with neutropenia is its limited activity against Gram-positive infection, which represents over 50% of isolates in major cancer treatment centers of the United States and Europe. Addition of a Gram-positive agent to the initial coverage remains a matter of controversy. CNS and viridans streptococci are the leading Gram-positive causes of bacteremia in neutropenic patients. The viridans streptococcus is associated with severe neutropenia, oral mucositis, administration of high-dose cytosine arabinoside, treatment of peptic ulcer with H2-receptor antagonists, and the prophylactic use of fluoroquinolone [16]. The risk of bacteremia from nosocomial infection with CNS may be reduced by outpatient treatment.

A second problem is the increase in quinolone-resistant Gram-negative infection [17, 18]. Other studies suggest that the prophylactic use of fluoroquinolone increases the occurrence of fluoroquinolone-resistant *Escherichia coli* bacteremia. This resistant form has been reported almost exclusively from European cancer treatment centers and is still not isolated as frequently in Japan as compared in the West. In view of this, single-agent ciprofloxacin seems to be acceptable in Japan.

Our results are based on a retrospective study and must therefore be interpreted with caution. Although risk has to be very carefully assessed over the telephone, we are optimistic that, in the future, if videophones are in common use, the accuracy of assessment by telephone, including the evaluation of PS, may improve. It is a problem that of the 27 patients considered to be successfully treated by oral ciprofloxacin, 6 had fever that persisted for more than 4 days. We must emphasize the importance of telephone contact with outpatients. Besides a more accurate risk assessment model, there is a need for patient education and the establishment of an emergency support system on the hospital side. If our results can be confirmed in a randomized trial, it may be possible to improve the quality of life of these patients and reduce the cost of their care.

In conclusion, for low-risk febrile patients with neutropenia, risk assessment over the telephone may be convenient, and close daily medical scrutiny may be not routinely required in the outpatient.

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Gynecologic Oncology 108 (2008) 226–233
Gynecologic Oncology
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Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: A Japanese Gynecologic Oncology Group study ☆

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Received 20 April 2007
Available online 26 November 2007

Abstract

Objective. To establish an optimal adjuvant therapy for intermediate- and high-risk endometrial cancer patients, we conducted a multi-center randomized phase III trial of adjuvant pelvic radiation therapy (PRT) versus cyclophosphamide–doxorubicin–cisplatin (CAP) chemotherapy in women with endometrioid adenocarcinoma with deeper than 50% myometrial invasion.

Methods. Among 385 evaluated patients, 193 patients received PRT and 192 received CAP. The PRT group received at least 40 Gy. The CAP group received cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m^2) and cisplatin (50 mg/m^2) every 4 weeks for 3 or more courses.

Results. No statistically significant differences in progression-free survival (PFS) and overall survival (OS) were observed. The 5-year PFS rates in the PRT and CAP groups were 83.5% and 81.8% respectively, while the 5-year OS rates were 85.3% and 86.7% respectively. These rates were also not significantly different in a low- to intermediate-risk group defined as stage IC patients under 70 years old with G1/2 endometrioid adenocarcinoma. However, among 120 patients in a high- to intermediate-risk group defined as (1) stage IC in patients over 70 years old or with G3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology), the CAP group had a significantly higher PFS rate (83.8% vs. 66.2%, log-rank test $P=0.024$, hazard ratio 0.44) and higher OS rate (89.7% vs. 73.6%, log-rank test $P=0.006$, hazard ratio 0.24). Adverse effects were not significantly increased in the CAP group versus the PRT group.

Conclusion. Adjuvant chemotherapy may be a useful alternative to radiotherapy for intermediate-risk endometrial cancer.

Keywords: Endometrial cancer; Intermediate risk; Adjuvant radiotherapy; Adjuvant chemotherapy; Cisplatin-based chemotherapy

Introduction

The number of patients with endometrial cancer is increasing in Japan as well as in the United States and other countries [1]. The number of patients with recurrent endometrial cancer is also increasing. Approximately, 10% to 15% of patients with early-stage endometrial cancer will experience recurrences [2,3]. To reduce the recurrence rate, adjuvant chemotherapy or radiotherapy has been applied, but a definite standard therapy has not yet been established.

For stage III–IV endometrial cancer, Randall et al. [4] reported the results of a Gynecologic Oncology Group (GOG) randomized Phase III trial of whole abdominal irradiation (WAI)

☆ The participating institutions for all studies described in this report are listed in the Appendix.

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doi:10.1016/j.ygyno.2007.09.029

and platinum–doxorubicin (AP) chemotherapy. This study had a large impact on treatment since adjuvant therapy for advanced endometrial cancer had been limited mainly to radiotherapy, such as whole abdominal irradiation, pelvic irradiation, and vaginal brachytherapy.

