STATE of the Art

in ovarian cancer management

再発卵巣癌 治療の現状と将来展望

九州大学大学院 医学研究院生殖病態生理学教授 加藤 聖子

九州大学大学院 医学研究院生殖病態生理学講師 矢幡 秀昭

はじめに

卵巣癌に対する初回化学療法は，GOG 158やAGOスタディによりpaclitaxel(PTX)＋carboplatin(CBDCA)併用療法（TC療法）が標準的レジメンとして全世界に幅広く認められるようになっている[1)2)]。また，最近ではJGOG 3016試験の結果よりdose dense TC療法がconventional TC療法よりprogression free survival (PFS), overall survival (OS) で有意に上回り[3)4)]，2013（平成25）年11月には分子標的治療薬であるbevacizumab（アバスチン®）が卵巣癌に保険適応となり，初回標準治療が大きく変わろうとしている。しかし，Ⅲ，Ⅳ期上皮卵巣癌症例の場合では初回化学療法をもってしても，optimal surgeryのなされた症例の70%が，suboptimal surgeryの場合はその90%が2年以内に再発すると言われる[5)]。すなわち，再発卵巣癌患者への対応を迫られることは日常臨床で珍しいことではなく，化学療法，手術療法，放射線療法，緩和医療など治療の選択肢は多岐にわたり，2010年版卵巣がん治療ガイドラインでも図1のようなフローチャートで示されている。

再発卵巣癌に対しては化学療法が治療の中心となるが，セカンドライン化学療法の選択に当たっては，奏効した

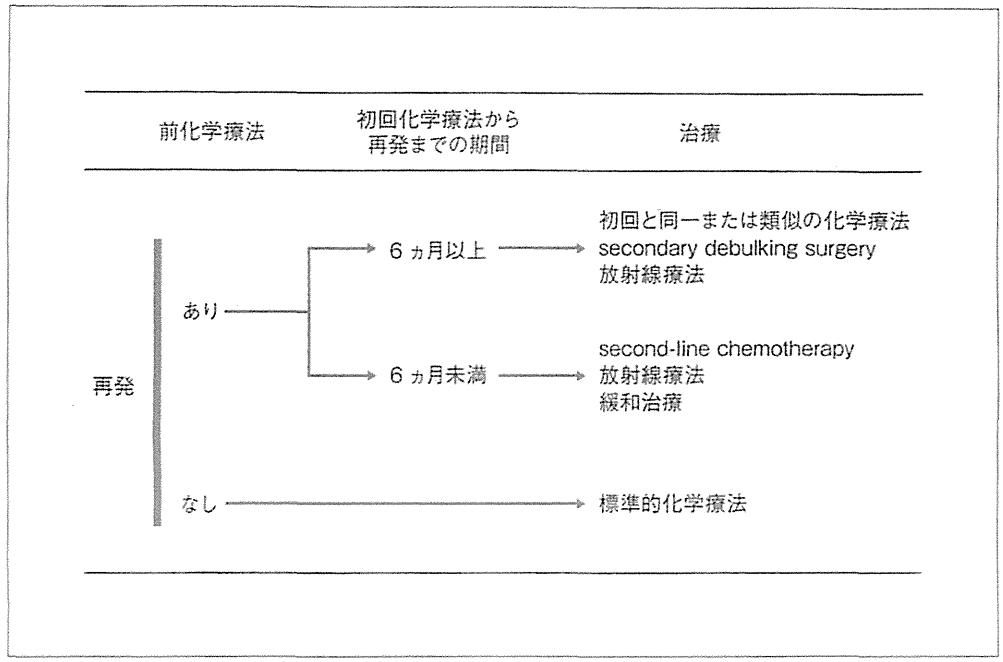

図1　本邦における再発卵巣癌治療

（文献6より引用）

初回化学療法終了後から再発までの期間(treatment-free interval：TFI）がその奏効率に相関することが知られている。Blackledgeら[7]は，再発卵巣癌に対する化学療法の奏効率はTFIが6ヵ月未満のものが10%であったのに対し，18ヵ月以上のものは94%と，TFIに相関することを報告した。また，Markmanら[8]は12ヵ月以上のプラチナ製剤無治療期間があれば再度，プラチナ製剤を含む化学療法が効果のあるレジメンと成りえることを報告した。このような考え方はタキサン製剤でも当てはまると考えられている。

これを受けて現在ではTFIが6ヵ月以上の再発をプラチナ製剤感受性再発，6ヵ月未満の再発をプラチナ製剤抵抗性再発，初回化学療法中の増悪症例をプラチナ製剤不応性再発に分類し，セカンドライン化学療法のレジメンを選択することが行われている。

また，secondary debulking surgery（SDS）は卵巣癌治療ガイドライン2010年版では再発卵巣癌において標準治療としての推奨はなされていないが，感受性再発を対象としては予後改善に寄与する報告が散見される。一方，bevacizumabなどの分子標的治療薬も初回治療のみではなく，将来的には再発卵巣癌治療において日常診療の大きな柱の1つとなる可能性がある。

そこで，本項では化学療法，手術療法，分子標的治療薬について再発卵巣癌治療の現状と将来展望について解説する。

化学療法

1.プラチナ製剤感受性再発

プラチナ製剤を含む前化学療法から6ヵ月以上経過した再発例には初回と同一，あるいは類似の化学療法が推奨される。そのため，初回の標準化学療法がTC療法の場合には，再度TC療法あるいはPTXをdocetaxel hydrate（DTX）に置き換えたDC療法が選択されることが多い。ただし，神経毒性などの有害事象によっては，ほかのプラチナ製剤を含むレジメンに変更する。ほかのプラチナ製剤併用療法としてirinotecan hydrochloride hydrate（CPT-11）などが用いられることもある（cisplatin（CDDP）＋CPT-11）。

2003年に報告されたICON 4とAGOスタディ[9]によ

る再発卵巣癌に対するrandomized control trial（RCT）では前治療としてタキサン製剤＋プラチナ製剤併用療法が43%，CBDCA単剤やCAP療法が48%に行われ，TFIは6ヵ月以上の802例の再発症例が対象であった。これらに対し，従来のプラチナ製剤を含む治療が392例に，PTX＋プラチナ製剤による治療が410例になされ，PTX＋プラチナ製剤併用療法の方がtime to progression（TTP）で9ヵ月と12ヵ月（p＝0.0004），mean survival time（MST）で24ヵ月と29ヵ月と有意に予後良好であった。また，GEICOスタディ[10]では前治療にプラチナ製剤を用いた6ヵ月以上のTFIを有する計81例を対象としたRCTが行われた。CBDCA単剤療法に40例，PTX＋CBDCA療法に41例が割り振られ，結果はresponse rate（RR）が50%と75.6%（p＝0.017），TTPが33.7週と49.1週（p＝0.021）とPTX＋CBDCA療法が優れており，MSTに関してもPTX＋CBDCA療法群ではmedian OSに達していないものの有意に予後良好であった。

また，AGO-OVAR2.5スタディ[11]ではTFIは6ヵ月以上を対象としてCBDCA単剤療法に178例，CBDCA＋gemcitabine hydrochloride（GEM）併用療法178例で，RRが30.9%と47.2%（p＝0.0016），TTPが5.8ヵ月と8.6ヵ月（p＝0.031）とCBDCA＋GEM療法が有意に優れていた。SWOG 0200スタディ[12]ではCBDCA単剤療法に30例，CBDCA＋liposomal doxorubicin（PLD）併用療法31例で，RRが32%と67%（p＝0.02），TTPが8ヵ月と12ヵ月（p＝0.02）とPLDを併用した方が有意に優れていた。

以上より，プラチナ製剤感受性再発卵巣癌に対してはプラチナ製剤にタキサン製剤，GEM，PLDなどとの併用療法が推奨される。それでは，プラチナ製剤とは何を組み合わせればよいのであろうか。CALYPSO スタディ[13]において，CBDCAにPTXあるいはPLDを組み合わせた比較第Ⅲ相試験が行われた。PTX＋CBDCA療法509例とPLD＋CBDCA療法467例において，TTPが9.3ヵ月と11.3ヵ月（p＝0.05）とPLDを併用してもPTX＋CBDCA療法に劣らないことが証明された。しかし，OSにおいては33.0ヵ月と30.7ヵ月で有意差はなく[14]，これはCALYPSO スタディに登録後のクロスオーバーの違いが原因と考えられた。すなわち，PTX＋CBDCA療法後にPLDを投与された症例が68%であったのに対し，PLD＋CBDCA療法後にPTXを投与された症例は43%と有意に少なかった（p＜0.001）。また，現在，GOTIC-003/iPLAS試験としてPLD＋CBDCA療法とGEM＋CBDCA療法の第Ⅲ相試験が進行中であり，本邦からのエビデンスとして，この結果も待たれるところである。

以上よりTFI 6ヵ月以上の再発例はプラチナ製剤感受性を保持していると考えられ，セカンドライン化学療法としてはプラチナ製剤との2剤併用療法が第一選択であると考えられる。

2. プラチナ製剤抵抗性再発

この再発例に対するセカンドライン化学療法は初回治療から短いTFI後に行われるため，まずはその患者が化学療法可能な状態にあるかを判断することが肝要である。すなわち，体腔液貯留などによるperformance status（PS）の低下，前化学療法の影響による血液毒性や非血液毒性などを十分に考慮する必要がある。また，奏効率の向上は必ずしも生存率の向上には寄与しないため，場合によっては緩和医療などを選択し，quality of life（QOL）の改善に主眼を置くことも考慮されるべきである。

化学療法を行える場合，単剤療法が治療の中心となる。Budaら[15]はTFIが12ヵ月未満（75%は6ヵ月未満）の再発卵巣癌に対するRCTでPTX単剤106例とPTX＋epirubicin hydrochloride（EPI）併用療法106例の比較を行ったところ，奏効率は37%と47%，TTPは6ヵ月と6ヵ月，MSTは14ヵ月と12ヵ月と両群間に有意差はなかったが，Grade3/4の好中球減少が18%と37%と有害事象は併用療法群に有意に多く（p＜0.05），多剤併用療法の有用性を見出せなかったことを報告した。また，Bolisら[16]はTFIが6ヵ月未満の再発卵巣癌に対するRCTで，PTX単剤40例とPTX＋EPI併用療法41例の比較を行った。Budaらと同様，骨髄毒性が強くなるだけで，併用療法による上乗せ効果は証明されなかった。

これらの報告に基づき，日本婦人科腫瘍学会編・卵巣がんガイドライン2010年版でも，6ヵ月未満の再発に対する化学療法は単剤による治療が標準であると示されている。現在，本邦で再発卵巣癌に対して保険適応のある薬剤はPTX，PLD，GEMのほかにCPT-11，topote-

