[Review Article]

がん領域における研究者主導臨床試験の安全性情報マネジメント

Clinical Safety Data Management in Investigator-Initiated, Oncology Clinical Trials

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1　わが国の臨床試験の安全性情報管理

臨床試験において安全性情報を適切に収集することは，試験的治療（試験薬・試験機器・試験的手技など）の安全性の評価を正しく実施するために必須である。また，臨床試験に参加する被験者の保護，ならびに将来その試験的治療が適切に実施されるためにも不可欠である。

現在，本邦の臨床試験は，目的および規制要件(規制を受ける法令や通知，指針等）により，医薬品の承認申請を目的とする治験とそれ以外の臨床試験(研究者主導臨床試験ならびに先進医療)に区別されている。この区別によって，報告対象・報告期限・報告先は若干異なっている。

治験は，医薬品・医療機器の製造販売承認を得ることを目的に実施される臨床試験であり，関係する企業，医師，医療従事者は，安全性情報の管理についても薬事法や「医薬品の臨床試験の実施の基準に関する省令（GCP 省令)」などの法規を遵守しなければならない。先進医療として実施する臨床試験では，将来そのデータが承認申請資料の一部となりうることを考慮し，厚生労働省の医政局・医薬食品局・保健局が合同で発出した通知[1]に基づき，適切な安全性情報の管理を行わなければならない。

治験以外の研究者主導臨床試験においては，「臨床研究に関する倫理指針」などの各種倫理指針[2]に従うことになる。倫理指針は，研究機関が自主的に遵守することを目的に制定されているため，法的拘束力はない。しかしながら，研究者は指針の枠組みの中で収集ならびに報告が必要となる安全性情報について，臨床試験の内容（疾患や病態の特殊性等）を考慮したうえで，プロトコルや手順書に独自の安全性情報管理手順を定めて試験を実施している。

さらに，この区別は医療機関での試験実施体制にも違いをもたらしており，特に研究者主導臨床試験

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表 1 安全性情報の取扱いに関連する法規

ICH-E2A
ICH-E2D
ICH-GCP（E6）
NCI Guidelines：Adverse Event Reporting Requirements
医薬品の臨床試験の実施の基準に関する省令（平成 9 年厚生省令第 28 号）
医薬品の臨床試験の実施の基準（GCP）の内容（中央薬事審議会答申）（平成 9 年 3 月 13 日）
「「医薬品の臨床試験の実施の基準に関する省令」のガイダンスについて」の一部改正等について（平成 25 年 4 月 4 日薬食審査発 0404 第 4 号）
臨床研究に関する倫理指針
先進医療通知（医政発 0731 第 2 号，薬食発 0731 第 2 号，保発 0731 第 7 号）（2012 年 7 月 31 日）
薬事法施行規則等の一部を改正する省令（平成 24 年 12 月 28 日薬食発 1228 第 1 号）

では，治験と比べて CRC などのサポート体制が十分でないために，安全性情報の管理は試験担当医師のみが関与している場合が多い。

また，がん領域の臨床試験では有害事象の評価基準として NCI CTCAE（Common Terminology Criteria for Adverse Events）が一般的に用いられているが，CTCAE による“Grade 評価”と法規による“重篤”の定義をいかにマッチングするかについてこれまでほとんど議論されてこなかったために，研究者間の統一見解が得られていない。

これらの理由から，研究代表者や研究事務局はプロトコル単位で安全性情報の管理手順を確認しなければならない。一方，参加医療機関ではサポート体制が不十分であるにもかかわらず，研究者は研究グループやプロトコルごとに異なる安全性情報の報告手順に個別に対応しなければならない現状にある。

JGOG（Japanese Gynecologic Oncology Group：婦人科悪性腫瘍研究機構）データセンターでは，2011 年より臨床試験の種類別に「関連法規に定められた安全性情報の遵守事項」ならびに「CTCAE と重篤な有害事象（Serious Adverse Event：SAE）の関係性」を整理して標準化することにより，研究者主導臨床試験の安全性情報管理の確実性と効率性の向上に取り組んでいる。

2 がん領域の研究者主導臨床試験における重篤な有害事象報告体制の現状

がん領域の研究者主導臨床試験の多くは，多施設共同臨床試験グループ主導で実施されている。臨床試験グループでは，各種規制やガイドラインに準じた有害事象報告体制を策定し，それぞれに運用している。詳細な臨床情報の報告を義務づける対象となる重篤な有害事象や報告期限，報告内容等は臨床試験グループごとに若干異なっているのが現状である。それゆえに参加医療機関の研究者は，グループごとに異なる規準と手順に従って当該臨床試験の有害事象報告を行わなければならない。海外の状況をみると，米国では NCI が定めた規準により，NCI がスポンサーとなる Cooperative group では共通の有害事象報告を規準に重篤な有害事象報告がなされている。現在，日本にはこのような共通規準が存在しない点は今後の大きな課題といえる。

3 JGOG 臨床試験における重篤な有害事象報告の旧体制（2011 年 8 月まで）

臨床試験の安全性情報管理に関連する規制の主なものを表 1 に示す。

北里大学臨床研究機構臨床試験コーディネーティング部は，これまで JGOG の臨床試験をはじめとするさまざまな研究者主導がん臨床試験において，データセンター業務の一環として安全性情報の管理を担当してきた。

JGOG 試験では，ICH-E2A ガイドライン，ICH-E2D ガイドライン，臨床研究に関する倫理指針，NCI Guidelines：Adverse Event Reporting Requirements および日本臨床腫瘍研究グループ（Japan Clinical Oncology Group：JCOG）が公開している安全性情報取り扱いガイドライン[3,4]などを参考にしながら，2011 年 8 月まで表 2 に示す規定に則り，安全性情報の収集を行ってきた。

しかし，この規定は「入院」を重篤度の指標としていなかったため，ICH ガイドラインや臨床研究に関する倫理指針に厳密には準拠していなかった。入院の対象となる事象が本邦と欧米で異なることは推測できたが，JGOG がスポンサーとなって日本主導型国際共同試験を実施するにあたり，参加各国の報告要件を満たす必要があった。

表 2 JGOG 臨床試験における報告対象事象（改訂前）

有害事象		医療機関からデータセンターへの報告と期限	倫理指針による報告義務
内容	因果関係		
プロトコル治療中もしくは最終プロトコル治療日から 30 日以内のすべての死亡	問わない	急送報告 一次報告：72 時間以内 二次報告：15 日以内	報告対象
予期されない Grade 4 の非血液毒性	あり		報告対象
最終プロトコル治療日から 31 日以降の死亡	あり	通常報告 15 日以内	報告対象
予期される Grade 4 の非血液毒性	あり		報告対象
予期されない Grade 2，3 の有害事象	あり		一部対象 （重篤事象のみ対象）
永続的または顕著な障害 再生不良性貧血，骨髄異形成症候群，二次がん	あり		一部対象 （未知事象のみ対象）
その他重大な医学的事象	あり		一部対象 （未知事象のみ対象）

表 3 JGOG 臨床試験における報告対象事象（改訂後）

	Grade 1	Grade 2		Grade 3				Grade 4 & 5	
				未知		既知			
	未知/既知	未知	既知	*入院/入院の延期を要する	*入院/入院の延期を要さない	*入院/入院の延期を要する	*入院/入院の延期を要さない	未知	既知
関連なし	不要	不要	不要	10 日以内	不要	10 日以内	不要	10 日以内	10 日以内
関連を否定できない	不要	10 日以内	不要	10 日以内	10 日以内	10 日以内	不要	**24 時間 5 日以内	5 日以内

*「入院」の定義：集中治療を要する入院を指し、試験開始前に計画された入院や、被験者の負担を軽減する目的等で計画された入院、検査目的のための入院は除く。

**Grade 4 および 5 の未知の事象については，発生後 24 時間以内に何らかの報告で通知し，5 日以内に報告書の提出を要する。ただし，原疾患の進行による死亡が明らかな事象に対しては，24 時間通知は不要だが，報告書は提出しなければならない。