Adjuvant therapy for early-stage endometrial cancer has also been limited mainly to radiation therapy. In the National Comprehensive Cancer Network (NCCN) Guidelines for 2006, Version 2 [5], adjuvant therapy was selected based on a combination of characteristics such as surgical staging, grade and risk factors (advanced age, lymphovascular space invasion, tumor size, depth of invasion, etc.). Radiation therapy was recommended for all patients except those with IA/G1 or G2 lesions and those with IB/G1 lesions without risk factors. Chemotherapy was also not included as an adjuvant therapy for stage I/II endometrial cancers. In the FIGO annual report [1], adjuvant radiotherapy was selected roughly twice as often as adjuvant chemotherapy for patients with stage IC, IIA, or IIB endometrial carcinoma.

Recently, some large series of randomized studies regarding adjuvant radiotherapy for early-stage endometrial cancers were performed by Aalders et al. (NRH study) [6], Creutzberg et al. (PORTEC study) [2,7] and Keys et al. (GOG 99 study) [8]. In these three series, the loco-regional recurrence rate was significantly lower in the pelvic irradiation group versus the no adjuvant therapy or brachytherapy groups. However, none of the studies recognized a significant survival benefit. Moreover, the rate of adverse gastrointestinal effects was higher in the pelvic irradiation group after pelvic lymphadenectomy or lymph node sampling in both the PORTEC study [7] and the GOG study [8].

In view of this background, physicians have been concerned as to whether adjuvant therapy is effective for improving the progression-free survival (PFS) and overall survival (OS) of patients with early-stage endometrial cancer. The GOG began a randomized study (GOG 156 study, data not published) consisting of pelvic radiation and chemotherapy (doxorubicin plus cisplatin) treatment groups for patients with stage IB, IC, IIA, and IIB endometrial cancer. However, this trial was closed due to low accrual rates. The Japanese Gynecologic Oncology Group (JGOG) began a randomized study comparing pelvic radiotherapy to platinum-based combined chemotherapy to clarify which modality was more effective for improving the PFS and OS of endometrial cancer patients with deeper than 50% myometrial invasion, including FIGO stage IC to IIIC. Most of the enrolled patients had IC, IIA, IIB, or IIIA intermediate-risk endometrial cancer.

Methods

Patient selection and eligibility criteria

Patient accrual for this study occurred from 1994 to 2000 at 103 member institutions of the JGOG. The eligibility criteria for this study were International Federation of Gynecology and Obstetrics (FIGO) stage IC–IIIC endometrial carcinoma with deeper than 50% myometrial invasion and absence of any prior chemotherapy, irradiation, or surgery for the treatment of any other cancer. Patients with stage II or III without deeper than 50% myometrial invasion were ineligible for this study. Patients were required to be under 75 years old, to have a WHO performance status of 0 to 3, and to have undergone an initial surgery, including total abdominal hysterectomy and bilateral salpingo-oophorectomy, with no residual tumor. Patients with other active cancers or without adequate liver, renal, or bone marrow functions were excluded. All patients agreed to the randomized study design and provided informed consent. Surgical staging consisted ideally of pelvic and/or paraaortic lymphadenectomy. A central pathology review was not performed. Treatment was initiated within 4 weeks of surgery. Treatment was initiated within 4 weeks of surgery.

Pelvic irradiation was given in an open field using the anterio-posterior parallel opposing technique. The scheduled dose of irradiation was 45 to 50 Gy within 4 to 6 weeks, with 9 to 10 Gy of irradiation administered per week (5 working days per week). Subsequently, additional irradiations were performed in 11 cases (5.7%) with paraaortic lesions and in 6 patients (3.1%) who received brachytherapy.

The chemotherapy group received cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m^2), and cisplatin (50 mg/m^2) (CAP chemotherapy) every 4 weeks for 3 or more courses. Dose modifications of doxorubicin and cisplatin were as follows: a 25% reduction of both drugs was allowed for body weight less than 40 kg or age greater than 70 years old, and a 50% reduction was allowed in patients with G3 or G4 myelosuppression.

Study design and randomization

This trial utilized a straightforward randomization among two groups: pelvic radiation and chemotherapy. An allocation table was prespecified based on a

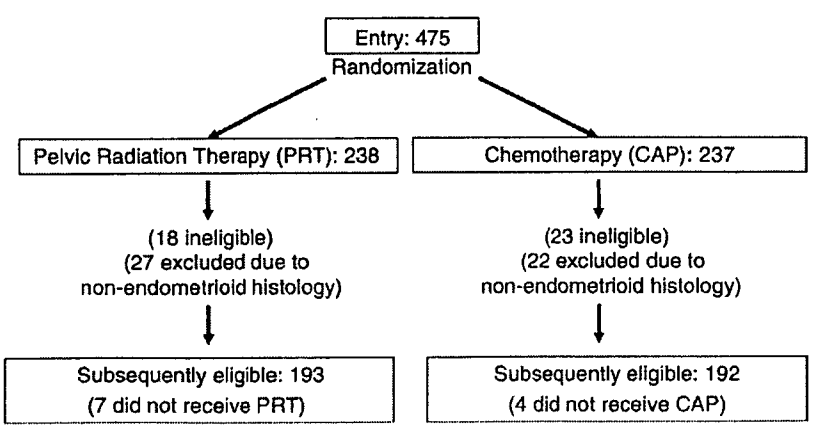

Fig. 1. Flow chart of patients in JGOG study 2033. The initial enrollment was 475 patients, 41 of whom were ineligible due to myometrial invasion of less than 50%, histological diagnosis of sarcoma, or rapid progression of disease after enrollment. An additional 49 patients with non-endometrioid histology were excluded.