表1　プラチナ製剤抵抗性再発卵巣癌で使用される本邦での保険適応薬

薬剤	投与量	スケジュール
PTX	180mg/m²	Day 1，3週毎
GEM	800-1,000mg/m²	Day 1,8,15，4週毎
CPT-11	100mg/m²	Day 1,8,15，4週毎
TOP	1.5mg/m²	Day 1-5、3週毎
VP-16	50mg/m²	Day 1-21(内服)，3週毎
PLD	40-50mg/m²	Day 1，4週毎
DTX	70mg/m²	Day 1，3週毎

can(TOP), DTX, etoposide(内服)(VP-16)がある(表1)。

Gordonら[17]はPLDとTOPの比較試験を報告した。PLD 50mg/m²の4週間投与群239例とTOP 1.5mg/m²のDay1-5の3週間投与群235例での解析結果では6ヵ月以内のプラチナ製剤抵抗性再発は各々PLD 130例(54%)，TOP 124例(53%)であったが，RRは12.3%と6.5%(p＝0.118)，PFSは9.1週と13.6週(p＝0.733)，MSTは35.6週と41.3週(p＝0.455)と両群間に有意差を認めなかった。また，その後の報告[18]ではプラチナ製剤感受性再発に限るとMSTは107.9週と70.1週(p＝0.017)とPLD群で有意に良好であり，Grade3/4の血液毒性はTOP群で有意に高かったことから，PLDは有効な薬剤であると結論付けている。現在，本邦ではJGOG 3018試験としてプラチナ製剤抵抗性再発・再燃mullerian carcinomaにおけるPLD 50mg/m²に対する40mg/m²の非劣性試験として，第Ⅲ相比較試験が進行中である。

Mutchら[19]はPLDとGEMの比較試験を報告した。PLD 50mg/m²のDay1の4週間投与群96例とGEM 1,000mg/m²のDay1,8の3週間投与群99例での比較試験ではRRが8.3%と6.1%，PFSが3.1ヵ月と3.6ヵ月，OSが13.5ヵ月と12.7ヵ月と両群間に有意差がないことを報告し，GEMもPLD同様にプラチナ製剤抵抗性再発に受け入れられる薬剤であることを報告した。

しかしながら，薬剤の選択に当たっては，いまだgolden standardとなる薬剤は決まっていないのが現状である。そのため，使用する薬剤の選択に当たっては，各薬剤の副作用などを十分に患者に説明したうえで，選択した薬剤での副作用が患者のQOLを損なわないように薬剤を選択することが肝要である。

表2　SDS適応基準(Chiら)

TFI(月)	単発	多発(癌性腹膜炎なし)	癌性腹膜炎
6-12	推奨	考慮	禁忌
12-30	推奨	推奨	考慮
>30	推奨	推奨	推奨

(文献23より引用)

表3　SDS適応基準(Oksefjellら)

TFI(月)	限局病巣	播種病巣
0-5	考慮	禁忌
6-11	推奨	禁忌
12-23	推奨	禁忌
>24	推奨	考慮

(文献24より引用)

手術療法

前項で述べたように再発卵巣癌の治療の中心は化学療法であるが，SDSと呼ばれる手術療法を選択することも少なからず存在する。では，どのような症例が手術療法の対象となるのであろうか。本邦ではOndaら[20]が手術を行う条件として①再発腫瘍径6cm未満，②単発再発，③無病期間12ヵ月以上，④肝転移なしの4因子のうち，3因子以上を予後良好群として手術療法の適応とすることを推奨している。また，AGOグループ[21]では①PS 0，②再発時腹水500mL未満，③初回手術時残存腫瘍なしの3因子を満たせば，SDSにて2/3以上の割合で完全切除ができると報告している。また，Tianら[22]は予後不良因子として①無病期間16ヵ月未満(2.4点)，②PS 2-3(2.4点)，③腹水あり(3.0点)，④初回手術時残存腫瘍あり(1.5点)，⑤進行期Ⅲ/Ⅳ期(0.8点)，⑥CA125 105U/mL以上(1.8点)の6因子に括弧内の一定の点数をつけ，その合計が4.7点を下回れば手術適応とすることを提唱している。

一方，Chiら[23]やOksefjellら[24]は無病期間と再発の形態により手術適応を表2，3のように分類し，その組

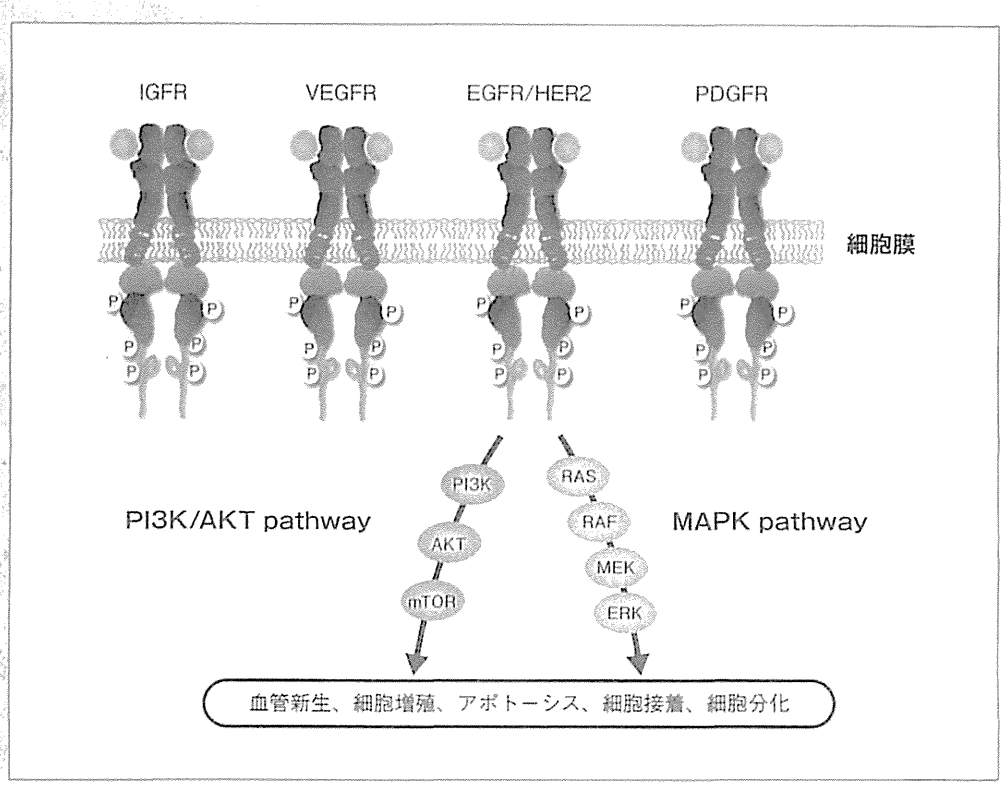

図2　細胞の増殖シグナル伝達

み合わせにより手術療法を検討することを推奨している。ただし，臨床の現場において，その手術適応は上述のような杓子定規で決まるものではなく，各施設での臨床経験や他科(外科，泌尿器科など)との連携など総合的な判断のもとに決定されるものである。

分子標的治療薬

分子標的治療薬は主に細胞外膜でリガンドおよび受容体を標的とするものと，細胞膜内にあるアミノ酸残基のキナーゼ・ドメインを標的とする薬剤があり，図2のような癌細胞の増殖シグナルの各部位の阻害部位によって，血管新生阻害薬，増殖因子受容体・シグナル伝達阻害薬，DNA修復・転写制御因子阻害薬などに分類される。

血管新生阻害薬であるbevacizumabがGOG 218試験，ICON 7試験の結果より卵巣癌初回治療においてTC療法に併用することによりPFSを有意に延長させることが証明され，本邦でも保険収載されるに至った。再発卵巣癌でのbevacizumabの有効性についても感受性再発および抵抗性再発で2つの第Ⅲ相試験が報告されている。OCEANS試験[25]では感受性再発卵巣癌484例に対してGEM＋CBDCA療法とGEM＋CBDCA療法にbevacizumab 15mg/kg併用後，増悪するまでbevacizumab単独を維持療法として追加した群とを比較し，PFSが8.4ヵ月と12.4ヵ月であり，bevacizumabの維持療法を行った群で有意にPFSを延長させた(p＜0.0001)。また，奏効率も57.4%と78.5%，奏効期間も7.4ヵ月と10.4ヵ月であり，有意に良好であった（p＜0.0001)。しかし，OSでは35.2ヵ月と33.3ヵ月であり，差は認められなかった。また，AURELIA試験[26]では抵抗性再発卵巣癌(腹膜癌，卵管癌を含む)361例において，化学療法(weekly PTX，TOP，PLD)単独群と化学療法にbevacizumab（15mg/kg/3weeksあるいは10mg/kg/2weeks）を併用した群を比較した。PFSでは3.4ヵ月と6.7ヵ月であり，有意に併用群で延長した（p＜0.001)。現在，感受性再発卵巣癌に対してTC療法にbevacizumabの上乗せ効果を検討したGOG 213試験の症例集積は終了しており，この試験結果も待たれるところである。

Mammalian target of rapamycin（mTOR）は細胞質内に存在するセリン・スレオニンキナーゼであり，細胞の分裂や成長，生存における調節因子としての役割を果たしている。mTOR1阻害薬であるtemsirolimusにおいてBehbakhtら[27]は再発または初回治療抵抗性の卵巣癌・腹膜癌患者54例においてtemsirolimus（25mg/body/1week）を投与して54例中13例に6ヵ月以上のPFSが得られ，5例にPRが認められたと報告している。また，同様にmTOR1阻害薬であるeverolimusを用いてJGOG 3021試験として再発卵巣明細胞腺癌に対する第Ⅱ相臨床試験が計画されており，明細胞腺癌の治療に対する新たな知見が期待される。

DNA修復阻害薬であるPARP阻害薬はBRCA経路の異常を有する癌細胞においてゲノム不安定性を生じ，抗腫瘍効果を発揮するが，BRCA1やBRCA2の遺伝子変異がない症例でもBRCA-nessと呼ばれるDNA修復機能異常を認めるため，卵巣漿液性腺癌などに有効である。Olaparibは経口のPARP阻害薬であり，Ledermannら[28]は第Ⅱ相試験ではあるが，感受性再発漿液性卵巣癌においてプラチナ製剤ベースの化学療法でPRあるいはCRが得られた症例をolaparib群136例，placebo群129例に割り振り，PFSが8.4ヵ月と4.8ヵ月（$p<0.001$）とolaparibの維持療法を行った群でPFSが有意に優れていた。しかし，OSの延長が見込めないことから2011年12月に第Ⅲ相試験への展開が中止となっていたが，2013年9月に第Ⅲ相試験が再開された。今後，本試験の結果も待たれる。一方，iniparibはPARP1阻害薬であるが，プラチナ製剤感受性再発卵巣癌41例においてGEM＋CBDCA療法にiniparibを追加投与した第Ⅱ相試験が行われ，奏効率は65％であり，PFSは9.5ヵ月であった。

