厚生労働科学研究費補助金

がん臨床研究事業

局所限局小細胞肺がんの集学的治療に関する研究

平成１６年～１８年度　総合研究報告書

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主任研究者　田村　友秀

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厚生労働科学研究費補助金（がん臨床研究事業）
（総合）研究報告書

局所限局小細胞肺がんの集学的治療に関する研究

主任研究者　田村　友秀　国立がんセンター中央病院　総合病棟部長

研究要旨
限局期小細胞肺がんの予後改善を目的に、「エトポシド＋シスプラチン療法と加速多分割胸部放射線療法の同時併用後のEP療法と塩酸イリノテカン＋シスプラチン療法の第III相比較試験」を全国37施設の研究グループで実施し、平成18年10月までに281例の症例集積を完了した。平成19年3月の定期モニタリング結果では、主たる毒性は、好中球減少、食欲不振、感染など予期されたものであり、十分許容範囲であった。登録全例の生存期間も良好であった。追跡期間は5年であり、平成23年に最終解析を予定している。

分担研究者　西條長宏
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副院長
分担研究者　西脇　裕
国立がんセンター東病院
臨床検査部長
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副部長
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病院長
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企画調査室長　兼
呼吸器内科部長
分担研究者　横山　晶
新潟県立がんセンター新潟病院
副院長
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愛知県がんセンター
部長
分担研究者*2 樋田豊明
愛知県がんセンター中央病院
呼吸器内科部長
分担研究者　根来俊一
兵庫県成人病センター
呼吸器科部長
分担研究者　今村文生
地方独立行政法人大阪府立病院機構　大阪府立成人病センター
呼吸器内科部長
分担研究者　松井　薫
独立行政法人大阪府立病院機構
大阪府立呼吸器・アレルギー医療センター
医務局長
分担研究者　中川和彦
近畿大学医学部内科学教室
腫瘍内科部門
助教授
分担研究者　河原正明
独立行政法人国立病院機構
近畿中央胸部疾患センター
統括診療部長
分担研究者*3 上岡　博
岡山大学医学部医歯薬学総合研究科　血液・腫瘍・呼吸器内科学
助教授
分担研究者*4 木浦勝行
岡山大学医学部医歯薬学総合研究科　血液・腫瘍・呼吸器内科学
助教授

*1　平成16年4月1日～平成17年3月31日
*2　平成17年4月1日～平成19年3月31日
*3　平成16年4月1日～平成17年3月31日
*4　平成17年4月1日～平成19年3月31日

A. 研究目的

限局期小細胞肺がんの予後改善を目的として、エトポシド＋シスプラチン(EP)療法1コースと加速多分割胸部放射線療法(AH-TRT)の同時併用(EP/AH-TRT)後に、塩酸イリノテカン＋シスプラチン（IP）療法3コースを追加する治療法の有用性を検証するため、従来の標準的治療であるエトポシド+シスプラチン(EP)療法3コースの治療法を対照とした大規模第III相比較試験を計画し、

適正に実施する。

B. 研究方法

［研究形式］

全国37施設の研究グループによる第III相無作為化比較試験。エンドポイントは生存期間。3 年生存率を現在の 30%から 45%に向上させることを見込む。これは限局期小細胞肺がんの治癒率（5 年生存率）を 10-15%上げることに相当する。

［対象症例］

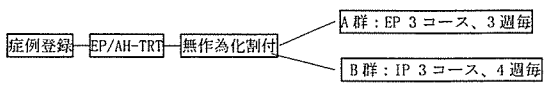
限局期小細胞肺がんの初回治療例で、70 才以下、ECOG Performance Status (PS) 0-1、主要臓器機能が保持された症例。患者本人の自由意思による文書同意を必須とする。

［症例登録と無作為化割り付け］

公定書協会臨床研究データセンター（国立がんセンター研究所がん情報研究部内）での中央登録・無作為化割付け方式をとる。無作為化割り付けの調整因子は施設と PS。

［治療内容］

EP 療法 1 コースと AH-TRT を同時併用後、EP あるいは IP 療法 3 コースを実施する。



EP 療法：	エトポシド	100 mg/m²	day 1,2,3
	シスプラチン	80 mg/m²	day 1,8,15
IP 療法：	イリノテカン	60 mg/m²	day 1,8,15
	シスプラチン	60 mg/m²	day 1