Table 1
Patient characteristics

		Pelvic radiation therapy (PRT) (%)		Chemotherapy (CAP) (%)		Total	Univariate P (%)
	n	193		192		385	
Age	Average	58.7		59.3		59.0	P=0.431
	SD	7.5		8.6		8.1	
Menopause	Premenopause	35	18.1	35	18.2	70	P=0.981
	Postmenopause	158	81.9	157	81.8	315	
Co-morbidity	None	123	63.7	127	66.1	250	P=0.619
	Any	70	36.3	65	33.9	135	
Performance status	0	169	87.6	165	85.9	334	P=0.562
	1	22	11.4	19	9.9	41	
	2	2	1.0	6	3.1	8	
	3	0	0.0	2	1.0	2	
Hysterectomy	Simple	55	28.5	40	20.8	95	P=0.298
	Extended	94	48.7	108	56.3	202	
	Radical	43	22.3	42	21.9	85	
	Other	1	0.5	2	1.0	3	
Postoperative stage	IC	123	63.7	112	58.3	235	P=0.387
	IIA	10	5.2	8	4.2	18	
	IIB	10	5.2	25	13.0	35	
	IIIA	28	14.5	22	11.5	50	
	IIIB	0	0.0	1	0.5	1	
	IIIC	22	11.4	24	12.5	46	
Tumor grade	G1	107	55.4	106	55.2	213	P=0.542
	G2	53	27.5	64	33.3	117	
	G3	33	17.1	20	10.4	53	
	Unknown	0	0.0	2	1.0	2	
Myometrial invasion	>1/2, <2/3	113	58.5	104	54.2	217	P=0.317
	>2/3, <serosa	72	37.3	76	39.6	148	
	Serosa	7	3.6	7	3.6	14	
	Beyond serosa	1	0.5	5	2.6	6	
Lymphovascular space invasion	Negative	100	51.8	103	53.6	203	P=0.892
	Positive	72	37.3	72	37.5	144	
	Unknown	21	10.9	17	8.8	38	
Cervical involvement	Negative	156	80.8	142	74.0	298	P=0.128
	Positive	37	19.2	49	25.5	86	
Parametrial invasion	Negative	176	91.2	172	89.6	348	P=0.334
	Positive	7	3.6	11	5.7	18	
	Unknown	10	5.2	9	4.7	19	
Peritoneal cytology	Negative	169	87.6	171	89.1	340	P=0.749
	Positive	23	11.9	21	10.9	44	
	Unknown	1	0.5	0	0.0	1	
Adnexal metastasis	Negative	181	93.8	178	92.7	359	P=0.675
	Positive	12	6.2	14	7.3	26	
Pelvic LN metastasis	Negative	163	84.4	164	85.4	327	P=0.901
	Positive	21	10.9	22	11.5	43	
	n.d.	9	4.7	6	3.1	15	
Paraaortic LN metastasis	Negative	51	26.4	55	28.6	106	P=0.363
	Positive	1	0.5	3	14.9	4	
	n.d.	141	73.1	134	7.8	275	

CAP: cyclophosphamide, doxorubicin, and cisplatin.
n.d.: not done.

simple randomization. Each participant was assigned by central telephone system. The primary endpoint was OS and secondary endpoints were PFS and the incidence of toxicity.

The required sample size was estimated as 173 for each group, with a significance level of 5% and a power level of 80% using Schoenfeld's sample size formula [9] for the log-rank test and assuming a 13% difference in the OS rate at 5 years (5-year OS rates of 80% for the CAP group and 67% for the PRT group). These figures for the 5-year OS rate were calculated based on data from the FIGO annual report [10], assuming an eligible case distribution of 60% stage I patients, 20% stage II patients, and 20% stage III patients.

Statistical methods

Statistical analyses were performed for all eligible patients on an intent-to-treat principle. All statistical analyses were performed using SAS Release 8.02 (Statistical Analysis Software, Cary, NC, USA). Prognostic factors were analyzed by chi-square test, and survival curves were calculated by the Kaplan–Meier method [11]. A log-rank test [12] was used to test for survival differences. A multivariate analysis using the Cox proportion hazards model [13] was performed to assess the hazard ratio of the prognostic factors for PFS and OS. All reported P-values are based on two-sided tests with $P<0.05$ taken as significant.