おわりに

卵巣癌の患者数は現在も増加傾向にあり，それに伴い再発治療を行う機会も増えることが予想される。再発治療の中心となる化学療法の選択に当たり，薬剤やレジメンの選択に当たっては，プラチナ製剤感受性再発であればプラチナを含む2剤併用療法である程度の生存期間の延長が期待できる。一方，プラチナ製剤抵抗性再発では根治が困難であることを認識したうえで，単剤での化学療法が中心となるが，治療に当たっては患者，家族と十分に話し合い，場合によっては緩和治療への移行も選択肢となりうることを認識して臨む必要があると考えられる。また，化学療法に加えて手術療法や分子標的薬を加えた集学的治療も，今後多数のエビデンスの集積により，発展していくと考えられる。ただし，現段階においてPFSを改善するもののOSも改善するような分子標的薬は存在しない。今後はPFSのみでなく，OSをも改善するような再発治療が登場することを切望する。

そのためには，再発メカニズムの解明が重要である。近年，再発や転移において長期増殖能・薬剤耐性・免疫寛容・運動能，浸潤能の亢進などの特性を有する癌幹細胞の関与が注目されている。卵巣癌の癌幹細胞のマーカーが明らかとなり，初回治療後に生き残った少数の癌幹細胞を標的とした治療法が開発されれば，再発を防ぐことが可能になり卵巣癌の根治も決して夢ではない。

● References

1) Ozols RF, Bundy BN, Greer BE, et al. Phase Ⅲ trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage Ⅲ ovarian cancer : a Gynecologic Oncology Group study. J Clin Oncol. 2003 ; 21 : 3194-3200.

2) Du Bois A, Luck HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst. 2003 ; 95 : 1320-1329.

3) Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer : a phase 3, open-label, randomized controlled trial. Lancet. 2009 ; 374 : 1331-1338.

4) Katsumata N, Yasuda M, Isonishi S, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016) : a ranzomised, comtrolled, open-label trial. Lancet Oncol. 2013 ; 14 : 1020-1026.

5) Sabbatini P, Spriggs DR. Consolidation for ovarian cancer in remission. J Clin Oncol. 2006 ; 24 : 537-539.

6) 日本婦人科腫瘍学会（編）. 卵巣がん治療ガイドライン第3版. 東京：金原出版；2010.

7) Blackledge G, Lawton F, Redman C, et al. Response of patients in phase Ⅱ studies of chemotherapy in ovarian cancer: Implications for patients treatment and the design of phase Ⅱ trials. Br J Cancer. 1989 ; 59 : 650-653.

8) Markman M, Rothman R, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J Clin Oncol. 1991 ; 9 : 389-393.

9) Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-

based chemotherapy in women with relapsed ovarian cancer : the ICON4/AGO-OVAR-2.2 trial. Lancet. 2003 ; 361 : 2099-2106.

10) Gonzalez-Martin AJ, Calvo E, Bover I, et al. Randomized phase II trial of carboplatin versus paclitaxel and carboplatin in platinum-sensitive recurrent advanced ovarian carcinoma : a GEICO study. Ann Oncol. 2005 ; 16 : 749-755.

11) Pfister J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carbopratin in patients with platinum-sensitive recurrent ovarian cancer : an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol. 2006 ; 24 : 4699-4707.

12) Markman M, Moon J, Wilczynski S, et al. Single agent carboplatin versus carboplatin plus pegylated liposomal doxorubicin in recurrent ovarian cancer : final survival results of a SWOG (S0200) phase 3 randomized trial. Gynecol Oncol. 2010 ; 116 : 323-325.

13) Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinumsensitive ovarian cancer in late relapse. J Clin Oncol. 2010 ; 28 : 3323-3329.

14) Wagner U, Marth C, Largillier R, et al. Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients. Br J Cancer. 2012 ; 107 : 588-591.

15) Buda A, Floriani I, Rossi R, et al. Randomised controlled trial comparing single agent paclitaxel vs epidoxorubicin plus paclitaxel in patients with advanced ovarian cancer in early progression after platinum-based chemotherapy: an Italian Collaborative Study from the Mario Negri Institute, Milan, G.O.N.O. group and I.O.R. group. Br J Cancer. 2004 ; 90 : 2112-2117.

16) Bolis G, Parazzini F, Scarfone G, et al. Paclitaxel versus epidoxorubicin plus paclitaxel as second-line therapy for platinum-refractory and -resistant ovarian cancer. Gynecol Oncol. 1999 ; 72 : 60-64.

17) Gordon AN, Fleagle JT, Guthrie D, et al. Recurrent epithelial ovarian carcinoma : a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol. 2001 ; 19 : 3312-3322.

18) Gordon AN, Tonda M, Sun S, et al. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. Gynecol Oncol. 2004 ; 95 : 1-8.

19) Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol. 2007 ; 25 : 2811-2818.

20) Onda T, Yoshikawa H, Yasuhi T, et al. Secondary cytoreductive surgery for recurrent epithelial ovarian carcinoma : proposal for patients selection. Br J Cancer. 2005 ; 92 : 1026-1032.

21) Harter P, du Bois A, Hahmann M, et al. Surgery in recurrent ovarian cancer : the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial. Ann Surg Oncol. 2006 ; 13 : 1702-1710.

22) Tian WJ, Chi DS, Sehouli J, et al. A risk model for secondary cytoreductive surgery in recurrent ovarian cancer : an evidence-based proposal for patient selection. Ann Surg Oncol. 2012 ; 19 : 597-604.

23) Chi DS, McCaughty K, Diaz JP, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. Cancer. 2006 ; 106 : 1933-1939.

24) Oksefjell H, Sandstad B, Trope C, et al. The role of secondary cytoreduction in the management of the first relapse in epithelial ovarian cancer. Ann Oncol. 2009 ; 20 : 286-293.

25) Aghajanian C, Blank SV, Goff BA, et al. OCEANS : a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012 ; 30 : 2039-2045.

26) Pujade-Lauraine E, Hilpert F, Weber B, et al. AURELIA : A randomized phase III trial evaluating bevacizumab plus chemotherapy for platinum-resistant recurrent ovarian cancer. J Clin Oncol. 2012 ; 30 : abstr 5002.

27) Behbakht K, Sill MW, Darcy KM, et al. Phase II trial of the mTOR inhibitor, temsirolimus and evaluation of circulating tumor cells and tumor biomarkers in persistent and recurrent epithelial ovarian and primary peritoneal malignancies : A Gynecologic Oncology Group study. Gynecol Oncol. 2011 ; 123 : 19-26.

28) Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012 ; 366 : 1382-1392.

Gynecologic Cancer InterGroup (GCIG) Consensus Review for Cervical Adenocarcinoma

Hiroyuki Fujiwara, MD, PhD, Harushige Yokota, MD, PhD,† Bradley Monk, MD,‡ Isabelle Treilleux, MD,§ Mojgan Devouassoux-Shisheboran, MD,|| Alison Davis, MD,¶ Jae-Weon Kim, MD, PhD,# Sven Mahner, MD,** Michael Stany, MD,†† Sandro Pignata, MD,‡‡ Isabelle Ray-Coquard, MD, PhD,§ and Keiichi Fujiwara, MD, PhD§§*

Abstract: Cervical adenocarcinoma is known to be less common than squamous cell carcinoma of the cervix comprising approximately 25% of all cervical carcinomas. Differences in associated human papillomavirus types, patterns of spread, and prognosis call for treatments that are not always like those for squamous cancers. In this review, we report a consensus developed by the Gynecologic Cancer InterGroup surrounding cervical adenocarcinoma for epidemiology, pathology, treatment, and unanswered questions. Prospective clinical trials are needed to help develop treatment guidelines.

Key points: Differences between adenocarcinoma and squamous cell carcinoma, and Individualization of the therapy

Key Words: Cervical Cancer, Adenocarcinoma, Pathology, Staging, Clinical management

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Cervical cancer is the third most common cancer in women worldwide. Most cases are of squamous cell carcinoma (SCC) histology. Less common types include adenocarcinoma (AC), adenosquamous (AS) (generally considered together), and several rare histological subtypes. In the 1950s and 1960s, the proportion of cervical cancers that were either AC or AS was only 5% to 10%; but recent studies suggest that the proportion of cases with AC has increased, and currently, SCC represents approximately 75% of cases of invasive cervical carcinoma, whereas AC comprises approximately 20% to 25%. Reasons

*Jichi Medical University, Shimono-City, Japan and GOTIC; †Saitama Cancer Center, Saitama-City, Japan and GOTIC; ‡University of Arizona, Phoenix, AZ and GOG; §Centre Leon Berard, Lyon, France and GINECO; ||Hospices Civils de Lyon, Lyon, France and GINECO; ¶The Canberra Hospital, Canberra, Australia and ANZGOG; #Seoul National University College of Medicine, Seoul, Korea and KGOG; **Universtatsklinikum Hamburg-Eppendorf, Hamburg, Germany and AGO; ††Walter Reed National Military Medical Center, Bethesda, MD and GOG; ‡‡Istituto Nazionale Tumori "Fondazione G. Pascale" – IRCCS, Milan, Italy and MITO; and §§Saitama Medical University International Medical Center, Hidaka-City, Japan and GOTIC.

Address correspondence and reprint requests to Keiichi Fujiwara, MD, PhD, Saitama Medical University International Medical Center, Hidaka-City, Japan.
E-mail: fujiwara@saitama-med.ac.jp.

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for the increase in AC compared to SCC is likely multifactorial. A relative increase is likely due to the success of the screening program with Papanicolaou test leading to a fall in invasive SCC. Papanicolaou testing is not as effective in detecting preinvasive and invasive AC, which is generally located in the endocervical canal rather than on the ectocervix. Furthermore, preinvasive adenocarcinoma in situ cytology is less consistently described and recognized. The increasing incidence may also relate to other risk factors including obesity and reduced parity.

Currently, AC and AS carcinoma of the cervix are treated similar to SCC. However, there is increasing evidence to suggest that these subtypes behave differently, with different epidemiology, prognostic factors, patterns of spread, and failure after treatment. Emerging evidence also suggests that AC may be more radio resistant. Owing to the relative rarity of this tumor subtype, randomized studies have been challenging. This review summarizes the current data and provides some direction where treatment may differ between histological subtypes. Given the paucity of data, no attempt is made to create consensus guidelines but rather to summarize our existing understanding of this uncommon cancer.