同時に，2010 年に高度医療評価制度（現在は先進医療 B）を用いた臨床試験を開始したことに伴い，臨床研究に関する倫理指針ならびに先進医療に関する通知に規定されている，個別詳細情報の報告が必要な有害事象が漏れることなく収集できるよう，報告義務のある有害事象カテゴリを変更した（表 3：改訂後）。

4 JGOG 臨床試験における重篤な有害事象報告の新体制（2011 年 8 月以降）

現在の JGOG における重篤な有害事象報告は，「JGOG 臨床試験重篤な有害事象の取り扱いに関する手順」に則り行われる。2011 年 8 月に制定されたこの手順書では，表 3 に示すとおり報告義務のある有害事象カテゴリを大幅に変更した。特に重要な変更点は，報告対象事象の定義を「入院を考慮した重篤度」と「CTCAE の Grade 基準」にて明確に区分した点である。この定義については，次項「5 重篤の定義」で解説する。

この手順書に規定された重篤な有害事象のカテゴリは，JGOG 試験の共通テンプレートとして使用され，JGOG 参加医療機関の研究者に対する重篤な有害事象報告対象に関する周知徹底をはかるためにも活用した。すべての JGOG 試験で共通の定義を用いることにより研究者に周知徹底をはかり，報告漏れをなくすことが期待されたが，その効果については定かではない。実際に現在でも，データセンターにおいて提出された症例報告書の内容から重篤な有害

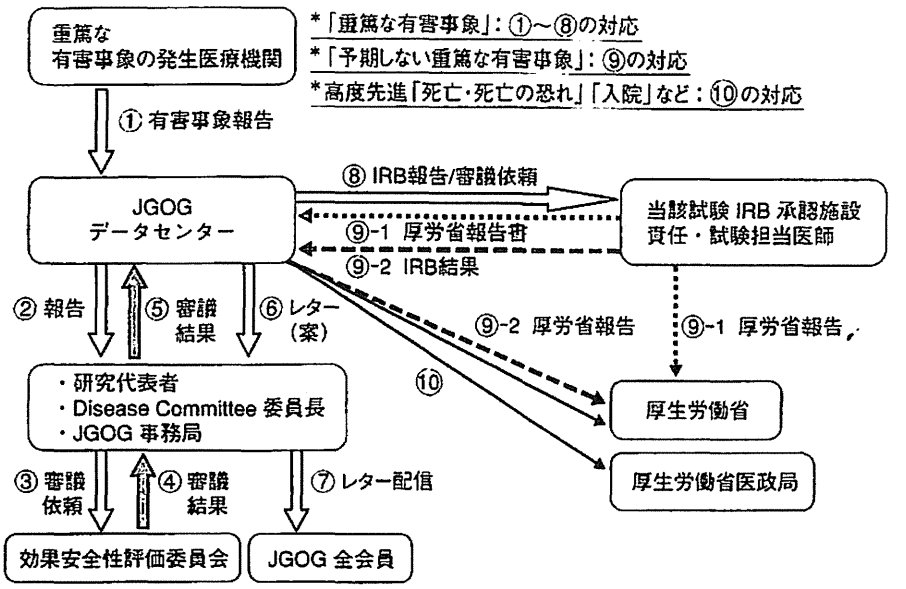

図 1　重篤な有害事象報告フローチャート

事象の報告漏れを発見することがある。

収集された重篤な有害事象情報については，「JGOG 効果安全性評価委員会規程」に則り，当該事象に関する判断の妥当性（因果関係・予見性・重篤性），試験継続の可否，プロトコルならびに同意説明文書改訂の要否，規制当局への報告要否，研究者への周知の必要性（早急な周知，ラインリストでの周知，報告不要）について審議が行われる。

報告された重篤な有害事象については，研究代表者ならびに JGOG 事務局への報告，効果・安全性評価委員会の審議，すべての研究実施医療機関への情報提供，必要に応じて規制当局への報告完了までを，データセンターが全面的にサポートしている（図1）。

5　重篤の定義

ICH において，臨床試験における重篤な有害事象は以下のように定義されている（ICH-E2A より抜粋[5]）。

- results in death,
- is life-threatening, (The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

また，がん臨床試験ではすべての有害事象が CTCAE を用いて報告され，重症度は次の 5 段階 Grade にて定義されている[6,7]（Grade 説明文中のセミコロン（；）は「または」を意味する）。

Grade 1：軽症；症状がない，または軽度の症状がある；臨床所見または検査所見のみ；治療を要さない

Grade 2：中等度；最小限/局所的/非侵襲的治療を要する；年齢相応の身の回り以外の日常生活動作の制限

Grade 3：重症または医学的に重大であるが，ただちに生命を脅かすものではない；入院または入院期間の延長を要する；活動不能/動作不能；身の回りの日常生活動作の制限

Grade 4：生命を脅かす；緊急処置を要する

Grade 5：AE による死亡

ICH の重篤度の定義に CTCAE の Grade（重症度）を対比させて考えると，以下のように定義することができる。

(1) 死に至る（→Grade 5）

(2) 生命を脅かす（→Grade 4 の非血液毒性）

(3) 治療のための入院もしくは入院期間の延長が必要となる（→Grade 3 以上かつ入院）

ただし,「入院」とは集中治療を要する入院を指し，試験開始前に計画された入院や，被験者の負担を軽減する目的等で計画された入院，検査目的のための入院は除く

(4) 永続的もしくは顕著な障害や機能不全に陥る

(5) 先天異常もしくは生まれながらの欠陥がある

(6) 試験責任医師が医学的に重要な事象と判断する（→未知の Grade 2 または 3 を含む）

がん領域の臨床試験において，このような有害事象のカテゴリ化は米国 NCI スポンサーの臨床試験グループでは一般的に用いられている方法である。

さらに報告対象事象を明確にするために，有害事象の重篤度と重症度について詳細な検討を行った結果を以下に示す。

「(2) 生命を脅かす：is life-threatening」は CTCAE の Grade 4 に相当すると考える。抗がん剤（殺細胞性抗がん剤）を用いた試験では，薬剤の特性により Grade 3〜4 の白血球/好中球や血小板減少をはじめとする血液細胞の毒性が起こりやすい。しかしながら，多くの血液細胞の毒性は，適切な対症療法を実施すれば生命を脅かす状態に至ることはきわめてまれである。したがって，すべての個別症例の詳細情報を収集することは不要であると判断し，通常の殺細胞性抗がん剤を使用する臨床試験では Grade 5 以外のすべての血液細胞の毒性を報告対象から除外している。

「(3) 治療のための入院もしくは入院期間の延長が必要となる：requires inpatient hospitalization or prolongation of existing hospitalization」は CTCAE の Grade 3 以上に相当すると考える。通常，Grade 3 以上の事象は重篤な有害事象に該当すると考えて問題ないが，有害事象の重症度すなわち被験者の臨床症状の重症度の判断は画一的に判断できない場合がある。たとえば「Grade 3 であるが入院治療を行わなかった」あるいは「Grade 2 であるが入院による治療を行った」という報告がまれに発生することがある。CTCAE では観察された有害事象が複数の Grade の定義に該当する場合には，総合的に判断してもっとも近い Grade に分類する（Nearest match の原則[6,7]）。研究者はこの考え方に則り有害事象の Grade を判定するため，このような Grade と入院の不一致が発生することもありうる。

重篤な有害事象として収集が必要な，詳細臨床情報について検討した結果，JGOG では原則として，CTCAE の Grade 3 以上と判定されかつ入院治療を実施した場合のみを，入院による集中治療が臨床的に必要と判断された「重篤な有害事象」とみなすこととした。Grade 2 で入院治療を行った場合には，結果的に入院による治療は行ったが集中治療を要するほどの重症度ではなかったとみなし，原則として報告対象からは除外することにした。この例として，Grade 2 で入院を伴うイレウスや嘔吐等がある。これは，入院が必須でなくとも患者の希望や付き添いがいないため患者の通院が困難な場合など，有害事象の重症度以外の要因によって入院することが少なくないことを考慮したものである。また，なかには Grade 3 の状態であっても臨床的には入院治療が必要なほど重症ではない事象も存在する。この例として，Grade 3 でも入院を伴わないざ瘡様皮疹や斑状丘疹状皮疹，末梢性感覚ニューロパチー，高血圧，臨床検査値異常（AST 上昇や ALT 上昇）などがある。ただしこのような場合は，当該医療機関の研究者の事象に対する判断を尊重して，重篤性の判断を行うこととした。