Results

As shown in the trial profile (Fig. 1), the initial enrollment was 475 patients, 41 of whom were ineligible due to myometrial invasion of less than 50%, histological diagnosis of sarcoma, or rapid progression of disease after enrollment. An additional 49 patients with non-endometrioid histology were excluded. As a result, 385 patients were eligible for this trial. Seven patients in the PRT group did not receive PRT and 4 patients in the CAP group did not receive CAP.

As shown in Table 1, the study groups were well balanced for patient characteristics including age, postmenopausal status, co-morbidity, type of hysterectomy, postoperative stage, tumor grade, myometrial invasion, lymphovascular space invasion, cervical involvement, parametrial invasion, peritoneal cytology, adnexal metastasis, pelvic lymph node metastasis, and para-aortic lymph node metastasis. None of these characteristics was significantly different between groups in univariate analysis. The distribution of postoperative stages was 61.0% IC, 13.8% II, 13.0% IIIA, and 11.9% IIIC. Pelvic lymphadenectomy was performed in 96.1% of the patients, and paraaortic lymphadenectomy was performed in 28.6% of the patients.

The analysis was performed using data finalized on April 14, 2005. The median follow-up periods in the PRT and CAP groups were 59.5 (2.2–60.8) months and 60.8 (5.0–60.8) months, respectively.

Protocol compliance

Treatment was completed in 98.9% (184/186) and 97.3% (183/188) of the patients in the PRT and CAP groups, respectively. We regarded pelvic radiation as being completed when the total radiation dose reached 40 Gy and regarded chemotherapy as being completed when the number of CAP courses reached three. The median total doses were 50 Gy of pelvic irradiation and 1309 mg/m^2 cyclophosphamide, 120 mg/m^2 doxorubicin, and 180 mg/m^2 cisplatin. The median number of CAP courses was 3, ranging from 1 to 7. The median duration of treatment was 5.1 weeks and 11.4 weeks in the PRT and CAP groups, respectively.

Table 3
Sites of initial recurrence

Recurrence sites*	PRT	CAP
	n=193	n=192
Pelvis	11	5
Vagina only	2	9
Intrapelvic recurrence	13 (6.7%)	14 (7.3%)
Peritoneal cavity	2	2
Liver	3	1
Lung	11	15
Paraaortic lymph node	3	10
Others	7	3
Extrapelvic recurrence	26 (13.5%)	31 (16.1%)
Total recurrent cases	30 (15.5%)	33 (17.2%)

*Including multiple recurrence.
CAP: cyclophosphamide, doxorubicin, and cisplatin.
PRT: pelvic radiation treatment.

Adverse effects

G3 and G4 toxicities were experienced in 1.6% (3/193) of the PRT and 4.7% (9/192) of the CAP groups. Bowel obstructions were the main complication in the PRT group, and myelosuppression was detected in the CAP group. No treatment-related deaths occurred in either group.

Prognostic factors

We performed univariate analyses to detect prognostic factors in all eligible patients. The statistically significant prognostic factors predicting worse PFS were age (≧60 years vs. <60 years), co-morbidity, clinical staging (IIIA vs. II vs. IB vs. IA), tumor grade (G2/3 vs. G1), myometrial invasion (beyond serosa vs. serosa vs. ≧2/3 to < serosa vs. ≧1/2 to <2/3), pelvic lymph node metastasis, adnexal involvement, cervical involvement, peritoneal cytology, and surgical staging (IIIC vs. IIIA vs. IIB vs. IIA vs. IC). For OS, the statistically significant prognostic factors were age, co-morbidity, clinical staging, tumor grade, myometrial invasion, pelvic lymph node metastasis, lymphovascular space invasion, and surgical staging.

Table 2
Multivariate analysis of prognostic factors

Prognostic factors	PFS				OS			
	Hazard ratio	95% confidence interval		P-value	Hazard ratio	95% confidence interval		P-value
		Lower	Upper			Lower	Upper	
Treatment (CAP vs. PRT)	1.07	0.651	1.762	0.788	0.72	0.399	1.290	0.268
Age (≧60 vs. <60)	1.92	1.142	3.210	0.014	3.30	1.634	6.646	0.001
Co-morbidity	1.61	0.974	2.647	0.063	2.24	1.226	4.109	0.009
Tumor grade	1.55	1.125	2.137	0.007	1.64	1.115	2.418	0.012
Cervical involvement	2.28	1.352	3.829	0.002	n.d.	n.d.	n.d.	n.d.
Peritoneal cytology	2.07	1.091	3.920	0.026	n.d.	n.d.	n.d.	n.d.
Pelvic lymph node metastasis	n.d.	n.d.	n.d.	n.d.	4.25	2.235	8.072	<0.001

CAP: cyclophosphamide, doxorubicin, and cisplatin.
PRT: pelvic radiation treatment.
n.d.: not done.