EPIDEMIOLOGY

Whereas AC and SCC share many similar risk factors, there are also some differences. Both SCC and AC are associated with human papillomavirus (HPV) infection; however, there are some differences in the pattern of this association. Adenocarcinoma is associated with a higher likelihood of HPV-16 and HPV-18, which is present in more than 80% of cases.[1] Human papillomavirus 18 accounts for approximately 50% of AC but only 15% of SCC.[2] Squamous cell carcinoma is also associated with a wider diversity of uncommon HPV subtypes.

The use of oral contraceptives has been associated with an increased relative risk of cervical cancer, but the risk is similar for both SCC and AC.[3] In contrast, smoking is strongly associated with SCC of the cervix but seems to be less associated with AC.[4] Adenocarcinoma has been linked to several other risk factors more commonly associated with endometrial cancer, including obesity[1] and nulliparity.[5]

PROGNOSTIC FACTORS

The prognostic significance of histological subtype remains controversial. However, most studies suggest a worse prognosis for AC compared to SCC, with a 10% to 20% difference in 5-year overall survival (OS) rates.[6,7]

Clinical stage remains the most important prognostic factor for all cervix cancer subtypes, including AC. One study[8] involving 305 patients with AC found 5-year OS reduced from 80% in International Federation of Gynecology and Obstetrics stage I to 37% in stage 2 and less than 11% in stage 3. The difference between SCC and AC prognosis in early-stage cervical cancer is controversial. Kasamatsu et al[9] showed no difference, but Hopkins et al[10] showed a worse prognosis in AC compared with SCC. Nevertheless, it becomes more apparent as the stage increases.[8,10] Hopkins et al reported that patients with stage II squamous cell disease had a 62% survival compared with patients with AC who had 47% survival ($P = 0.01$); patients with stage III squamous cell disease had a 36% survival, compared with patients with AC who had 8% survival ($P = 0.002$).[10]

An example of the difficulty in ascertaining the prognostic significance of cell type is seen among prospective clinical trials performed by the Gynecologic Oncology Group (GOG). The GOG has a long history of combing AC and SCC together in their studies. On behalf of the GOG, Monk et al[11] retrospectively reviewed data from 335 women with primary, previously untreated, histologically confirmed invasive (stages IIB to IVA) cervical carcinoma who received weekly cisplatin and pelvic radiation while participating in similar arms of 2 GOG studies (protocols 120 and 165). This ancillary data project was only able to demonstrate a trend in worse survival for AC compared to SCC (PFS: hazard ratio, 1.40; $P = 0.147$ and OS: hazard ratio, 1.32: $P = 0.261$). This nonstatistical difference may clearly be a result of small numbers as only 11.4% had AC.[11]

Tumor size is also a significant prognostic factor. Differences in prognosis are less evident with small tumors but increase with larger tumor size. Several studies have shown that tumors greater than 4 cm had a poorer prognosis in AC compared with SCC.[7] Adenocarcinoma has also been reported to have a higher likelihood of lymph node involvement, compared to SCC, and a worse prognosis.[12]

For stage I AC, survival was significantly related to tumor differentiation, lymph node status, and amount of residual disease present in the cervix after radical hysterectomy. Survival was not significantly influenced by histologic subtype, patient's age, number of positive lymph nodes, or tumor size greater than 3 cm.[13]

Adenosquamous carcinoma is generally included with AC in most studies.[14] However, there are some data suggesting that AS has a poorer prognosis compared with AC.[15,16]

Patterns of Dissemination and Recurrence

There are also differences in the pattern of dissemination of advanced or recurrent disease with a possible higher rate of ovarian metastases seen with AC than SCC (5.31% vs 0.79%) and also a higher tendency for intra-abdominal carcinomatosis and hematogenous metastases compared with SCC.[17] Outcome for patients with ovarian metastasis is generally believed to be very poor and not related to International Federation of Gynecology and Obstetrics stage and histological type. The presence of ovarian metastasis has no correlation with lymph node involvement or parametrial invasion. Kuji et al[18] found that peritoneal cytology was positive in 9 patients (3.9%), with 3 (2.2%) of 139 patients having SCC and 6 (6.7%) of 89 patients having AC. Thirty percent of patients with SCC who had positive cytology had a recurrence, whereas all patients with AC had recurrence. In this single study, multivariate analysis revealed that peritoneal cytology ($P = 0.029$) and histological type ($P = 0.004$) were independent prognostic factors.[18]

One possible reason for the poor prognosis associated with AC in some studies might be a lower sensitivity to radiotherapy[19] as well as a higher rate of lymph node metastasis.[7,12] Subset analyses of several studies suggest higher recurrence rates after radiation in AC compared to SCC.[20] However, one study also shows a higher local control rate for

AC with postoperative adjuvant radiotherapy than for SCC.[20] In a prospective GOG trial, Peters et al[21] reported a similar prognosis for patients with AC and SCC when adjuvant treatment involved chemoradiotherapy after radical hysterectomy.

Tang et al[22] recently reported a large phase 3 study in 880 patients with stages IIB to IVA AC comparing concurrent chemoradiation therapy (CCRT) to chemoradiation with one cycle of cisplatin and paclitaxel followed by radiation then 2 further cycles of cisplatin/paclitaxel. Results showed an improved disease-free ($P < 0.05$), survival ($P < 0.05$), and long-term tumor control ($P < 0.05$) in patients receiving neoadjuvant and consolidation chemotherapy in addition to radiotherapy.[22]

There have also been several small studies in AC and substudies of patients with cervical cancer with metastatic disease receiving platinum-based combination chemotherapy showing activity similar if not better than seen with SCC. The GOG protocol 240 demonstrated that chemotherapy plus bevacizumab significantly improved OS in advanced and recurrent cervical cancer.[23] In an unplanned hypothesis generating subgroup analysis, the benefit conferred by bevacizumab was not sustained among the 27% with AC histology, suggesting that AC is a different disease than SCC when treated with antiangiogenesis therapy. Three other phase 3 GOG studies of chemotherapy in this setting have also been reviewed (179, 204, and 240). Binary exchange analysis was performed using the Pearson test to evaluate response rate, the Kaplan-Meier method to estimate progression-free survival and OS, and the Cox proportional hazards model to estimate the effect of histology on progression-free survival and OS. Eligible patients (N = 994) were evaluated, of whom 25% (n = 246) had AC/AS and 75% (n = 748) had SCC. There were no significant differences in response rates and time to response between histologic subgroups. The hazards of progression and death for AC + AS vs SCC were 1.13 (95% confidence interval [CI], 0.97–1.33; $P = 0.119$) and 0.97 (95% CI, 0.82–1.15; $P = 0.747$), respectively. The hazards of progression and death for AC vs SCC + AS were 1.01 (95% CI, 0.84–1.23; $P = 0.893$) and 0.89 (95% CI, 0.73–1.10; $P = 0.277$), respectively. The GOG protocol 240 was underpowered for AC/AS to draw any conclusions regarding the efficacy of incorporation of antiangiogenesis therapy in these uncommon histologies. Given the relative infrequency of AC + AS, these pooled data support the hypothesis that these histologic subtypes are not significantly different in their biologic response to systemic therapy in the recurrent/metastatic setting.[24]

PATHOLOGY

Fifty percent of cervical ACs are exophytic or polypoid, but 15% of patients have no visible lesion especially for early invasive AC or adenocarcinoma in situ.[25] In cases of invasive AC, immunohistochemistry is usually used to separate a primary endocervical tumor from an endometrial tumor, for instance, carcinoembryonic antigen and p16 expression (a surrogate of HPV) together with the absence of hormone receptors and vimentin favor a cervical origin.

Cervical ACs are subdivided into several categories[25] including endocervical, mucinous, villoglandular, endometrioid, clear cell, serous, mesonephric ACs, and AS carcinomas.

Endocervical AC of usual type represents the most frequent subtype of cervical ACs (90% of cases).

Mucinous ACs are subdivided into gastric type including its variant adenoma malignum, intestinal type, and signet-ring cell type. The adenoma malignum variant of gastric-type AC is the most difficult diagnosis because their well-differentiated tumor glands are difficult to distinguish from normal endocervical glands. In this case, the key histological feature is the depth of invasion together with clinical data. Somatic mutations of the *STK11* gene responsible for the Peutz-Jeghers syndrome have been described in 55% of these tumors.[26] The gastric-type cervical AC[27,28] is composed of glands with a pyloric phenotype (voluminous, clear, pale eosinophilic cytoplasm and distinct cell borders) and immunoprofile (HIK1083 and MUC6 expression). There is no association with HPV. Patients with this type of mucinous carcinomas have a poor prognostic with a decreased 5-year survival rate of 30% versus 77% for usual-type AC.

Villoglandular AC of the cervix is rare, showing a distinct exophytic and villopapillary growth. When superficially invasive, this variant has an excellent prognosis with very rare lymph node metastases.

Endometrioid (5% of cervical ACs), serous, and clear cell ACs are less frequent and exhibit the same morphological and phenotypic features of their endometrial and/or ovarian counterparts. Diagnosis of cervical serous AC should be made only when an ovarian or endometrial tumor has been excluded. As it is the case with vaginal tumors, cervical clear cell AC is associated with in utero exposure to diethylstilbestrol.

Finally, mesonephric AC, which arises from mesonephric remnants, is a very rare tumor located in the lateral and posterior wall of the cervix. The main characteristics of these tumors are the presence of eosinophilic hyaline secretion within tubules and the coexpression of both CD10 and vimentin in the absence of hormone receptors.[29]

In contrast to SCCs, which are the most frequent tumors of the cervix, a few molecular alterations have been described for ACs. Gene expression profiling showed upregulation of 4 genes (*CEACAM5*, *TACSTD1*, *S100P*, and *MSLN*) belonging to the tetraspanins family that might be associated with tumor progression.[30] More recently, oncogenic mutations have been identified in *PI3KCA* (25%) and *KRAS* (17.5%) genes.[31]

PRIMARY TREATMENT

The currently recommended treatment for AC of the uterine cervix, according to each disease stage, is described later in the text based on the National Comprehensive Cancer Network guideline.[32] Clear treatment differences between AC and SCC are not evidence based.

Adenocarcinoma in situ

Simple total hysterectomy (the cone is considered for fertility preservation)

Stage IA Adenocarcinoma

Invasions of 3 to 5 mm: type-B radical hysterectomy with retroperitoneal lymph node dissection Invasions of less than 3 mm: simple total hysterectomy is recommended. In cases where fertility preservation is needed, conization or trachelectomy is considered.

Stage IB/II AC

Radical hysterectomy or CCRT for patients with small tumors, less than 2 cm, and negative lymphovascular space invasion, the survival difference between AC and SCC is negligible, so the treatment strategy for the patients with AC should be same as that for the patients with SCC.