さらに「(6) 試験責任医師が医学的に重要な事象と判断する」と規定することで，研究者が報告を必要と判断したすべての事象は，重篤な有害事象として取り扱うようにしている。これには未知の Grade 2 または 3 の事象を含むものとした。未知の Grade 1 の事象については，重篤な有害事象報告としては情報収集しないが，半年に 1 度の頻度でデータセンターが作成して公開するモニタリングレポートに掲載することとした。

6 規制当局等への緊急報告対象となる有害事象と報告タイムライン

ここでは，規制当局等への緊急報告対象となる有害事象と報告タイムラインについて，指針および通知別にまとめる。

1）臨床研究に関する倫理指針[8]

第 2. 3 (9) において，「臨床研究に関連する予期しない重篤な有害事象および不具合等が発生した場

合」，すなわち「予期せぬ重篤な有害事象（Suspected Unexpected Serious Adverse Events, SUSAE）」は速やかな報告義務がある。「予期できない」副作用とは，副作用のうち，治験薬概要書に記載されていないもの，または記載されていてもその性質や重症度が記載内容と一致しないものをいう。また，既承認の医薬品等に関わる臨床試験の場合は，治験薬概要書の代わりに添付文書の情報を予期性判断の参考資料にすることができる。添付文書には記載されていないが，臨床試験結果等からすでに発生が規制当局に報告されている有害事象については，プロトコルに明記することにより「予期できる」既知の事象として取り扱うことができる。

2）先進医療に関する通知[1]

第4項の7（5）において，①死に至る又は生命を脅かす症例については，発生を知った日より7日以内に届け出ること，②次に掲げる症例（①に掲げるものを除く。）であって，当該症例の発生又は発生数，発生頻度，発生条件等の発生傾向が実施計画書等から予測できないものについては，発生を知った日より15日以内に届け出ること。

ア　重篤な有害事象等の治療のために別の入院又は入院期間の延長が必要とされる症例（ただし，重篤な有害事象等の治療のために入院したが，安静治療等により特段の対応を行っていない場合等は当該症例に該当するが，重篤な有害事象等の検査を行うための入院又は入院期間の延長が行われた場合，重篤な有害事象等が治癒又は軽快しているものの経過観察のための入院が行われた場合等は，当該症例に該当しない。）

イ　日常生活に支障をきたす程度の永続的または顕著な障害・機能不全に陥る症例（先天異常を来すもの，機器の不具合を含む）

ウ　ア又はイに掲げる症例のほか，患者を危機にさらすおそれがあるもの，①又はア若しくはイに掲げる症例に至らないよう診療が必要となるもの等の重篤な症例（例：集中治療を要する症例等）

なお，代替可能なすでに保険収載されている治療法等において同様の重篤な有害事象等が発生することが明らかにされている場合にあっても，報告すること。

すなわち，Grade 4，5に該当するすべての重篤な有害事象ならびに「予期せぬ重篤な有害事象（Suspected Unexpected Serious Adverse Events, SUSAE）」は，それぞれ規定された期日内に報告義務がある。

3）ICH-E2A[5]およびICH-E2D[9]

承認前に得られる安全性情報についてはICH-E2A，承認後についてはICH-E2Dにおいて，死亡や生命を脅かすものに加えて，被験薬との関連が疑われ（Suspected），予測できない（Unexpected）重篤な副作用（Serious Adverse Reaction）は，「予期せぬ重篤な副作用（SUSAR）」として，規制当局への報告が義務づけられている。報告期限は，ICH-E2Aにおいては死亡および生命を脅かすものは7日以内，それ以外は15日以内とされている。ICH-E2Dにおいては，すべて15日以内となっている。

これらの規制を遵守して安全性情報を収集し，必要に応じて期限内に当局報告できるように，「JGOG重篤な有害事象の取り扱いに関する手順」では報告期限のある重篤な有害事象を前述の表3のように定義した。治験以外のいかなる種類の臨床試験（通常の研究者主導臨床試験，先進医療として実施する臨床試験，国際共同臨床試験）においても，当該試験が遵守すべき安全性情報を収集できる統一規準になったと考えている。

この改訂後のJGOG規定では，臨床研究の倫理指針において報告が必須でない事象（Grade 2または3の因果関係を否定できない未知で非重篤の有害事象）についても報告対象に含んでいる。そのために，先進医療や国際共同試験でない，いわゆる通常の研究者主導臨床試験においては，より厳しい規定となっているともいえる。しかしながら，研究者の重篤な有害事象に対する認識，さらに「どのような有害事象について速やかな個別詳細報告が必要かという認識」を統一して周知徹底することを重視する，という観点から，試験の種類別にSAE報告期限のルールを分けるよりも，すべての臨床試験において同じテンプレートで運用できるように規定を統一している。ただし，治験の場合はGCP省令を遵守した運用としている。

表 4 GOG 試験における主な試験の急送報告対象事象（AdEERS 報告）[1]（2013 年 5 月現在の運用）

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grade 4 & 5[2]	Grade 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	With Hospital-ization	Without Hospital-ization	With Hospital-ization	Without Hospital-ization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hours；3 Calendar Days	7 Calendar Days

[1]第 II および第 III 相試験で試験薬最終投与日から，30 日以内に生じた有害事象の報告要件。ただし，CTEP-IND に基づく試験薬の最終投与より 30 日を越えて生じた，関連の可能性あり，おそらく関連あり，明らかに関連ありの有害事象は以下の報告が必要である。

AdEERS にて発生後 24 時間以内に通知，3 日以内に完全報告書の提出を要するもの：

- Grade 4 および 5 の未知の事象

AdEERS にて発生後 7 日以内に報告：

- 入院を要する，または入院を延長させる Grade 3 の未知の事象
- Grade 5 の既知の事象

[2]明らかに病気の進行による死亡は AdEERS 24 時間報告は必要ないが，完全報告書の提出が必要とされる。

7 米国 NCI スポンサーの臨床試験グループにおける重篤な有害事象報告体制

本邦の 18 医療機関は GOG-Japan として米国 GOG（Gynecologic Oncology Group）が実施する臨床試験に参加しており，北里大学臨床研究機構は GOG-Japan コーディネーティングセンターとして，すべての重篤な有害事象を一元管理している。GOG 試験では，米国での規制要件を遵守するように重篤な有害事象報告の対象と手順の要約がプロトコルに記載されており（表 4），その詳細は NCI がスポンサーとなるすべての臨床試験共通のガイドライン[8]として公表されている。

GOG への重篤な有害事象報告は，自動有害事象急送報告システム（Adverse Event Expedited Reporting System：AdEERS）を用いて行う[10]。AdEERS とは，医療機関の研究者や CRC などの研究協力者が，インターネットを介して電子的に重篤な有害事象に関連する臨床情報や検査データを入力し，瞬時にその情報が GOG の安全性情報担当者ならびに当該試験の研究代表者へ配信され，内容確認ならびに必要に応じて追加情報が収集された後に，同じシステム上の情報を NCI および FDA（Food and Drug Administration）へ送信・共有できるシステムである。GOG 試験のみならず，米国 NCI がスポンサーとなる臨床試験では，臨床試験の種類を問わず統一システムとして利用されているため，医療機関での認知度は高い。

国内で発生した GOG 試験の重篤な有害事象は，まず研究者より GOG-Japan コーディネーティングセンターに報告される。その後，重篤な有害事象報告書の作成，当該事象の AdEERS 報告要否の確認，報告書作成のサポート（期日内報告と記載内容の確認），NCI/GOG からの追加報告リクエストに関する対応，GOG-Japan 委員長ならびに JGOG 事務局への報告，効果安全性評価委員会への報告と審議，すべての試験実施医療機関への情報提供，必要に応じて規制当局への報告完了までの一連の作業を，GOG-Japan コーディネーティングセンターの担当者が支援している。