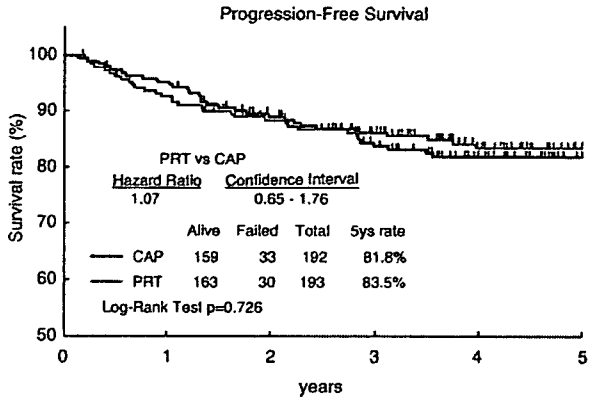

Fig. 2. Progression-free survival rates of all patients in the PRT (pelvic radiation treatment) group and CAP (cyclophosphamide, doxorubicin, and cisplatin) group. Kaplan–Meier analysis. Data for both groups nearly overlap, with no statistical difference.

The significant prognostic factors were used to perform a multivariate analysis with a Cox regression model (Table 2). The multivariate analysis showed that age (≧60 years) and tumor grade (G2/3) were the most important poor prognostic factors for both PFS and OS in this trial.

Recurrence sites

Table 3 presents data on sites of initial recurrence. Thirty recurrences (15.5%) occurred in the PRT group, and 33 recurrences (17.2%) occurred in the CAP group. The patterns of recurrence were similar in both treatment groups. Specifically, the incidence of intrapelvic recurrence sites, such as the pelvis or vagina, was 6.7% (13/193) in the PRT group and 7.3% (14/192) in the CAP group, while the incidence of extrapelvic recurrence sites, such as the peritoneal cavity, liver, lung, paraaortic lymph nodes, and others, was 13.5% (26/193) and 16.1% (31/192) respectively.

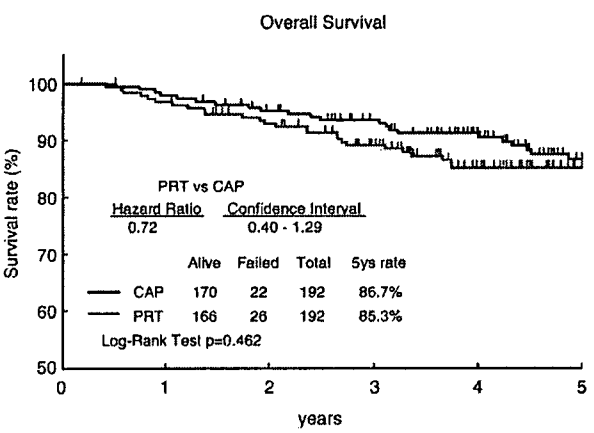

Fig. 3. Overall survival rates in the PRT (pelvic radiation treatment) group and CAP (cyclophosphamide, doxorubicin, and cisplatin) group. Kaplan–Meier analysis. Overall survival rates in both groups were also similar, with no statistical difference.

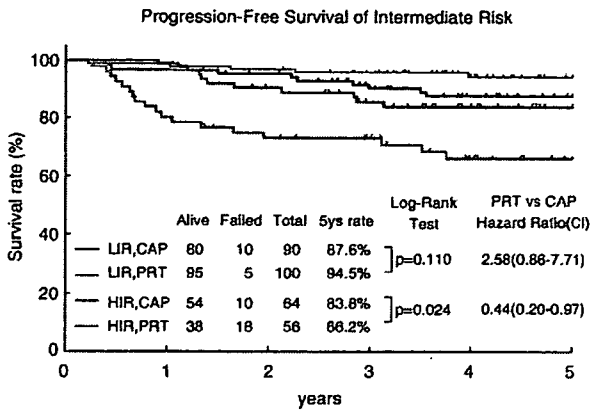

Fig. 4. Progression survival rates of intermediate risk in the PRT (pelvic radiation treatment) group and CAP (cyclophosphamide, doxorubicin, and cisplatin) group. Low–intermediate risk (LIR) was defined as stage IC patients under 70 years of age and with G1/2 endometrioid adenocarcinoma. High–intermediate risk (HIR) was defined as (1) stage IC patients over age 70 years or having G3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology) patients with deeper than 50% myometrial invasion in the corpus. Among LIR patients, PFS rates at 5 years in the PRT and CAP groups were not statistically different. However, among HIR patients, the CAP group had significantly higher PFS rate.

Outcome

Fig. 2 presents the PFS rates of all patients in both randomized treatment groups. Data for the two groups nearly overlap. PFS rate at 5 years was 83.5% in the PRT group and 81.8% in the CAP group. The hazard ratio was 1.07 (95% CI, 0.65–1.76; $P=0.726$).