Although literatures showed inferior survival of stage IB1 (<4 cm),[33] radical hysterectomy or CCRT is the standard care because of the lack of evidence that adjuvant chemotherapy is efficacious to improve the survival.

In patients with tumor sizes greater than 4 cm and progressively advanced disease, CCRT is the primary treatment.[34] A pretherapeutic aortic nodal staging by laparoscopy has been proposed.[35,36]

Some Asian studies suggested that the prognosis of AC is worse than SCC in patients with pathologically high-risk factors after radical hysterectomy.[14,37]

Neoadjuvant chemotherapy followed by radical hysterectomy has been controversial[38,39]; however, it is of great interest by using less toxic regimen, docetaxel and carboplatin.[40]

Stage IIIA/IVA AC

Concurrent chemoradiation therapy (CCRT) mainly uses weekly administration of cisplatin. Standard radiotherapy (RT) technique is as follows[41]: Patients generally receive 40- to 45-Gy whole pelvic RT with 10-MV x-rays using either parallel-opposed anteroposterior or 4-field box beams, with 1.8 to 2 Gy per fraction and 5 fractions weekly. An extended field to the para-aortic region is not routinely given for patients without imaging findings of para-aortic lymphadenopathy. The parametria receives a boost of 57.6 Gy or less to 58 Gy using a parallel-opposed anteroposterior field with a 4-cm-wide midline block in patients with stage IIB or greater disease. The intracavitary brachytherapy boost is usually given using an iridium 192 source. The typical dose to point A was 4.3 Gy per fraction for 6 fractions, with 2 fractions weekly. The median cumulative dose and biologically equivalent dose to point A was 70.8 and 90 Gy, respectively, with the a/b ratio for tumor effects assumed to be 10 Gy. For patients with lower vaginal tumor extension, bladder or rectal invasion, or persistent bulky tumor after 44 to 45 Gy of initial RT, the external beam doses to the low pelvis are increased to 50 to 54 Gy without a central block, followed by either intracavitary brachytherapy or an additional primary tumor boost of 70 or less to 72 Gy without brachytherapy.

There is a report showing that CCRT with paclitaxel plus cisplatin is potentially more effective than single-agent cisplatin.[42]

Stage IVB AC

Systemic chemotherapy with platinum and paclitaxel is reasonable in patients with good performance status and is similar to those with recurrent disease.

TREATMENT OF METASTATIC DISEASE AND RELAPSE

The frequency of ovarian metastasis is higher in AC than in SCC (5% vs 0.8%).[17] The differences in the sites of recurrence suggest that SCC predominantly disseminates lymphatically, whereas AC may do so hematogenously.[17] The frequency of distant metastasis is higher in AC than in SCC.[7,43]

Chemotherapy Regimen

At present, the same chemotherapy regimen might be recommended for both AC and SCC[44]: paclitaxel plus cisplatin as standard treatment[45] and paclitaxel and carboplatin as alternative treatment (JCOG 0505). The effectiveness of paclitaxel[46,47] or docetaxel plus carboplatin[48] have been reported for AC. Adding bevacizumab is an option.[23]

Should AC be studied separately from SCC?

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REFERENCES

1. Castellsague X, Diaz M, de Sanjose S, et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. *J Natl Cancer Inst.* 2006;98:303–315.
2. Sherman ME, Wang SS, Carreon J, et al. Mortality trends for cervical squamous and adenocarcinoma in the United States. Relation to incidence and survival. *Cancer.* 2005;103:1258–1264.
3. Smith JS, Green J, Berrington de Gonzalez A, et al. Cervical cancer and use of hormonal contraceptives: a systematic review. *Lancet.* 2003;361:1159–1167.
4. Appleby P, Beral V, Berrington de Gonzalez A, et al. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. *Int J Cancer.* 2006;118:1481–1495.
5. Wang SS, Sherman ME, Hildesheim A, et al. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976–2000. *Cancer.* 2004;100:1035–1044.
6. Davy ML, Dodd TJ, Luke CG, et al. Cervical cancer: effect of glandular cell type on prognosis, treatment, and survival. *Obstet Gynecol.* 2003;101:38–45.
7. Eifel PJ, Burke TW, Morris M, et al. Adenocarcinoma as an independent risk factor for disease recurrence in patients with stage IB cervical carcinoma. *Gynecol Oncol.* 1995;59:38–44.
8. Baalbergen A, Ewing-Graham PC, Hop WC, et al. Prognostic factors in adenocarcinoma of the uterine cervix. *Gynecol Oncol.* 2004;92:262–267.
9. Kasamatsu T, Okada S, Tsuda H, et al. Early invasive adenocarcinoma of the uterine cervix: criteria for nonradical surgical treatment. *Gynecol Oncol.* 2002;85:327–332.
10. Hopkins MP, Morley GW. A comparison of adenocarcinoma and squamous cell carcinoma of the cervix. *Obstet Gynecol.* 1991;77:912–917.
11. Monk BJ, Tian C, Rose PG, et al. Which clinical/pathologic factors matter in the era of chemoradiation as treatment for locally advanced cervical carcinoma? Analysis of two Gynecologic Oncology Group (GOG) trials. *Gynecol Oncol.* 2007;105:427–433.
12. Irie T, Kigawa J, Minagawa Y, et al. Prognosis and clinicopathological characteristics of IB-IIB adenocarcinoma of the uterine cervix in patients who have had radical hysterectomy. *Eur J Surg Oncol.* 2000;26:464–467.
13. Hopkins MP, Schmidt RW, Roberts JA, et al. The prognosis and treatment of stage I adenocarcinoma of the cervix. *Obstet Gynecol.* 1988;72:915–921.
14. Mabuchi S, Okazawa M, Matsuo K, et al. Impact of histological subtype on survival of patients with surgically treated stage IA2-IIB cervical cancer: adenocarcinoma versus squamous cell carcinoma. *Gynecol Oncol.* 2012;127:114–120.
15. Look KY, Brunetto VL, Clarke-Pearson DL, et al. An analysis of cell type in patients with surgically staged stage IB carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol.* 1996;63:304–311.
16. Farley JH, Hickey KW, Carlson JW, Rose GS, et al. Adenosquamous histology predicts a poor outcome for patients with advanced-stage, but not early-stage, cervical carcinoma. *Cancer.* 2003;97:2196–2202.
17. Shimada M, Kigawa J, Nishimura R, et al. Ovarian metastasis in carcinoma of the uterine cervix. *Gynecol Oncol.* 2006;101:234–237.
18. Kuji S, Hirashima Y, Komeda S, et al. The relationship between positive peritoneal cytology and the prognosis of patients with FIGO stage I/II uterine cervical cancer. *J Gynecol Oncol.* 2014;25:90–96.
19. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage IB-IIA cervical cancer. *Lancet.* 1997;350:535–540.
20. Rotman M, Sedlis A, Piedmonte MR, et al. A phase III randomized trial of postoperative pelvic irradiation in stage IB cervical carcinoma with poor prognostic features: follow-up of a Gynecologic Oncology Group study. *Int J Radiat Oncol Biol Phys.* 2006;65:169–176.
21. Peters WA 3rd, Liu PY, Barrett RJ 2nd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol.* 2000;18:1606–1613.
22. Tang J, Tang Y, Yang J, et al. Chemoradiation and adjuvant chemotherapy in advanced cervical adenocarcinoma. *Gynecol Oncol.* 2012;125:297–302.
23. Tewari KS, Sill MW, Long HJ 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. *New Engl J Med.* 2014;370:734–743.
24. Seamon LG, Java JJ, Monk BJ, et al. Prognostic impact of histology in recurrent and metastatic cervical carcinoma: a Gynecologic Oncology Group Study. 15th miennial meeting of the Gynecologic Cancer Society; 2014, Melbourne, Australia; 2014.
25. Kurman RJ, Carcangiu ML, Herrington S, et al. *WHO Classification of Tumours of Female Reproductive Organs.* Lyon, France: IARC Press; 2014.
26. Kuragaki C, Enomoto T, Ueno Y, et al. Mutations in the STK11 gene characterize minimal deviation adenocarcinoma of the uterine cervix. *Lab Invest.* 2003;83:35–45.
27. Kojima A, Mikami Y, Sudo T, et al. Gastric morphology and immunophenotype predict poor outcome in mucinous adenocarcinoma of the uterine cervix. *Am J Surg Pathol.* 2007;31:664–672.
28. Mikami Y, Kiyokawa T, Hata S, et al. Gastrointestinal immunophenotype in adenocarcinomas of the uterine cervix and related glandular lesions: a possible link between lobular endocervical glandular hyperplasia/pyloric gland metaplasia and 'adenoma malignum'. *Mod Pathol.* 2004;17:962–972.
29. Kenny SL, McBride HA, Jamison J, et al. Mesonephric adenocarcinomas of the uterine cervix and corpus: HPV-negative neoplasms that are commonly PAX8, CA125, and HMGA2 positive and that may be immunoreactive with TTF1 and hepatocyte nuclear factor 1-beta. *Am J Surg Pathol.* 2012;36:799–807.
30. Chao A, Wang TH, Lee YS, et al. Molecular characterization of adenocarcinoma and squamous carcinoma of the uterine cervix using microarray analysis of gene expression. *Int J Cancer.* 2006;119:91–98.
31. Wright AA, Howitt BE, Myers AP, et al. Oncogenic mutations in cervical cancer: genomic differences between adenocarcinomas and squamous cell carcinomas of the cervix. *Cancer.* 2013;119:3776–3783.
32. NCCN Clinical Practice Guidelines in Oncology, Cervical Cancer. 2014. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.
33. Galic V, Herzog TJ, Lewin SN, et al. Prognostic significance of adenocarcinoma histology in women with cervical cancer. *Gynecol Oncol.* 2012;125:287–291.