8 研究者主導臨床試験における安全性情報管理の今後の課題

多くのがん臨床試験の安全性情報管理を担当してきた経験から，研究者および臨床試験グループが今後積極的に取り組まなければならないと思われる安全性情報管理の課題として，4 つの側面を強調して

おきたい。

①個々の試験単位ではなく，臨床試験グループとして，できるだけシンプルで統一された安全性情報の手順書を整備すること，そしてそれを研究者に周知徹底すること（手順書整備と教育）。

②安全性情報管理に関する法規は改正・改訂が行われるため，キャッチアップできる体制を整えること（レギュレーション対応）。

③タイムリーに安全性情報を収集・配信するために安全性情報管理のIT化を推進すること（IT化）。

④安全性情報担当者を臨床試験の実施医療機関と中央管理機構の両方に配置して，それぞれの役割を明確にすること（責務の明確化とマンパワーの充実）。

ま と め

がん領域では新薬開発や適応拡大への期待が高く，さらに集学的治療のエビデンスを構築する必要があることから，研究者主導臨床試験の実施が不可欠である。がんの臨床試験では疾患そのものの重症度が高く，かつ試験薬剤の毒性が強いという特徴から，他の疾患領域に比べて副作用の発現頻度が高く，重篤な有害事象の発現数も多い。しかしながら，医療機関における研究者主導臨床試験の安全性情報管理に関するCRCなどの支援体制は十分とはいえない。

このような現状において，臨床試験を安全で科学的に実施するには，重篤な有害事象を含む安全性情報を漏らすことなく確実かつ迅速に収集し，必要な情報を全参加医療機関ならびに規制当局へ伝達する「安全性情報の管理体制」の整備が必須となる。まず，安全性情報をタイムリーに漏れなく収集するには，できるだけシンプルに統一された報告手順（報告すべき事象・報告期限・報告書に記載すべき内容等）を規定して研究者に周知徹底することが必要である。そして，医療機関における安全性情報管理の支援体制整備（支援スタッフの確保を含む）にはこれまで以上に積極的に取り組まなければならない。さらに重要となるのは，データセンターなどの臨床試験グループの中央機構の役割である。中央機構には安全性情報担当者を配置し，医療機関に対するきめ細やかなサポートを提供しつつ安全性情報を集約管理できる人的体制整備，ならびにインターネットなどを活用した安全性情報管理システム開発等を推進する環境整備が望まれる。

抄　　録

本邦のがん領域の研究者主導多施設共同臨床試験では，研究グループや個別の研究ごとに若干異なる有害事象の報告規準を用いている。その背景には，日本では試験の目的および規制要件（規制を受ける法令や通知，指針等）によって，治験とそれ以外の臨床試験（研究者主導臨床試験および先進医療）が区別されているために，報告対象となる有害事象・報告期限・報告先が異なることがあげられる。また，がん領域の臨床試験では有害事象の評価基準としてNCI CTCAEが一般的に用いられているが，CTCAEによる“Grade評価”と法規による“重篤”の定義をいかにマッチングするかについてこれまでほとんど議論されてこなかったために統一見解に至っていないことも一因である。

本稿では，北里大学臨床研究機構臨床試験コーディネーティング部がデータセンターの役割を担うJGOGにおける有害事象の報告規定制定の背景とその実施体制を例に示し，がん領域における研究者主導臨床試験の有害事象報告体制整備の重要性について述べた。

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EXPERT OPINION

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Principle and evolving role of intraperitoneal chemotherapy in ovarian cancer

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Introduction: Intraperitoneal (i.p.) chemotherapy has been extensively studied in the ovarian cancer field. Despite the fact that three large randomized trials that were conducted in the United States showed survival benefit, meta-analysis also showed survival benefit and the National Cancer Institute (NCI) released a clinical announcement recommending i.p. chemotherapy for optimally debulked advanced stage ovarian cancer in 2006, i.p. chemotherapy has not been widely accepted by the gynecologic oncology community, mainly because of its toxicities.

Areas covered: In this review, previously available evidence, new evidence published since the NCI clinical announcement and ongoing clinical trials will be discussed.

Expert opinion: Three currently ongoing randomized Phase III trials will provide extremely important information about whether a less toxic i.p. regimen using carboplatin will be beneficial for patients with advanced ovarian cancer. They are important because it may be possible to solve many of the questions or unmet needs in i.p. chemotherapy by combining these three trials.

Keywords: bevacizumab, carboplatin, dose-dense chemotherapy, intraperitoneal chemotherapy, neoadjuvant chemotherapy, ovarian cancer

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1. Introduction

In spite of an enormous effort in the past few decades, improvement of the prognosis of epithelial ovarian cancer has been limited. One of the most characteristic features of ovarian cancer is the intraperitoneal (i.p.) spread of disease, even in the early occurrence. Therefore, it has been considered reasonable to administer anticancer agent directly into the i.p. cavity. This approach has been extensively investigated both preclinically and clinically.

The i.p. chemotherapy was first adopted for palliative purposes to control ascites of various intra-abdominal malignancies in the 1950s. Since 1978, i.p. chemotherapy has been used as a form of therapeutic intervention. After extensive Phase I and Phase II trials, three large Phase III trials have been conducted in the United States [1-3], and survival benefit was demonstrated by meta-analysis. However, i.p. chemotherapy has not been adopted as a standard chemotherapy yet.

In this review article, we will discuss the principles and clinical aspects and future perspectives of i.p. chemotherapy for ovarian cancer.

2. Basic concept of i.p. chemotherapy

The primary concept of i.p. chemotherapy is to directly expose the tumor tissue to an extremely high concentration of anticancer agent by perfusing inside the peritoneal cavity. However, some proportion of anticancer agent infused into peritoneal

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Article highlights.

- Basic concept of i.p. chemotherapy is reviewed.
- Clinical Trials that showed superiority of i.p. chemotherapy are discussed.
- Pharmacological and clinical evidence to support i.p. carboplatin-based chemotherapy are provided.
- New evidence surrounding i.p. chemotherapy since 2006 are considered.
- Unanswered questions and clinical trial design for the future are discussed.

This box summarizes key points contained in the article.

cavity will go into the capillary blood vessels adjacent to the peritoneum and systemic circulation, and then return to the inner core of tumor tissue through tumor microcirculation [4]. The drug concentration in the inner core of the tumor depends on the drug pharmacokinetics.

The factors that determine the effect of i.p. chemotherapy are as follows [4]:

1) direct penetration of anticancer agent into the tumor tissue from the tumor surface;
2) diffusion of anticancer agent into the inner core of tumor tissue through systemic blood circulation; and most importantly
3) antitumor effect of the agent for ovarian cancer.

Based on these determinant factors, an ideal anticancer agent for i.p. chemotherapy is one that is very systemically effective against ovarian cancer, that penetrates deep into the tumor, and that stays in the peritoneal cavity for prolonged periods as this would result in a low incidence of systemic adverse effects, while providing satisfactory drug concentrations in the inner core of tumor tissue. However, things are not that easy because penetration of anticancer drugs from the tumor surface is limited to a few millimeters. Also, ensuring that the agent remains in the peritoneal cavity for a long time while maintaining a high concentration in the inner core of the tumor is a pharmacologically contradictory phenomenon.

In brief, because of the structure of mesothelium, larger or water-insoluble agents stay longer in the peritoneal cavity but concentration of the inner core of the tumor is low (**Figure 1A**), whereas smaller molecules or water-soluble agents can go into inner core of the tumor easily but stay for a shorter time in the peritoneal cavity (**Figure 1B**) [4].

Table 1 shows the list of anticancer agents for i.p. chemotherapy and their molecular mass, water solubility and (peritoneal cavity:plasma) ratio of drug levels. As shown in the **Table 1**, larger molecular mass and water insolubility correlate well with a larger peritoneal:plasma ratio. As for those agents showing a larger peritoneal:plasma ratio in spite of smaller molecular mass and good water solubility, such as 5-fluorouracil (5-FU), it suggests that those agents are metabolized in the liver through the portal vein.