Fig. 3 shows that the OS rates in both groups were also similar, with no statistical difference. The OS rate at 5 years was

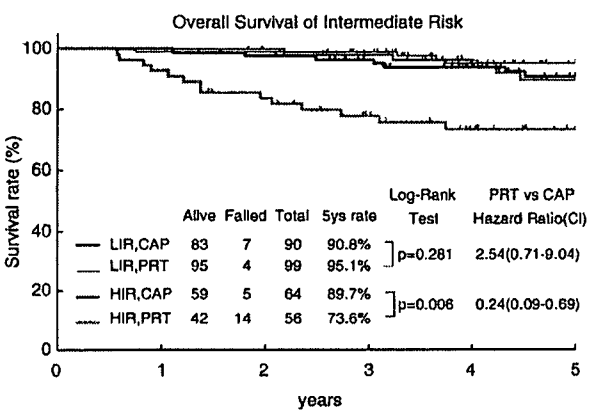

Fig. 5. Overall survival rates of intermediate risk in the PRT (pelvic radiation treatment) group and CAP (cyclophosphamide, doxorubicin, and cisplatin) group. Low–intermediate risk (LIR) was defined as stage IC patients under 70 years of age and with G1/2 endometrioid adenocarcinoma. High–intermediate risk (HIR) was defined as (1) stage IC patients over age 70 years or having G3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology) patients with deeper than 50% myometrial invasion in the corpus. Among LIR patients, OS rates at 5 years in the PRT and CAP groups were not statistically different. However, among HIR patients, the CAP group had significantly higher OS rate.

85.3% in the PRT group and 86.7% in the CAP group (log-rank test $P=0.462$). The hazard ratio was 0.72 (95% CI, 0.40–1.29; Cox proportion hazards model $P=0.268$).

Overall, 48 patients died, of whom 26 had been assigned to the PRT group and 22 to the CAP group. In the PRT group, 21 deaths were related to endometrial cancer, 1 death to another cancer, and 2 deaths to other diseases. In the CAP group, 13 deaths were related to endometrial cancer, 4 deaths to other cancers, and 4 deaths to other diseases.

We performed a subgroup analysis, defining the criteria for low- to intermediate-risk (LIR) and high- to intermediate-risk (HIR) subgroups. When LIR was defined as stage IC patients under 70 years of age and with G1/2 endometrioid adenocarcinoma, among 190 LIR patients, PFS rates at 5 years in the PRT and CAP groups were 94.5% and 87.6% respectively ($P=0.110$) (Fig. 4), and OS rates at 5 years in the PRT and CAP groups were 95.1% and 90.8% respectively ($P=0.281$) (Fig. 5). The HIR subgroup was defined as (1) stage IC patients over age 70 years or having G3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology) patients with deeper than 50% myometrial invasion in the corpus. Among these 120 patients, the CAP group had significantly higher PFS rate (83.8%) (hazard ratio 0.44, 95% CI, 0.20–0.97; $P=0.024$) (Fig. 4) and OS rate (89.7%) (hazard ratio 0.24, 95% CI, 0.09–0.69; $P=0.006$) (Fig. 5) versus the PRT group (66.2% and 73.6%, respectively).

We performed another analysis for high-risk group. For 75 cases in high-risk group, OS rates and PFS rates were not statistically different between PRT group and CAP group. The OS rate at 5 years was 75.8% in the PRT group and 71.1% in the CAP group (log-rank test $P=0.667$). The hazard ratio was 1.123 (95% CI, 0.42–3.04; $P=0.819$). The PFS rate at 5 years was 78.6% in the PRT group and 64.4% in the CAP group (log-rank test $P=0.169$). The hazard ratio was 1.847 (95% CI, 0.73–4.65; $P=0.193$).

Discussion

This study by the Japan Gynecologic Oncology Group is the first report of a randomized controlled study comparing adjuvant pelvic RT with chemotherapy for early-stage endometrial cancer with deeper than 50% myometrial invasion. We observed no statistically significant differences in survivals in the two regimens. We also found that adverse effects were not significantly increased in a platinum-based combined chemotherapy group, and we showed that chemotherapy significantly improved PFS and OS in HIR patients, versus pelvic radiation.

The eligibility criteria for this study were FIGO stage IC–IIIC endometrial carcinoma with deeper than 50% myometrial invasion. The majority (77.4%) of registered patients had stage IC or II lesions, and only 11.9% had stage IIIC lesions. We therefore believe that the efficacy of pelvic radiation and chemotherapy as adjuvant treatments for early-stage endometrial cancer was compared appropriately.