34. Gien LT, Beauchemin MC, Thomas G. Adenocarcinoma: a unique cervical cancer. *Gynecol Oncol.* 2010;116:140–146.
35. Ramirez PT, Jhingran A, Macapinlac HA, et al. Laparoscopic extraperitoneal para-aortic lymphadenectomy in locally advanced cervical cancer: a prospective correlation of surgical findings with positron emission tomography/computed tomography findings. *Cancer.* 2011;117:1928–1934.
36. Ramirez PT, Milam MR. Laparoscopic extraperitoneal paraaortic lymphadenectomy in patients with locally advanced cervical cancer. *Gynecol Oncol.* 2007;104 (2 suppl 1):9–12.
37. Huang YT, Wang CC, Tsai CS, et al. Clinical behaviors and outcomes for adenocarcinoma or adenosquamous carcinoma of cervix treated by radical hysterectomy and adjuvant radiotherapy or chemoradiotherapy. *Int J Radiat Oncol Biol Phys.* 2012;84:420–427.
38. Katsumata N, Yoshikawa H, Kobayashi H, et al. Phase III randomised controlled trial of neoadjuvant chemotherapy plus radical surgery vs radical surgery alone for stages IB2, IIA2, and IIB cervical cancer: a Japan Clinical Oncology Group trial (JCOG 0102). *Br J Cancer.* 2013;108:1957–1963.
39. Kim HS, Sardi JE, Katsumata N, et al. Efficacy of neoadjuvant chemotherapy in patients with FIGO stage IB1 to IIA cervical cancer: an international collaborative meta-analysis. *Eur J Surg Oncol.* 2013;39:115–124.
40. Takekida S, Fujiwara K, Nagao S, et al. Phase II study of combination chemotherapy with docetaxel and carboplatin for locally advanced or recurrent cervical cancer. *Int J Gynecol Cancer.* 2010;20:1563–1568.
41. Huang YT, Wang CC, Tsai CS, et al. Long-term outcome and prognostic factors for adenocarcinoma/adenosquamous carcinoma of cervix after definitive radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011;80:429–436.
42. Nagai Y, Toita T, Wakayama A, et al. Concurrent chemoradiotherapy with paclitaxel and cisplatin for adenocarcinoma of the cervix. *Anticancer Res.* 2012;32:1475–1479.
43. Eifel PJ, Morris M, Oswald MJ, et al. Adenocarcinoma of the uterine cervix. Prognosis and patterns of failure in 367 cases. *Cancer.* 1990;65:2507–2514.
44. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol.* 2009;27:4649–4655.
45. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol.* 2004;22:3113–3119.
46. Curtin JP, Blessing JA, Webster KD, et al. Paclitaxel, an active agent in nonsquamous carcinomas of the uterine cervix: a Gynecologic Oncology Group Study. *J Clin Oncol.* 2001;19:1275–1278.
47. Kastritis E, Bamias A, Efstathiou E, et al. The outcome of advanced or recurrent non-squamous carcinoma of the uterine cervix after platinum-based combination chemotherapy. *Gynecol Oncol.* 2005;99:376–382.
48. Nagao S, Fujiwara K, Oda T, et al. Combination chemotherapy of docetaxel and carboplatin in advanced or recurrent cervix cancer. A pilot study. *Gynecol Oncol.* 2005;96:805–809.

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Phase III placebo-controlled double-blind randomized trial of radiotherapy for stage IIB–IVA cervical cancer with or without immunomodulator Z-100: a JGOG study

T. Sugiyama[1], K. Fujiwara[2*], Y. Ohashi[3], H. Yokota[4], M. Hatae[5], T. Ohno[6], Y. Nagai[7], N. Mitsuhashi[8], K. Ochiai[9] & K. Noda[10]

[1]Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Morioka; [2]Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka; [3]Department of Biostatistics, School of Public Health, The University of Tokyo, Tokyo; [4]Department of Gynecology, Saitama Cancer Center, Saitama; [5]Department of Obstetrics and Gynecology, Kagoshima City Hospital, Kagoshima; [6]Gunma University Heavy Ion Medical Center, Maebashi; [7]Department of Obstetrics and Gynecology, University of the Ryukyus, Okinawa; [8]Department of Radiation Oncology, Tokyo Women's Medical University School of Medicine, Tokyo; [9]Department of Obstetrics and Gynecology, Jikei University School of Medicine, Tokyo; [10]Department of Obstetrics and Gynecology, Kinki University, Osakasayama, Japan

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Background: Based on the result of our previous study showing better overall survival (OS) at the lower dose (0.2 μg) of immunomodulator Z-100 than higher dose (40 μg) in patients with locally advanced cervical cancer who received radiotherapy, we conducted a placebo-controlled double-blind randomized trial.

Patients and methods: Patients of stages IIB–IVA squamous cell carcinoma of the uterine cervix were randomly assigned to receive Z-100 at 0.2 μg (Z) or placebo (P). The study agent was given subcutaneously twice a week during the radiotherapy, followed by maintenance therapy by administering once every 2 weeks until disease progression. Primary end point was OS, and secondary end points were recurrence-free survival, and toxicity.

**Correspondence to:* Prof. Keiichi Fujiwara, Department of Gynecologic Oncology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka-City, Saitama 350-1298, Japan. Tel: +81-42-984-4111; Fax: +81-42-984-4741; E-mail: fujiwara@saitama-med.ac.jp

Results: A total of 249 patients were randomized. Death events occurred extremely slower than expected, and Independent Data Monitoring Committee recommended to analyze the survival result prematurely. The 5-year OS rate was 75.7% [95% confidence interval (CI) 66.4% to 82.8%] for Arm Z and 65.8% (95% CI 56.2% to 73.8%) for Arm P ($P = 0.07$); hazard ratio was 0.65 (95% CI 0.40–1.04). Survival benefit in Arm Z was observed regardless of chemoradiation or radiation alone. There was no trend in recurrence-free survival between the two arms. Side-effects were not different between two arms.

Conclusion: Z-100 showed a trend of improvement on OS in locally advanced cervical cancer, although the statistical power was less than anticipated because survival rates were unexpectedly higher than expected for both arms. Validation of potential survival benefit of immune modulation should be made.

Trial registration: umin.ac.jp/ctr Identifier: C000000221.

Key words: cervical cancer of the uterus, chemoradiotherapy, radiotherapy, immunotherapy, dose of immunomodulator, Z-100

introduction

Although concurrent cisplatin-based chemoradiotherapy has been shown to improve the overall survival (OS) compared with radiotherapy alone [1, 2], prognosis of advanced cervical cancer is not satisfactory. To improve the efficacy of chemoradiotherapy further, other modalities have been investigated, such as adjuvant chemotherapy following chemoradiotherapy [3] or combining chemotherapy and immunotherapy [4].

Z-100 is a hot-water extract from human bacillus tuberculosis containing polysaccharides such as arabinomannan and mannan. It is an immunomodulatory agent, and its carcinostatic potential was reported in 1966 [5].

In recent preclinical studies, the administration of Z-100 in combination with the radiation showed the inhibitory action of pulmonary metastasis in tumor-bearing mice model [6]. Moreover, the combination of Z-100 with the radiation showed the prolongation of survival time in tumor-bearing mice model [6]. The effect of Z-100 was expressed by the improvement of the helper T-cell response from type 2 dominant to type 1 dominant state via upregulation of interferon-γ and interleukin-12 productions [7, 8].

We have conducted two clinical studies. The first study was a dose-finding randomized phase II trial (2 versus 20 versus 40 μg) with radiotherapy. In this study, 40 μg was the most effective dose in terms of tumor response [9]. Based on this result, we conducted a double-blind randomized phase III trial. At the time of designing the trial, a placebo-controlled trial comparing with 40 μg was attempted, but it was impossible to use placebo due to social and ethical considerations. Therefore, we conducted a randomized phase III trial comparing 0.2 (substitute to placebo) versus 40 μg of Z-100 with radiotherapy for stage III cervical cancer of the uterus [10]. Unexpectedly, OS was better in the low-dose group than in the high-dose group. We looked at the historical survival data and found that the 5-year survival rate of the high-dose Z-100 group appeared to be similar to that of radiotherapy alone [11].

Therefore, we hypothesized that low-dose Z-100 improved OS although administering a higher dose of Z-100 did not show survival benefit [10]. To prove this hypothesis, we conducted the current trial to test whether low-dose Z-100 demonstrates a survival benefit over placebo.

patients and methods

This is a double-blinded placebo-controlled phase III trial to compare the efficacy of low-dose (0.2 μg) Z-100 and placebo in patients with locally advanced cervical cancer.

patients

Eligible patients were the International Federation of Gynecology and Obstetrics (FIGO) stage IIB–IVA squamous cell carcinoma of the uterine cervix without having suspicion of para-aortic lymph node metastasis. The patients were scheduled to undergo radiotherapy with or without cisplatin-based concurrent chemotherapy. Patients must be between 20 and 79 years old with a performance status of 0, 1, or 2. For patients who were scheduled to undergo chemoradiotherapy, creatinine clearance must be greater or equal to 60 ml/min.

We excluded those patients who had double cancer, other invasive cancer treated within 5 years, renal disease except hydronephrosis due to cervical cancer. Patients who were allergic to platinum agents were excluded, if there were plans to treat the patients with chemoradiation.

Representative hematoxylin–eosin-stained microscopic slides of the primary site before radiotherapy were reviewed by the Central Pathology Review Committee. The Image Evaluation Committee confirmed that there was no para-aortic lymph node metastasis by computer tomography scan, and the tumor size was estimated by magnetic resonance imaging.

This trial was approved by each institutional ethical review board and all patients must sign the informed consent form.

randomization

Patients were randomly assigned in a ratio of 1:1 to receive Z-100 or placebo in a blinded manner by the central registration system. Randomization was carried out with dynamic allocation by minimization method with the biased-coin method. The allocation factors were FIGO stage (IIB versus IIIA versus IIIB low-intermediate versus IIIB high versus IVA), plan to perform combined use of cisplatin during the radiotherapy period (yes versus no), plan to perform adjuvant chemotherapy to response case (yes versus no) and facility. Stratification was made by degree of the parametrium, low-intermediate or high. Pelvic wall invasion is unilateral, and its degree is from low to medium. Low-intermediate was defined when parametrial invasion was unilateral or if the degree of parametrial invasion is not sure whether moderate or severe. When parametrial invasion was bilateral, or unilateral with definitely high it was classified to be high.

The study sponsor, study personnel, and patients remained masked to treatment assignment until completion of the study.

treatment schedule

administration of Z-100. Z-100 or placebo was administered twice a week during the radiotherapy, and also given once every 2 weeks during the follow-up period. Z-100 or placebo was administered until progression or recurrence.

radiotherapy

The radiotherapy was scheduled based on the guideline [12] from the Japan Society of Obstetrics and Gynecology. Patients were treated with a combination of external beam and intracavitary irradiation. External beam radiotherapy (EBRT) was delivered to the whole pelvis through anterior and posterior parallel-opposed portals or the 4-field box technique using ≥6-MV X-rays. The clinical target volume included the cervical tumor, uterus, parametrium, at least the upper half of the vagina, and the pelvic lymph nodes. EBRT was given at 1.8–2.0 Gy per fraction, five times per week. A central shield was inserted in the radiation field after delivering 30–40 Gy to the whole pelvis, in principle. The planned total dose to the pelvic sidewall was 50 Gy, but modification of the dose was allowed based on the tumor volume.