Since penetration of anticancer agents from the tumor surface is limited, the indication for i.p. chemotherapy should be restricted to the small residual disease if the i.p. chemotherapy is considered to be a regional therapy in the peritoneal cavity. In this setting, the ideal chemotherapy agents are large molecules such as paclitaxel or mitoxantrone. As shown in **Table 1**, platinum agents, which are the most effective against ovarian cancer, do not stay long in the peritoneal cavity; therefore, these are not suitable for the 'genuine' i.p. chemotherapy. However, these agents can easily enter the systemic circulation and ultimately reach the inner core of tumor tissue. Therefore, i.p. chemotherapy using platinum agents can be hypothesized to be one route of systemic chemotherapy.

3. Phase III trials of i.p. for ovarian cancer

There are eight published comparative studies of i.p. versus intravenous (i.v.) administration for ovarian cancer. Among them, three randomized trials conducted in the United States are the most important because the size of the trials was large enough.

The first randomized trial conducted by South Western Oncology Group (SWOG) and Gynecologic Oncology Group (GOG) 104 was published in 1996 [1]. In this trial, patients with small residual disease (< 2 cm) were randomized to receive six cycles of i.v. cyclophosphamide (600 mg/m^2) plus either i.p. or i.v. cisplatin. The dose of cisplatin was 100 mg/m^2 for both groups, and the treatment was repeated every 3 weeks for six cycles. In the 546 eligible patients, the estimated median survival was significantly longer in the i.p. group (49 months; 95% confidence interval [CI]: 42 – 56) compared to the i.v. group (41 months; 95% CI: 34 – 47). The hazard ratio (HR) for the risk of death was 0.76 (95% CI: 0.61 – 0.96; p = 0.02) in favor of i.p. therapy. Although moderate–to-severe abdominal pain was more frequent in the i.p. group, grade 3/4 granulocytopenia and tinnitus, clinical hearing loss and grade 2 – 4 neuromuscular toxic effects were significantly more frequent in the i.v. group.

At the same time, as this important result was published, the result of the GOG 111 trial was also published [5]. In this trial, it was shown that replacing cyclophosphamide with paclitaxel improved the median survival from 24 (95% CI: 21 – 30) to 38 (95% CI: 32 – 44) months (relative risk = 0.6; 95% CI: 0.5 – 0.8; p = 0.001) in advanced ovarian cancer. Therefore, the consensus at the time was that replacing cyclophosphamide with paclitaxel is more beneficial than applying i.p. administration of cisplatin.

The second i.p. trial was also conducted by GOG and SWOG, and the results were published in 2001 [2]. In this trial, the patients were randomized to either i.v. paclitaxel 135 mg/m^2 over 24 h followed by i.v. cisplatin 75 mg/m^2 every 3 weeks for six cycles, or i.v. carboplatin (area under the curve [AUC] = 9) every 28 days for two cycles, then i.v. paclitaxel 135 mg/m^2 over 24 h followed by i.p. cisplatin at 100 mg/m^2 every 3 weeks for six cycles. Improved

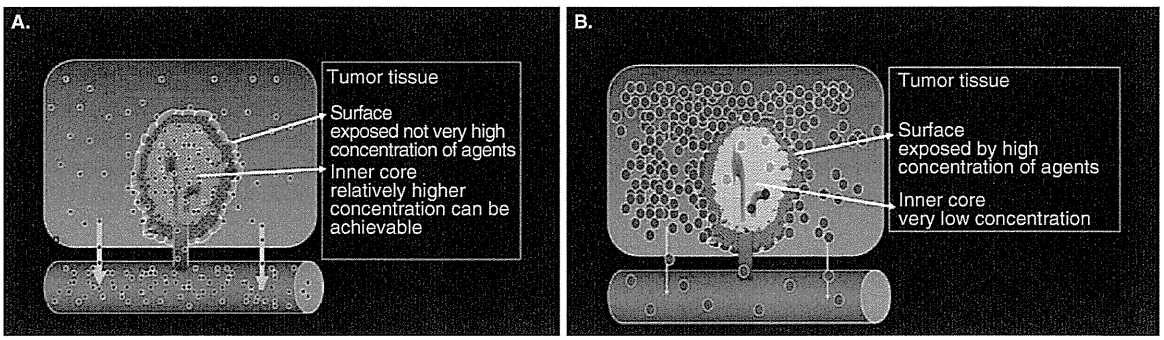

Figure 1. A. Schematic image of the distribution of chemotherapy agents with small molecular mass that was administered in the i.p. cavity. **B.** Schematic image of the distribution of chemotherapy agents with large molecular mass that was administered in the i.p. cavity.

Table 1. Ratio of drug level in peritoneal cavity:plasma by pharmacological characteristics of anticancer drugs.

Drug	Molecular mass	Water solubility	Ratio of drug level Peritoneal cavity:plasma	
			Peak	AUC
Cisplatin	300.05	+	20	12
Carboplatin	371.25	+	-	18
Mitomycin	334.33	±	71	-
Melphalan	305.20	-	93	65
Methotrexate	454.44	-	92	100
5-FU	130.08	±	298	367
Doxorubicin	543.53	±	474	-
Paclitaxel	853.92	-	-	1000
Mitoxantrone	517.40	-	-	1400

progression-free survival (PFS) (median: 28 vs 22 months; relative risk = 0.78; log rank $p < 0.01$, one tail) and overall survival (median: 63 vs 52 months; relative risk = 0.81; $p = 0.05$, one tail) of 426 assessable patients were observed in favor of the i.p. group. However, hematologic and non-hematologic toxicities ≥ grade 3 were significantly more frequent in the i.p. group. As a result, 18% of the patients received less than two courses of i.p. therapy. In spite of the significant survival improvement in this study, the gynecologic oncology community did not accept i.p. chemotherapy to be the standard treatment for ovarian cancer because there was a possibility that the addition of two cycles of carboplatin treatment may contribute to the improvement of survival and that toxicity was excessive in the i.p. arm.

The third trial was conducted by GOG [3]. In this study, 417 patients with optimally debulked stage III ovarian cancer were randomized either to i.v. paclitaxel (135 mg/m^2/24 h) followed by i.v. cisplatin (75 mg/m^2), or to i.v. paclitaxel (135 mg/m^2/24 h) followed by i.p. cisplatin (100 mg/m^2), plus i.p. paclitaxel (60 mg/m^2) on day 8. The relative risk of recurrence was 0.73 in the i.p. group as against i.v. group. The improvement in median overall survival was 15.9 months, with a treatment HR of 0.75 (95% CI: 0.58 – 0.97) favoring the i.p. study arm. The magnitude of improvement in median overall survival associated with i.p./i.v. administration of chemotherapy is similar to that observed with the introduction of either cisplatin or paclitaxel. The median duration of survival for the i.p. arm of this trial (66 months) was 10 months longer than that for the current standard treatment schedule (i.v. paclitaxel plus i.v. carboplatin treatment) arm of the GOG 158 trial (57 months). However, this survival advantage could be due to the addition of day 8 paclitaxel and not due to the i.p. delivery of cisplatin and paclitaxel. In addition, there were significantly more patients with grade 3/4 hematologic and non-hematologic toxicities in the i.p. arm compared to the i.v. arm. Because of these toxicities and/or catheter problems, 48% of patients in the i.p. arm received three or fewer i.p. treatments and only 42% patients received the planned six cycles of i.p. therapy. As discussed by Cannistra [6], 'it is remarkable that such a clinically meaningful survival advantage was observed, despite the high attrition rate in the intraperitoneal group, suggesting that a substantial benefit from intraperitoneal chemotherapy may occur within the first several cycles of treatment', and this trial raised important

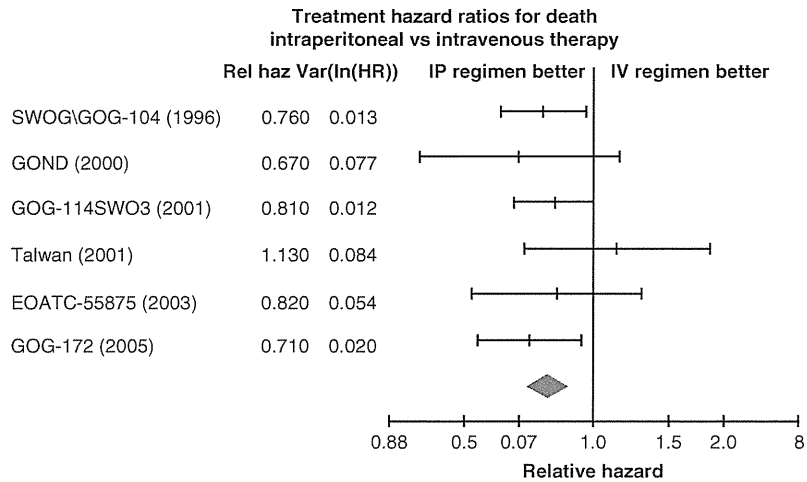

Figure 2. Result of meta-analysis for i.p. chemotherapy published as a NCI clinical announcement.

questions to be solved in the future because it is hypothesized that improving catheter complications may enhance the survival benefit by i.p. chemotherapy further.