All patients had undergone a hysterectomy and bilateral adnexectomy, and pelvic lymphadenectomy and paraaortic lymphadenectomy were performed in 96.1% and 28.6% of patients respectively. Paraaortic lymphadenectomy was not performed when no paraaortic lymph nodes were palpable and no enlarged paraaortic lymph nodes were detected preoperatively by computed tomography. We therefore regard our surgical staging as appropriate. However, our eligibility criteria were somewhat heterogeneous for the inclusion of post-surgical stage IC, IIA, IIB, IIIA, IIIB, and IIIC lesions.

To verify the efficacy of chemotherapy in intermediate- and high-risk groups, a subgroup analysis is potentially important. Generally, prognostic risk factors have been classified as low, intermediate, or high risks using different criteria [2,3,6,8,14,15]. In these previous reports, stage IC was definitely classified as intermediate risk. Stage III and IV were usually classified as high-risk, locally advanced. The GOG defined stage IC and II, without inclusion of IIIA (positive cytology) as intermediate risk. GOG Study 99 [8] defined HIR as (1) G2/3 tumors with lymphovascular space invasion and outer-third myometrial invasion, (2) age of 50 years or greater in addition to any two factors listed above, or (3) age of at 70 years or greater with any risk factor listed above. FIGO stages IB, IC, and II (occult disease) were defined as LIR.

In our subgroup analysis an LIR group comprised stage IC patients under 70 years of age with G1/2 endometrioid adenocarcinoma. Our HIR group comprised (1) stage IC patients who were over 70 years of age or had G3 endometrioid adenocarcinoma and (2) stage II or IIIA (positive cytology) patients with deeper than 50% myometrial invasion in the corpus. Our high-risk group comprised other stage IIIA patients with factors other than a positive peritoneal cytology and stage IIIB and IIIC patients.

PFS and OS rates for the PRT and CAP groups were the same in the LIR subgroup. In the HIR subgroup, however, we found significantly higher PFS and OS rates in the CAP group versus the PRT group. Since patients with FIGO stage IIIA endometrial cancer only with positive washing cytology have a better prognosis [5,16], we included patients with positive washing cytology in the HIR group, along with stage II disease patients. However, we recognize that the validity of this subset analysis is limited. Demonstration of a true advantage of chemotherapy requires a large-scale randomized controlled trial with stratification for risk factors including age and tumor grade prior to randomization.

In the early 1990s, the CAP regimen was used as the standard chemotherapy for endometrial cancer and ovarian cancer in Japan. Most Japanese gynecologists adopted CAP as the standard adjuvant chemotherapy rather than AP. In our trial, the dosage of doxorubicin was lower than in other trials using AP, such as GOG study 107/122/177 (60 mg/m^2) and GOG study 184 (45 mg/m^2) [17–19]. Due to this relatively low dose, G3 and G4 adverse effects were rare (4.7%), and protocol compliance was very high (95.3%) in the CAP group. The number of CAP courses was relatively small (median: 3 courses). Thus, cisplatin-based chemotherapy may be a feasible alternative to adjuvant pelvic radiation therapy for patients with intermediate-risk endometrial cancers. However, validation of a true efficacy of adjuvant chemotherapy for early-stage endometrial cancer, especially for LIR patients, requires a randomized controlled trial of no-treatment versus chemotherapy.

In HIR patients, chemotherapy was superior to radiation therapy. In patients with low-risk and LIR endometrial cancer, most recurrence sites are vaginal or intrapelvic, making pelvic

radiation or vaginal vault brachytherapy effective for reducing the loco-regional recurrence rate [7,20,21]. The reason for the superiority of chemotherapy in HIR patients is partly that extrapelvic recurrence cannot be prevented by pelvic radiation, as reported by Creutzberg et al. [7,14] and other investigators [6,8,20–22]. In this study, the incidence of recurrences at vaginal wall was lower in PRT group compared with CAP group, however, there was no significant difference in the incidences of extrapelvic recurrence between the PRT and CAP groups. In Japan, different types of hysterectomy, such as simple hysterectomy, extended hysterectomy (type II modified radical hysterectomy), and radical hysterectomy (type III), were performed in each institution. However, radical hysterectomy is selected only for those patients with macroscopically apparent cervical involvement in most of JGOG institutions. In addition, in this study, we included simple hysterectomy with a small amount of removal of vaginal cuff into extended hysterectomy. For this reason, the percentage of radical hysterectomy and modified radical hysterectomy is not thought to be high, and the influence of surgical procedure over the incidence of vaginal recurrence may be limited in our study.

In our study, we performed pelvic lymphadenectomy in 96% cases. Local recurrence rate was 2.6% in the cases of LIR and HIR with pelvic radiation treatment. Local recurrence rate in the radiotherapy group was 3.9% in PORTEC study [2,7] with no pelvic lymphadenectomy and 1.6% at 2 years in GOG study 99 [8] with selective pelvic and paraaortic lymphadenectomy. It seems that there is a tendency of low local recurrence rate in the intermediate-risk patients with pelvic lymphadenectomy in pelvic radiation treatment, however, we cannot simply compare those data as there are differences in the definition of intermediate risk.