With regard to intracavitary brachytherapy (ICBT), tandem and ovoid applicators were used, and X-ray-based 2D treatment planning was built for all patients. Either high-dose rate or low-dose rate treatment was given according to the institutional practice. Most common schedule of high-dose rate ICBT was 24 Gy in 4 fractions to point A, carried out weekly during central shielding EBRT. In low-dose rate ICBT, the prescribed dose to point A was 20–50 Gy in 2–3 fractions. The Radiotherapy Committee reviewed compliance with the radiotherapy.

When chemoradiotherapy was applied, cisplatin-based chemotherapy must be used. Weekly administration of cisplatin at 30–40 mg/m^2 and a total of 150–300 mg/m^2 were recommended. The decision to treat with chemoradiotherapy or radiotherapy alone was up to the physician's discretion based on each patient's condition.

response rate

Evaluations are to be made in five stages through gynecological palpation and rectal examination according to the following criteria. Complete response (CR): tumor disappeared (the size of the cervical section has returned to normal); partial response (PR): tumor is reduced by 50% or more; minor response (MR): tumor is reduced 25% or more; no change (NC): no change in tumor; progressive disease (PD): tumor increased in size. CR and PR are defined as 'respond case.' The response rates were calculated as follows. Response rate (%) = (number of respond case) × 100/number of evaluated cases.

adjuvant chemotherapy

Since the subset analysis in our previous study demonstrated a favorable result by administering adjuvant chemotherapy using oral 5-FU or tegafur-uracil, we allowed each institution to decide on the use of adjuvant chemotherapy. In other words, each institution had to declare before the trial started whether they would administer the adjuvant chemotherapy. For adjuvant chemotherapy, only oral agents of 5-FU, tegafur-uracil, or doxifluridine were allowed. These agents were administered daily until progression or unacceptable toxicity occurred.

adverse events

All adverse events regarding Z-100 or chemotherapy or radiotherapy were reported until the time of objective disease progression. The survey period of an adverse event is from the starting day of treatment to the final administration day +28 days. In case where an adverse event occurred the severity was to be judged as mild, moderate or severe. Late toxicity was evaluated according to RTOG-EORTC Late Radiation Morbidity Scoring Schema [13].

statistical analysis

end points. The primary end point of this study was OS, and recurrence-free survival, tumor response, and toxicity were the secondary end points.

The estimated total sample size was 240 to detect an 18% increase in the 5-year survival rate, assuming that the 5-year survival rate for the Z-100 group is 60% [i.e. a hazard ratio (HR) of 1.7 for placebo over Z-100.), significance level of 5% (two-sided), power of 80%, 2-year recruitment period, and 3.5-year follow-up period. We planned an interim analysis after 80 deaths to specify the follow-up period.

OS and recurrence-free survival were compared between treatment groups with a log-rank test; HRs [with 95% confidence interval (CI)] were calculated from score statistics of log-rank test; and Kaplan–Meier estimates were calculated for each treatment group. Tumor response rates were compared between treatment groups with Fisher's exact tests. Adverse events and laboratory abnormalities were reported by treatment group, category, and worst grade.

In efficacy analyses, OS was based on the full-analysis set (FAS) following the intention-to-treat principle and recurrence-free survival was based on the patients who had a tumor response in FAS. Toxicity analyses included all patients who received at least one dose of study drug. SAS (version 9.1.3) was used for statistical analysis.

results

The study opened September 2004 and closed for enrollment in October 2006. A total of 249 patients were enrolled from 61 institutions, and 123 patients were randomized to the Z-100 group and 126 patients were allocated to the placebo group (supplementary Figure S1, available at *Annals of Oncology* online).

patients characteristics

The demographic and clinical characteristics of the patients were similar in both groups (Table 1) in terms of age, performance status, stage, chemoradiotherapy or radiotherapy alone, and with or without adjuvant chemotherapy. Of patients, 70%–75% received chemoradiotherapy, and more than 90% received no adjuvant chemotherapy. The median doses and overall treatment time was also equivalent for both groups.

efficacy

The death events occurred much slower than expected (supplementary Figure S2, available at *Annals of Oncology* online). Therefore, the Independent Data Monitoring Committee recommended stopping the trial after the 5-year follow-up period was passed because it would take years to reach the required event number, but survival can be estimated with 5-year survival. Therefore, the committee decided further follow-up was unethical. The recalculated power was approximately 0.7 for this situation. The clinical cutoff date for the analyses presented here was November 2011. With a median follow-up of 70 months at the time of data cutoff, 67 deaths had occurred before unblinding.

Figure 1A shows the Kaplan–Meier curve for the OS of patients. The 5-year survival rate of the Z-100 group was 75.7%, whereas that of the placebo group was 65.8%. The HR of death was 0.65 (95% CI 0.40–1.04, $P = 0.07$). Although the overall

Table 1. Characteristic of the patients and radiotherapy

Characteristics	Z-100 group ($N = 121$)	Placebo group ($N = 122$)	P value
Age, years			
Mean (SD)	60 (11)	60 (12)	0.80[a]
Median (range)	61 (32–79)	62 (31–79)	
Performance status, no. of patients (%)			
0	97 (80)	101 (83)	0.43[b]
1	23 (19)	18 (15)	
2	1 (1)	3 (3)	
FIGO stage, no. of patients (%)			
II	55 (46)	52 (43)	0.93[b]
III	59 (49)	63 (52)	
IV	7 (6)	7 (6)	
Cisplatin, no. of patients (%)			
No	30 (25)	33 (27)	0.77[b]
Yes	91 (75)	89 (73)	
Adjuvant chemotherapy, no. of patients (%)			
No	114 (94)	111 (91)	0.46[b]
Yes	7 (6)	11 (9)	
External beam Radiotherapy, Gy			
Median total dose (range)	50 (45–60)	50 (45–60)	0.65[a]
Intracavitary brachytherapy, Gy[c]			
HDR median point A dose (range)[d]	24 (5–35)	24 (1–30)	0.49[a]
LDR median point A dose (range)[e]	30 (28–42)	36 (30–40)	0.55[a]
Overall treatment time, days			
Median (range)	49 (35–79)	50 (39–101)	0.08[a]

[a]Wilcoxon rank sum test.
[b]Fisher's exact test.
[c]In Z-100 group, three patients did not carry out the intracavitary brachytherapy.
[d]Z-100 group ($n = 115$), Placebo group ($n = 117$).
[e]Z-100 group ($n = 3$), Placebo group ($n = 5$).
HDR, high-dose rate; LDR, low-dose rate.

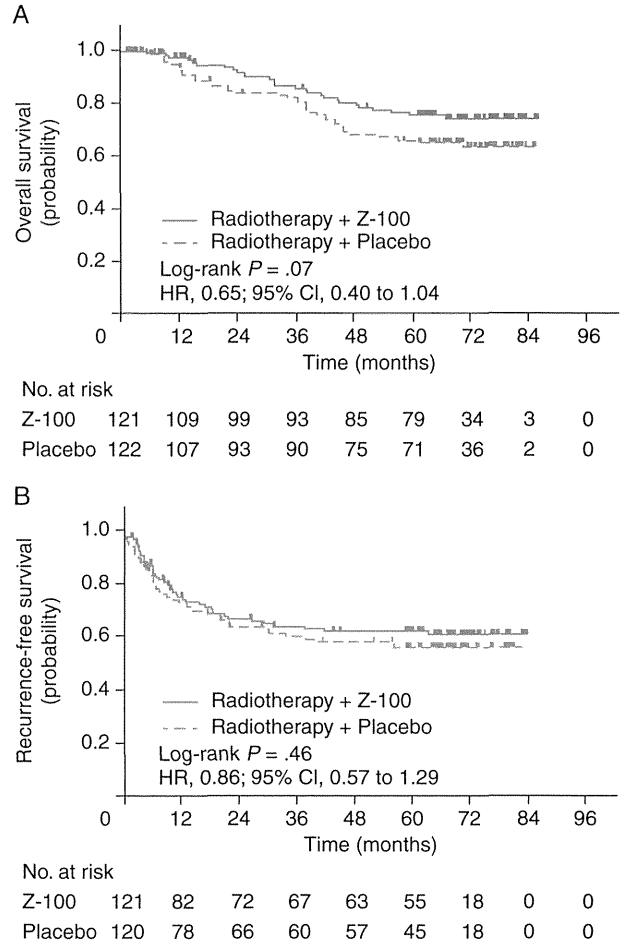

Figure 1. Overall survival curves and recurrence-free survival. Panel (A) shows overall survival. Panel (B) shows recurrence-free survival. The 5-year survival rates of patients assigned to Z-100 and those assigned to placebo are 75.7% versus 65.8% (A). HR, hazard ratio.

treatment time was longer in the placebo group, Cox regression with covariates including overall treatment time showed similar result (HR = 0.70).

There was no difference in recurrence-free survival between the two groups (Figure 1B). We carried out subset analysis on OS (Figure 2), and found that Z-100 improved the survival in almost all patients' populations, particularly for patients with stage III (Figure 2; $P = 0.03$), and the survival showed a trend in favor of the Z-100 group regardless of chemoradiotherapy or radiotherapy.

The response rate was 99% of the Z-100 group (CR 82, PR 37/120), the placebo group 99% (CR 66, PR 54/121). No significant difference in the response rate between the two groups.

Site of recurrence were summarized in Table 2. There was no difference between the treatment groups.

adverse events

Major adverse events during the radiotherapy or concurrent chemoradiotherapy were similar in both groups (Table 3). The late adverse events (the Z-100 group/the placebo group, number of case) of grade 3 or 4 was the hematological (2/1), gastrointestinal (3/3), renal or genitourinary (3/2), reproductive (0/3) and others (2/1). There was no difference in the late adverse events associated with radiotherapy between the two groups (supplementary Table S1, available at *Annals of Oncology* online).

discussion

This study is the first placebo-controlled double-blind randomized phase trial of the immunomodulating agent for locally advanced cervical cancer. The trial design of this study is an obvious strength of the study. It was unfortunate, however, that the difference in OS improvement was not statistically significant, because the events were fewer than expected, therefore further evaluation for this agent will be needed. Despite the statistical insignificance, we believe that this study shows clinical benefit of combination of Z-100. The magnitude of hazard reduction of death of the patients who received Z-100, where HR = 0.65, was similar to the results shown in the chemoradiotherapy trials in 1999 [1].