Based on the results of these three large randomized trials and another five small studies, GOG and National Cancer Institute (NCI) conducted a meta-analysis and concluded that i.p. chemotherapy is beneficial for optimally debulked stage III ovarian cancer patients. This important information has been released as a clinical announcement from the NCI US in January 2006 [7]. As shown in **Figure 2**, i.p. therapy was associated with a 21.6% decrease in the risk of death (HR = 0.79; 95% CI: 0.70 – 0.89). The expected median duration of survival for women with optimally debulked ovarian cancer receiving standard treatment is ~ 4 years. Therefore, this size reduction in the overall death rate is expected to translate into about a 12-month increase in overall median survival.

Despite these promising results, i.p. chemotherapy has not been accepted as standard treatment for advanced ovarian cancer.

The most important drawback is the platinum agent used in the i.p. trials, which is cisplatin. As is well known, cisplatin is more toxic than carboplatin, which is the standard platinum agent when given intravenously. Therefore, it is reasonable to consider replacing cisplatin with carboplatin for i.p. use, but there have been two reasons why carboplatin was not used for i.p. chemotherapy for long time.

4. Reasons why carboplatin was not used for i.p. chemotherapy

There are two reasons why carboplatin was not used for i.p. chemotherapy. One of them was an animal experiment which showed that ~ 6 to 10 times more carboplatin was required to obtain equivalent tissue platinum concentration compared to cisplatin [8]. In this study, Los *et al.* measured platinum distribution in rat peritoneal tumors after i.p. treatment with equimolar doses of carboplatin and cisplatin and found that no platinum was detected 0.5 mm from the periphery after carboplatin treatment, whereas 14 ppm was detected after cisplatin treatment. They also measured the total platinum concentration in the tumor model after various doses of carboplatin and cisplatin were administered into the i.p. cavity of mice and found that 10 times more carboplatin than cisplatin had to be injected to obtain comparable platinum concentrations in the tumors. However, the tissue concentration has not been shown to be predictive of efficacy in this animal model.

Based on this result, Markman *et al.* retrospectively analyzed their clinical data of a small number of patients and showed that the response rate was better in the cisplatin-based regimen [9], concluding that carboplatin may be inferior to cisplatin when used intraperitoneally. However, these studies assume equivalency of dose between carboplatin and cisplatin. For example, in the Los *et al.* study, the dose of cisplatin and carboplatin administered to the mice was calculated based on weight. The dose of carboplatin that was required to achieve the equivalent tissue platinum concentration that was achieved by administering cisplatin at 5 mg/kg was between 30 and 49.2 mg/kg. By comparison, standard i.v. doses of platinum agents as designed in contemporary clinical trials with paclitaxel are: cisplatin 75 mg/m^2 and carboplatin AUC of 6 to 7.5 mg/mL min. Since carboplatin is principally cleared through the kidneys, more reliable toxicity and efficacy data have been gained through dosing based on renal function. Based on a Phase I study by Bookman *et al.*, the dose of carboplatin at AUC of 7.5 was equivalent to 471 mg/m^2 and AUC of 6 was equivalent to 400 mg/m^2

[10]. Therefore, the dose of carboplatin must be at least 5 to 6 times more to achieve the equivalent clinical efficacy even when the cisplatin or carboplatin is administered intravenously. In the Markman *et al.* study, the dose of carboplatin was also too small (200 – 300 mg/m^2), comparing it to a considerably high dose of cisplatin (100 mg/m^2). The study also has another limitation because it was a retrospective analysis using a small number of patients. Therefore, an adequate evaluation of i.p. carboplatin using a reasonable dose and sample size is necessary.

5. Reasons why we believe carboplatin will be suitable for i.p. chemotherapy

5.1 Pharmacological analysis of i.p. carboplatin

Miyagi *et al.* published their pharmacological analysis of platinum concentrations in the serum and i.p. cavity after carboplatin was administered intravenously or intraperitoneally [11]. In this study, they demonstrated that 24 h platinum AUC in the serum was exactly the same regardless of i.p. or i.v. administration of carboplatin. However, 24 h platinum AUC in the peritoneal cavity was ~ 17 times higher when carboplatin was administered via the i.p. route.

Based on this result, they concluded that i.p. infusion of carboplatin is feasible, not only as an i.p. regional therapy but also as more reasonable route for systemic chemotherapy.

5.2 Clinical efficacy of i.p. carboplatin-based chemotherapy

Fujiwara *et al.* published the survival data of 165 patients with epithelial ovarian cancer who underwent i.p. carboplatin-based chemotherapy as a first-line treatment. They treated patients with stages I – IV epithelial ovarian cancer with either i.p. carboplatin alone (n = 22) or in combination with cyclophosphamide (n = 116) or paclitaxel (n = 27) [12]. In this retrospective analysis, the median survival of the patients with small (< 2 cm) residual disease was 51 months. Although the median survival of patients in this population treated with a dose of < 400 mg/m^2 carboplatin was 24.5 months, the median survival was not reached until 84 months when the carboplatin was dosed ≥ 400 mg/m^2.

In the 90 stage III/IV patients, including both small and bulky residual disease, median survival was 25 months with carboplatin dosed under 400 mg/m^2, whereas it was 51 months with carboplatin ≥ 400 mg/m^2 (p = 0.0137). The authors analyzed the potential reasons for the difference in outcome with different doses such as performance status, age and tumor grades between stage III/IV patients who received i.p. carboplatin ≥ 400 mg/m^2 and < 400 mg/m^2 and found that they were not significantly different. They concluded that the most significant prognostic factor by both univariate and multivariate analysis was carboplatin dosed above 400 mg/m^2. Although this study is a retrospective analysis, it is reasonable to argue that the data further support the prospective evaluation of i.p. carboplatin administration.

5.3 Toxicity of i.p. carboplatin plus i.v. paclitaxel

Two Japanese studies demonstrated toxicities with a combination of carboplatin and paclitaxel.

Fujiwara *et al.* performed a preliminary toxicity analysis of i.p. carboplatin in combination with i.v. paclitaxel [13]. In this study, a fixed dose of paclitaxel (175 mg/m^2) was analyzed for toxicity with escalating doses of carboplatin ranging from AUC of 5 to 7.5. Dose-limiting toxicity (DLT) was primarily thrombocytopenia requiring platelet transfusion. Three of the six patients in the cohort of AUC 7.5 experienced DLT. One of the six patients in the cohort at AUC 7 showed grade 3 thrombocytopenia. The incidence of grade 4 neutropenia was 33.3% for both cohorts. Therefore, the recommended dose of i.p. carboplatin in combination with 3 h i.v. paclitaxel infusion at 175 mg/m^2 could be AUC of 6 – 7.