胸部放射線療法(AH-TRT)： 45Gy/30fr./3weeks

［解析方法］

最終解析は症例集積終了5年後。中間解析2回、安全性モニタリング年2回。

［予定症例数］

270 例（無作為化割り付け 250 例）、集積期間 3 年。（後に 4 年に延長）

（倫理面の配慮）

(1)施設 IRB の承認(2)文書を用いた十分な説明後、被験者本人の自由意思による同意(3)個人情報の厳守(4)臨床試験審査委員会、効果・安全性評価委員会による第三者的監視機構の設置を必須とした。

C.研究結果

1．平成 17 年度までの経過

平成 13 年に厚生労働省「21 世紀型医療推進事業」に「限局期小細胞肺がんの予後改善を目指した集学的治療の研究」（主任研究者　西條長宏）を申請し、全国の肺がん診療の主要施設 37 施設で研究グループを組織した。実施計画書は、JCOG (Japan Clinical Oncology Group)の協力を得、平成 14 年 7 月、JCOG 臨床試験審査委員会の承認を受けた。平成 14 年 9 月より日本公定書協会臨床研究データセンターにおいて症例登録を開始した。平成 16 年度からは本研究班で試験を継続した。

2．平成 18 年度の研究実施経過

平成 18 年 10 月までに一次登録 281 例を集積し、症例登録を完了した。登録期間の 1 年延長を要したが、ほぼ順調なペースといえる。症例集積の推進策として、登録の少ない 4 施設を削除、新たに 4 施設を加えた。また、研究参加施設の近隣医療機関に、本研究の紹介パンフレットを配布し、患者紹介を依頼した。

平成 19 年 3 月の定期モニタリングでは、両群の症例の主要背景因子に偏りはなかった。主たる毒性は、白血球減少、好中球減少、食欲不振、発熱、感染など予測されたものであった。グレード 4 の好中球減少は、導入化学放射線療法（EP/AH-TRT）、EP 群、IP 群の治療において、それぞれ 74%、67%、31%であった。IP 療法で問題とされる下痢は、グレード 3 の毒性を 14 例にみている。発熱性好中球減少は、EP/AH-TRT、EP 群、IP 群において、それぞれ 29%、22%、16%に認めた。また、重篤な有害事象として、肺臓炎による死亡 2 例（EP 群、導入 EP/AH-TRT）、脳梗塞による死亡 1 例（IP 群）の他、錯乱・心筋梗塞（EP/AH-TRT 中）、高/低血糖（EP/AH-TRT 中）、低カリウム血症（IP 群）などが報告されている。治癒を目指した強力な併用療法であり、安全性についても全体として、許容範囲内であると判断する。生存期間については、観察期間が短いものの、一次登録からの全例の生存期間中央値 35 か月、2 年生存率 61%と良好であった。

D. 考察

我々は、進展期小細胞肺がんに対する IP 療法の有用性を第 III 相試験において検証し、新たな標準的治療法として確立させ、世界的な評価を得た。この IP 療法を限局期小細胞肺がんの化学放射線療法に組み込んだ本研究は、限局期小細胞肺がんに対する新たな標準的治療の確立のための最重要課題であると同時に独創的な研究であるといえる。本研究では、全国の主要 37 施設で構成する研究グループを組織し、JCOG の臨床試験支援機構の協力を得、適切なデザインの研究計画を作成、研究体制を整備した。平成 14 年 9 月に本試験の症例登録を開始し、平成 16 年からは本研究課題として試験を継続した。平成 18 年 10 月までに一次登録 281 例、二次登録 258 例を集積し、登録を完了した。計画より 1 年遅れたものの、ほぼ順調であったと考える。参加施設の入れ替え、近隣医療機関へのパンフレット配布と紹介依頼など推進策の成果といえる。定期モニタリングでは、ほぼ期待通りの良好な治療成績が得られている。毒性についても予期した範囲の程度・頻度で、安全性についても許容範囲と結論される。最終解析は平成 23 年に予定しており、新たな標準的治療

が確立されることを強く期待している。

E. 結論

限局期小細胞肺がんの予後改善を目指した「EP 療法と AH-TRT 同時併用後の EP 療法と IP 療法の第 III 相比較試験」は、平成 18 年 10 月に 281 例の症例集積を完了した。

平成 19 年 3 月の定期モニタリングでは、毒性は許容範囲で十分耐容可能と判断された。全体の生存期間も良好であった。

平成 23 年に最終解析を予定しており、次期第 III 相試験に向け、新たな試験治療の検討を開始した。

F. 健康危険情報

なし

G. 研究発表

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H.知的財産権の出願・登録状況

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

研究成果の刊行に関する一覧表

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