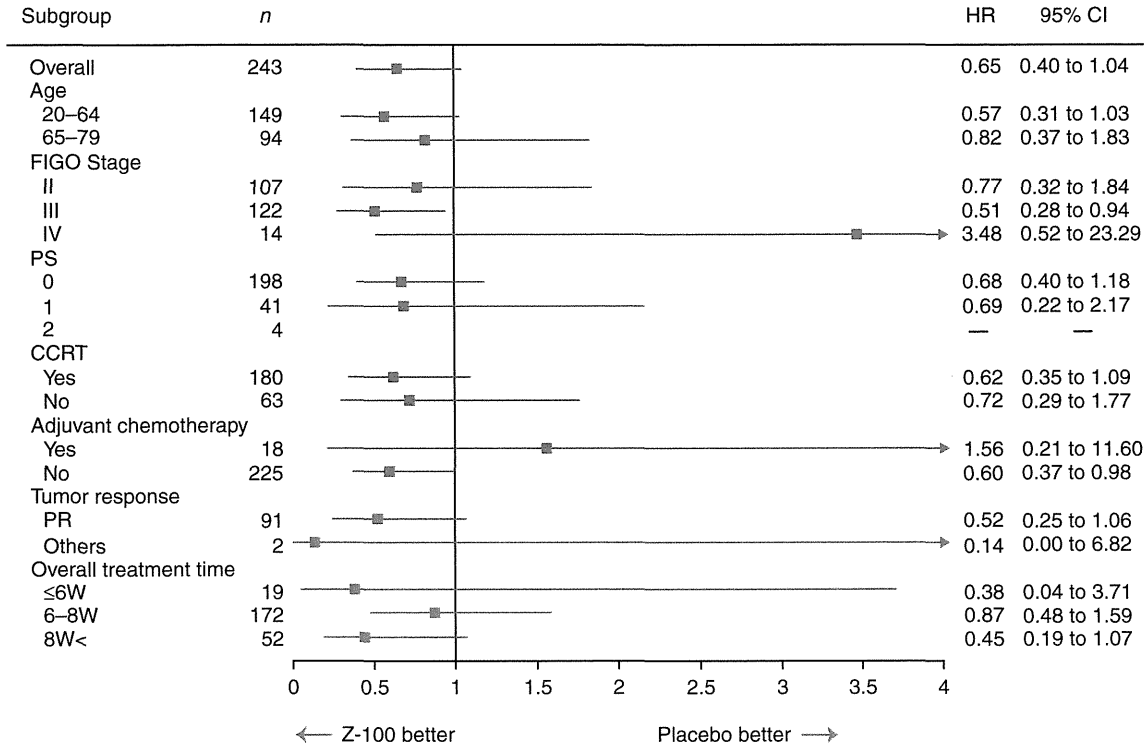

Figure 2. Hazard ratios for the risk of death, according to subgroup. Horizontal lines represent confidence intervals. PS, performance status; CCRT, concurrent chemoradiothrapy; HR, hazard ratio; CR, complete response; PR, partial response.

Table 2. Site of recurrence

Site of recurrence	Z-100 group		Placebo group	
	N	Death (%)	*N*	Death (%)
Local	11	9 (82)	20	15 (75)
Distant	31	16 (52)	25	14 (56)
Local + distant	2	1 (50)	3	2 (67)
Total	44	26 (59)	48	31 (65)

The reason of fewer occurrences of the events might be because more stage IIB patients were enrolled than we expected. At the time of planning of this study, Japanese gynecologic oncologists more likely perform radical hysterectomy for stage IIB cervical cancer. Also, more patients received chemoradiotherapy than we expected, although chemoradiotherapy was not widely accepted as the standard of care in the Japanese population. Because of these two factors, the survival of the placebo group appeared to exceed our predictions.

Subset analysis showed a significant improvement of OS in the stage III patients (Figure 2) in combination with Z-100. This observation was in contrast to the result from the meta-analysis study for chemoradiotherapy in cervical cancer, which demonstrated the HR of survival was significantly less in the stage III–IVA patients [2]. Therefore, Z-100 may be more effective for the patients with more advanced cases with radiotherapy.

In this trial, OS benefit was observed, but recurrence-free survival was not different from placebo. At this time, there is no good explanation for this observation; therefore, this might be a chance finding. However, it might be a common observation for the immunotherapy, as shown in the sipuleucel-T cancer vaccine trial for castration-resistant prostate cancer [14].

One possible explanation might be the enhancement of the systemic immune function by long exposure to Z-100. Also, more patients experienced distant recurrence in the Z-100 group ($n = 31$) than in the placebo group ($n = 25$), but almost the same number of patients died (16 versus 14). However, these observations are inconsistent with the results from our previous trial; therefore, the mechanism of this observation should be investigated fully in the future.

Z-100 has been shown to be safe in the current study as well as in our previous trials. Only a minor skin reaction at the injection site has been reported. This is in contrast to other immunotherapy agents, such as sipuleucel-T [14] or ipilimumab [15], which improved an OS but showed more adverse events. Z-100 did not enhance acute or late radiation-related toxicities.

This compound is convenient for both patients and health care providers because it can be administered as a subcutaneous injection, twice a week during radiotherapy and once every 2 weeks afterward.

The most important finding from this trial and our previous trial is that immunomodulatory agent like as Z-100 may improves OS in combination of radiotherapy for locally advanced cervical cancer, even though there is no dose dependency [10]. Therefore, finding the optimal dose and dosing schedule seems to be important to further improve the OS in future trials; however, it will be extremely difficult to conduct

Table 3. Adverse events during radiotherapy

Adverse events	Z-100 group (n = 122)			Placebo group (n = 122)			P value*
	Mild, N (%)	Moderate, N (%)	Severe, N (%)	Mild, N (%)	Moderate, N (%)	Severe, N (%)	
Hematological toxic							
Anemia	8 (7)	7 (6)	0	11 (9)	11 (9)	0	0.45
Leukopenia	6 (5)	3 (3)	0	10 (8)	8 (7)	4 (3)	0.04
Neutropenia	1 (1)	1 (1)	0	1 (1)	1 (1)	1 (1)	1.00
Nonhematological toxic							
Gastrointestinal							
Colitis	0	3 (3)	0	3 (3)	0	0	0.06
Dyspepsia	14 (12)	0	0	8 (7)	1 (1)	0	0.26
Constipation	24 (20)	3 (3)	0	29 (24)	4 (3)	0	0.69
Diarrhea	76 (62)	19 (16)	0	78 (64)	19 (16)	0	0.98
Intestinal obstruction	0	0	0	1 (1)	0	0	1.00
Nausea	67 (55)	14 (12)	1 (1)	57 (47)	22 (18)	1 (1)	0.41
Vomiting	40 (33)	12 (10)	1 (1)	37 (30)	15 (12)	0	0.80
Skin							
Radiation dermatitis	14 (12)	2 (2)	0	13 (11)	1 (1)	0	0.88
Dermatitis	8 (7)	0	0	10 (8)	1 (1)	0	0.63
Renal or genitourinary							
Cystitis	15 (12)	1 (1)	0	11 (9)	7 (6)	0	0.07
Dysuria	4 (3)	0	0	4 (3)	1 (1)	0	1.00
Pollakiuria	2 (2)	0	0	6 (5)	0	0	0.28
Renal dysfunction	0	1 (1)	0	2 (2)	0	0	0.50
Neurologic							
Dysgeusia	11 (9)	0	0	6 (5)	1 (1)	0	0.31
Headache	15 (12)	2 (2)	1 (1)	16 (13)	0	0	0.58
Peripheral neuropathy	3 (3)	0	0	1 (1)	0	0	0.62
Others							
Anorexia	41 (34)	14 (12)	1 (1)	39 (32)	17 (14)	3 (3)	0.75
Fatigue	33 (27)	5 (4)	1 (1)	34 (28)	5 (4)	0	1.00
Radiation-associated pain	5 (4)	3 (3)	0	5 (4)	3 (3)	0	1.00

*Fisher's exact test.

Mild: the symptom can be felt or sensible but tolerable. Moderate: the symptom mildly affects the daily life. Severe: the symptom severely affects a daily life.

these trials, because higher or lower dose of Z-100 than 0.2 μg may reduce the efficacy.

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disclosure

TS, KF, YO, MH, NM, KO, and KN have had an advisory role for ZERIA Pharmaceutical Co., Ltd. Other authors have declared no conflicts of interest.

references

1. Rose PG, Bundy BN, Watkins EB et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999; 340: 1144–1153.
2. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 2008; 26: 5802–5812.
3. Duenas-Gonzalez A, Zarba JJ, Patel F et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. J Clin Oncol 2011; 29: 1678–1685.
4. Wilailak S, Dangprasert S, Srisupundit S. Phase I clinical trial of chemoimmunotherapy in combination with radiotherapy in stage IIIB cervical cancer patients. Int J Gynecol Cancer 2003; 13: 652–656.
5. Maruyama C. On the treatment of malignant tumor with an extract from tubercle bacilli (in Japanese). Jpn J Dermatol 1966; 76: 399–404.
6. Oka H, Sasaki H, Shiraishi Y et al. Z-100, an immunomodulatory arabinomannan extracted from Mycobacterium tuberculosis strain Aoyama B, augments anti-tumor activities of X-ray irradiation against B16 melanoma in association with the improvement of type 1T cell responses. Biol Pharm Bull 2004; 27: 82–88.
7. Oka H, Shiraishi Y, Sasaki H et al. Antimetastatic effect of an immunomodulatory arabinomannan extracted from Mycobacterium tuberculosis strain Aoyama B, Z-100, through the production of interleukin-12. Biol Pharm Bull 2003; 26: 1336–1341.
8. Oka H, Emori Y, Sasaki H et al. Anti-tumor mechanism of Z-100, an immunomodulatory Arabinomannan extracted from Mycobacterium tuberculosis strain Aoyama B, on pulmonary metastases of B16F10 melanoma: restoration of helper T cell responses via suppression of glucocorticoid-genesis. Microbiol Immunol 2002; 46: 343–351.
9. Noda K, Ohashi Y, Okada H et al. Randomized phase II study of immunomodulator Z-100 in patients with stage IIIB cervical cancer with radiation therapy. Jpn J Clin Oncol 2006; 36: 570–577.
10. Noda K, Ohashi Y, Sugimori H et al. Phase III double-blind randomized trial of radiation therapy for stage IIIb cervical cancer in combination with low- or high-dose Z-100: treatment with immunomodulator, more is not better. Gynecol Oncol 2006; 101: 455–463.
11. Ueki M. The 36th annual report of the treatment, Gynecological Oncology Committee of Japan Society of Obstetrics and Gynecology (in Japanese). Acta Obstet Gynaecol Jpn 2001; 53: 1136–1169.
12. Japan Society of Obstetrics and Gynecology, The Japanese Society of Pathology, Japan Radiological society (eds). The General Rules for Clinical and Pathological Management of Uterine Cervical Cancer. Tokyo: Kanehara 1997.
13. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995; 31: 1341–1346.
14. Kantoff PW, Higano CS, Shore ND et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363: 411–422.
15. Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363: 711–723.