Based on this study, the GOG conducted a Phase I/feasibility study for i.p. carboplatin to determine the optimal dose with i.v. paclitaxel for future studies (GOG9917) [14]. In this study, they tried to find an appropriate dose for i.p. carboplatin in combination with fixed dose of paclitaxel at 175 mg/m^2. Twenty-one patients were entered on the dose-escalating phase for first cycle. Maximum tolerated dose of carboplatin at AUC 8, was tolerated for the first cycle, although thrombocytopenia was the dose-limiting factor over multiple cycles. An additional 69 patients were treated in expanded cohorts to assess the toxicities over four cycles. Four-cycle DLT required de-escalation to a carboplatin AUC of 6, and even at that dose, there were 14 dose-limiting toxic effects in 40 patients (35%). Seven DLTs were due to neutropenia and 6 DLTs were due to grade 3/4 thrombocytopenia. Six cycles of therapy were completed in 75% of eligible patients but dose adjustments were required. Therefore, by using an i.p. carboplatin dose of AUC 6 in combination with paclitaxel, the regimen can be administered with a high completion rate over multiple cycles. Because neutropenia is a frequent DLT, the addition of hematopoietic growth factors may permit a high completion rate, while maintaining this dose. Only 5 of 90 (5.6%) patients discontinued treatment because of a port problem.

6. New evidence surrounding i.p. chemotherapy strategies since NCI Clinical Announcement 2006

6.1 Dose-dense weekly administration of chemotherapy

Japanese Gynecologic Oncology Group (JGOG) conducted a randomized Phase III trial to compare the therapeutic effect and safety of administering carboplatin every 3 weeks in combination with conventional administration of paclitaxel at 175 mg/m^2 every 3 week versus dose-dense weekly

administration of paclitaxel at 80 mg/m^2 in patients with stage II – IV ovarian, fallopian tube or peritoneal cancers (JGOG3016) [15]. A total of 637 patients were randomized and 631 were eligible (dose-dense regimen, n = 312; conventional regimen, n = 319). Median PFS was longer in the dose-dense treatment group (28 months; 95% CI: 22.3 – 35.4) than in the conventional treatment group (17.2 months, 15.7 – 21.1; HR = 0.71; 95% CI: 0.58 – 0.88; p = 0.0015). Overall survival at 3 years was higher in the dose-dense regimen group (72.1%) than in the conventional treatment group (65.1%; HR = 0.75; 0.57 – 0.98; p = 0.03).

This result impacted on the design of i.p. chemotherapy trials that were planned to be conducted at that time. Since the winner arm of GOG172 trial had administered i.p. paclitaxel on day 8, it was unclear whether the survival benefit was obtained because of the i.p. administration of cisplatin or paclitaxel, or because of day 8 administration of paclitaxel [16].

6.2 Bevacizumab

GOG218 and ICON7 were the trials that investigated the efficacy and safety of incorporating an antiangiogenic agent, bevacizumab, in combination with paclitaxel and carboplatin followed by bevacizumab maintenance alone.

The GOG218 trial was a double-blind, placebo-controlled, Phase III trial. They randomly assigned patients with newly diagnosed stage III (incompletely resectable) or stage IV epithelial ovarian cancer having undergone debulking surgery to receive one of three treatments [17].

In this study, 1873 women were enrolled. The median PFS was 10.3 months in the control group, 11.2 in the bevacizumab-initiation group and 14.1 in the bevacizumab-throughout group. Relative to control treatment, the HR for progression or death was 0.908 (95% CI: 0.795 – 1.040; p = 0.16) with bevacizumab initiation and 0.717 (95% CI: 0.625 – 0.824; p < 0.001) with bevacizumab-throughout. At the time of analysis, 76.3% of patients were alive, with no significant differences in overall survival among the three groups. Toxicities were acceptable.

In the ICON7 trial, women with ovarian cancer were randomly assigned to carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m^2), given every 3 weeks for six cycles, or to this regimen plus bevacizumab (7.5 mg/kg), given concurrently every 3 weeks for five or six cycles and continued for 12 additional cycles or until progression of disease [18]. The primary end point was PFS.

A total of 1528 women from 11 countries were randomly assigned. PFS at 36 months was 20.3 months with standard therapy, as compared with 21.8 months with standard therapy plus bevacizumab (HR for progression or death with bevacizumab added = 0.81; 95% CI: 0.70 – 0.94; p = 0.004 by the log-rank test). In the updated analyses, PFS (restricted mean) at 42 months was 22.4 months without bevacizumab versus 24.1 months with bevacizumab (p = 0.04 by log-rank test). In patients at high risk for progression, the benefit was greater with bevacizumab than without it, with PFS (restricted mean) at 42 months or 14.5 months with standard therapy alone and 18.1 months with bevacizumab added, with respective median overall survival of 28.8 and 36.6 months. They concluded that bevacizumab improved PFS in women with ovarian cancer. The benefits with respect to both PFS and overall survival were greater among those at high risk for disease progression.

These two important trials influenced the study design of GOG252 i.p. trials, which incorporated the bevacizumab in all three arms of the trial.

6.3 Neoadjuvant chemotherapy

Although primary debulking surgery (PDS) followed by adjuvant chemotherapy (ACT) is a standard treatment strategy for advanced ovarian cancer, there has been a great deal of controversy about whether neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) and additional ACT should be beneficial for the selected patient population.

EORTC55071 is a prospective randomized trial, which compared treatment efficacy and quality of life of standard PDS + ACT versus NACT + IDS + ACT in the patients with stage IIIC or stage IV disease [19]. Of the 670 patients randomly assigned to a study treatment, 632 (94.3%) patients were eligible and started the treatment. The largest residual tumor was ≤ 1 cm in diameter in 41.6% of patients after PDS and in 80.6% of patients after IDS. Postoperative rates of adverse effects and mortality tended to be higher after PDS than after IDS. The HR for death (intention-to-treat analysis) in the group assigned to NACT followed by IDS, as compared with the group assigned to PDS + ACT, was 0.98 (90% CI: 0.84 – 1.13; p = 0.01 for noninferiority). Complete resection of all macroscopic disease (at primary or interval surgery) was the strongest independent variable in predicting overall survival.

This trial influenced the trial design of the Canadian OV21 trial.

These new data impacted on the trial design of i.p. studies. Among the three results, the most important one was the dose-dense weekly concept.

7. Trial designs of currently ongoing i.p. chemotherapy trials

GOG114 and GOG172 trials had a problem of trial design because of the addition of other factors such as two cycles of carboplatin at AUC9 (GOG114 trial) or administration of i.p. paclitaxel on day 8 (GOG172 trial). It is desirable to have a trial to show the pure advantage of i.p. chemotherapy with less toxicity. Also, it is important to incorporate new evidence that became available recently.

Currently, there are three ongoing randomized trials worldwide attempting to find the best strategy in the treatment for ovarian cancer.