The superiority of chemotherapy in HIR patients must also be considered in relation to the conclusions of GOG study 122 on advanced-stage endometrial cancer [4]. In stage III/IV endometrial cancer, AP chemotherapy was superior to whole-abdominal radiation as a therapeutic modality. Further investigation of the use of chemotherapeutic agents in patients with HIR endometrial cancer or high-risk endometrial cancer is needed. The JGOG has just finished accruing for a comparative phase II trial comparing three combined chemotherapy regimens (paclitaxel and carboplatin vs. docetaxel and cisplatin vs. docetaxel and carboplatin). These results are forthcoming.

In patients with early-stage endometrial cancer and deeper than 50% myometrial invasion, adjuvant platinum-based combined chemotherapy and pelvic radiation therapy each led to a good prognosis. In patients with HIR endometrial cancers, the aforementioned chemotherapy improved the prognosis significantly compared to pelvic radiation. Additional phase III randomized controlled trials are required to establish a standard adjuvant chemotherapy regimen including anthracyclin, taxane or platinum for intermediate-risk or high-risk endometrial cancer.

Acknowledgments

We thank the patients who participated in this study and their families. We thank Ms. Kyoko Tanaka (Kyowa Media Service) for her statistical review and comments.

The participating institutions for all studies described in this report are listed in Appendix A.

Appendix A

The following member institutions participated in this study: Akita City Hospital, Aomori Prefectural Central Hospital, Asahi General Hospital, Asahikawa Medical College, Asahikawa Red Cross Hospital, Chiba Kaihin General Hospital, Chiba Social Insurance Hospital, Chiba University, Daiyukai General Hospital, Dokkyo University School of Medicine, Fujita Health University, Gifu Prefectural Tajimi Hospital, Gifu University, Hakodate Goryokaku Hospital, Hamamatsu Medical Center, Himeji Red Cross Hospital, Hiroshima University, Hyogo Medical Center for Adults, Hyogo Prefectural Awaji Hospital, Hyogo Prefectural Tsukaguchi Hospital, Iwate Medical University, Iwate Prefectural Kuji Hospital, JA Kochi Hospital, Japanese Red Cross Akita Hospital, Jiaikai Imamura Hospital, Juntendo University Urayasu Hospital, Kagawa University, Kanazawa Medical University, Kanazawa University, Kanebo Memorial Hospital, Kansai Medical University, Kanto Central Hospital of the Mutual Aid Association of Public School Teachers, Kawasaki Medical School, Keio University, Keiyu Hospital, Kinki University, Kitasato University, Kobe University, Kokura Memorial Hospital, Kumamoto City Hospital, Kumamoto University, Kurashiki Central Hospital, Kurume University, Kyosai Tachikawa Hospital, Kyoto Prefectural University of Medicine, Kyoto Second Red Cross Hospital, Kyoundo Hospital, Kyushu University (Medical Institute of Bioregulation), Miyazaki Prefectural Nichinan Hospital, Nagaoka Red Cross Hospital, Nagasaki University, Nagoya Daini Red Cross Hospital, Nantan General Hospital, Nara Medical University, Nara Prefectural Hospital, National Hospital Organization Hokkaido Cancer Center, National Hospital Organization Iwakuni Clinical Center, National Hospital Organization Matsumoto National Hospital, National Hospital Organization Saitama National Hospital, National Hospital Organization Sendai Medical Center, National Hospital Organization Tokyo Medical Center, Ogaki Municipal Hospital, Ohta General Hospital (Nishinouchi Hospital), Oita University, Okayama Red Cross General Hospital, Okayama Saiseikai General Hospital, Osaka City General Hospital, Osaka General Medical Center, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Medical College, Osaka Police Hospital, Saga University, Saiseikai Central Hospital, Saiseikai Utsunomiya Hospital, Saitama Shakai-Hoken Hospital, Sapporo Medical University, Sapporo-Kosei General Hospital, Sasebo City General Hospital, Seirei Yokohama Hospital, Senboku Kumiai General Hospital, Shimane Prefectural Central Hospital, Shimane University, Shizuoka General Hospital, Shonai Hospital, Showa University, Showa University Fujigaoka Hospital, Social Insurance Tagawa Hospital, St. Marianna University School of Medicine, St. Marianna University School of Medicine Yokohama City Seibu Hospital, Takamatsu Red Cross Hospital, Teikyo University Ichihara Hospital, Tohoku University, Tokyo Medical and Dental University, Tokyo Medical University, Tokyo Women's Medical University, Tosei General Hospital, Tottori

Municipal Hospital, Tottori University, Toyama Medical and Pharmaceutical University, Toyama Prefectural Central Hospital, University of Tokushima, Yamagata University, Yamaguchi Grand Medical Center.

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