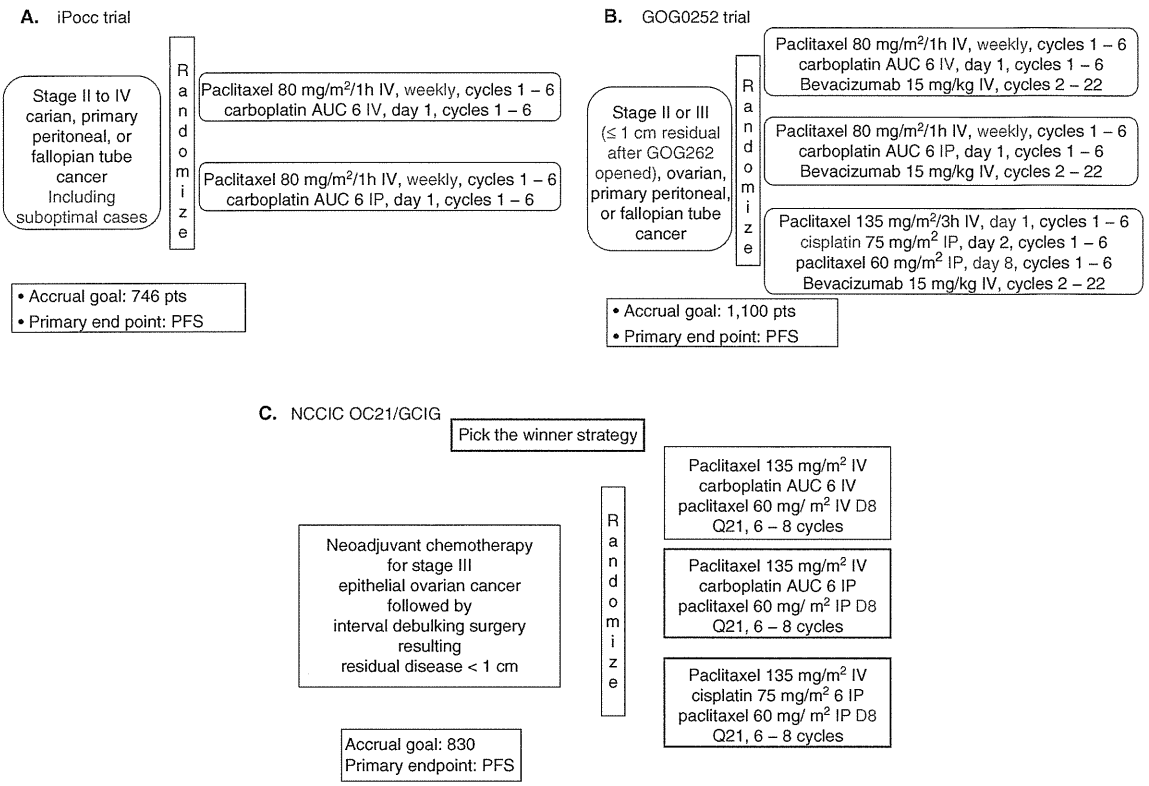

Figure 3. A. Schematic study design of iPocc trial. **B.** Schematic study design of GOG252 trial. **C.** Schematic study design of OV21 trial.

7.1 iPocc trial (GOTIC-001/JGOG3019)

After the JGOG3016 result became available, JGOG declared that dose-dense weekly administration of paclitaxel should be the standard chemotherapy regimen for the future JGOG trials. Accordingly, a new Japanese i.p. trial, iPocc trial (GOTIC-001/JGOG3019), was started in 2010 to compare the efficacy and safety of i.p. administration of carboplatin with standard i.v. administration in combination with dose-dense i.v. administration of paclitaxel [20]. The dose of paclitaxel is 80 mg/m^2 given every week for both arms, and carboplatin at AUC of 6 will be given every 3 weeks either intravenously (control arm) or intraperitoneally (experimental arm) (**Figure 3A**).

Unlike the other two ongoing trials, this is the trial that purely investigates the role of carboplatin for i.p. administration. In addition, this is the first trial that will include suboptimal stage III and stage IV patients to test the hypothesis that was proposed by Miyagi *et al.* [11].

7.2 GOG252 trial

The GOG252 Trial is a three-arm randomized Phase III study to compare the efficacy and safety of two i.p. chemotherapy regimens with standard i.v. chemotherapy. The standard chemotherapy arm and one of the i.p. arms are exactly the same as in the iPocc trial except for incorporating the administration of bevacizumab. Administration of bevacizumab is similar to the GOG218 trial [17], by being administered at 15 mg/kg every 3 weeks with carboplatin at AUC of 6 in combination with weekly dose-dense administration of paclitaxel at 80 mg/m^2 for five cycles followed by maintenance bevacizumab for 17 cycles (**Figure 3B**). Another i.p. chemotherapy regimen is the modified dosing schedule of the winner arm of the GOG172 trial [3]. The dose of cisplatin was reduced from 100 mg/m^2 to 75 mg/m^2. Bevacizumab was administered with a similar dosing schedule to the other two arms.

This trial was originally designed to administer paclitaxel every 3 weeks, but it was amended to utilize dose-dense weekly administration after the JGOG3016 trial was presented at American Society of Clinical Oncology (ASCO) 2006. The GOG252 trial has been already closed for accrual and for the data to be matured.

7.3 OV21 trial

The OV21 trial is an international study with Gynecologic Cancer Intergroup. The study design is somewhat unique (**Figure 3C**). Eligible patients are those with clinically stage III

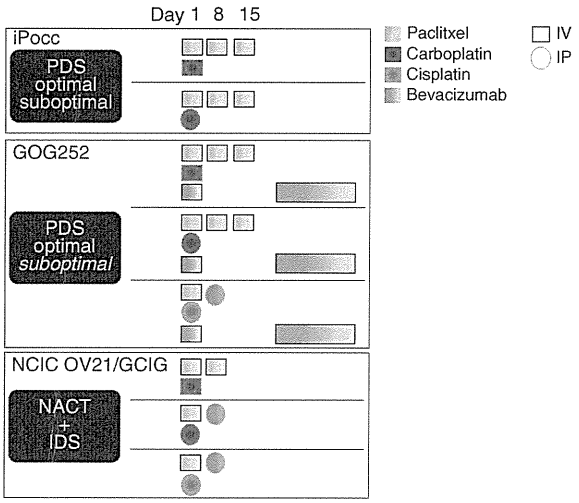

Figure 4. Comparison of iPocc, GOG252 and OV21 trial designs.

ovarian cancer who had received NACT followed by IDS, which resulted in the residual disease being < 1 cm (optimal). Those patients will be randomly assigned to either the i.v. arm or one of two i.p. arms. In the i.v. (control) arm, paclitaxel at 135 mg/m^2 and carboplatin at AUC 6 will be administered intravenously on day 1 followed by i.v. paclitaxel administration at 60 mg/m^2 on day 8. The original study was designed to administer paclitaxel at 175 mg/m^2 and carboplatin at AUC 6 on day 1, repeating every 3 weeks. However, it was amended to the current schedule when the JGOG3016 trial was presented at ASCO 2006. One of the i.p. arms is the replacement of administration of carboplatin from i.v. to i.p. Another arm is the modified GOG172 winner arm, similar to the GOG252 study, administering i.v. paclitaxel at 135 mg/m^2 on day 1 followed by i.p. administration of cisplatin at 75 mg/m^2 on day 2 and i.p. administration of paclitaxel at 60 mg/m^2 on day 8. These two i.p. arms are the objects to be chosen at the end of Phase II part, and winner will be compared with control arm as a Phase III study.

8. Future directions

These three trials have different designs, so it is not possible to answer all the questions regarding i.p. chemotherapy. However, as shown in Figure 4, it might be possible to resolve some of the questions by cross trial comparison, although it is not perfect because the power is not satisfactory. For example, the role of bevacizumab with i.p. chemotherapy with carboplatin will be elucidated by comparing the i.p. arms of iPocc and GOG252 trials. The role of the day 15 paclitaxel may be elucidated by comparing iPocc and OV21 trials.

9. Expert opinion

In spite of an enormous effort to improve the survival of ovarian cancer patients, prognosis of ovarian cancer is still poor. The i.p. chemotherapy is one of these approaches. Three large clinical trials conducted in the United States, GOG104, 114 and 172 trials, and meta-analysis showed survival benefit by giving cisplatin-based i.p. chemotherapy for optimally debulked stage III ovarian cancer patients.

As described in this review article, the main issue to improve in the i.p. chemotherapy is how we overcome the toxicities, mainly those caused by cisplatin. The most important question to solve the cisplatin-based toxicities is whether carboplatin can replace cisplatin. Based on the retrospective Phase I or Phase II studies, there are three Phase III trials to test whether i.p. carboplatin improves the survival over i.v. carboplatin administration.

Also, new evidence has been published, since the meta-analysis was conducted in 2006. These data include dose-dense weekly administration of paclitaxel, incorporation of bevacizumab and integration of NACT for selected patient population. It is important to incorporate this evidence into the future i.p. trial, but we believe it is most important to answer whether carboplatin can be a less-toxic substitute to cisplatin.

Currently ongoing three randomized Phase III trials will provide extremely important information about whether the i.p. carboplatin regimen will be beneficial. The iPocc trial will be the basis of other trials. Since GOG252 incorporated bevacizumab, the role of bevacizumab can be speculated by comparing iPocc trial and GOG252 trial. The role of i.p. therapy in patients with NACT can be estimated by comparing with iPocc and OV21. Although the GOG252 trial has been already closed for enrollment due to the full accrual, investigators of the gynecologic oncology field encourage participation in the iPocc or OV21 trial if one of them is available.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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• **This study is the randomized Phase III trial that purely compare the efficacy of i.p. versus i.v. carboplatin and trial design is discussed.**

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