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VARIA

Evaluation of systemic second-line therapy in recurrent or metastatic esophageal cancer

Xenia E. Bacinschi[1,3], Anca Zgura[1,3], Monica I. Stănuică[4], Laura Iliescu[2,3], Rodica M. Anghel[1,3]

Abstract: *Background: More than half of patients with locally advanced esophageal cancer are unresponsive to first-line chemotherapy. To date, there is no standard second-line regimen; new agents, such as immune-checkpoint inhibitors or anti-Neurotrophic Tropomyosin-Related Kinas agents, have only been recently recommended. This study aimed to assess the benefits of classical second-line chemotherapy in terms of survival and tolerance. Materials and Methods: This retrospective analysis assessed the benefits and tolerance of different second-line regimens of chemotherapy in progressive, locally advanced or metastatic oesophageal cancer treated at the department of Radiotherapy-Oncology at the Institute of Oncology between January 2011 and January 2017. Results: The analysis found 87 patient files with a median age 59.5 years (ranging between 41 and 84), of which 40.2% (35 patients) failed the first-line platinum and 5-fluorouracil combination. Histology favoured adenocarcinomas (63.2%). The patients were in good clinical condition, with ECOG 0–1 in 86.1% (74 patients), and less than five percent had more than three metastatic sites (3.4%, 3 patients). The regimens were mostly two-drug cytotoxic (53.9%, 47 patients): FOLFIRI in 18 patients (20.7%), FOLFOX in 18 patients (20.7%), vinorelbine–platinum combination in 11 patients (12.6%), and docetaxel in 40 patients (38.7%). The median treatment duration was 7.74 weeks (range 1 to 12). The general response rate was 47.1% (41 patients), including stable disease. The median time to progression was 7.61 weeks, with a range between 1.6 and 8.6 weeks, with no differences in this respect among the fourth type of treatment received (p = 0.170). Grade 3–4 toxicities, including neutropenia, gastrointestinal problems, and metabolic disorders, were observed in 44 patients (50.6%). The median event-free survival was 2 months (range between 1 and 6.3), and 63.2% (55 patients) subsequently received a third line of chemotherapy. Conclusion: Second-line chemotherapy is still the first-choice recommendation in all fit patients with advanced oesophageal cancer. The new agents are efficacious only in cases with PD-L1 positive or high microsatellite instability.*

Keywords: *second-line chemotherapy, locally advanced/metastatic oesophageal cancer, survival benefit, toxicity*

INTRODUCTION

Esophageal cancer has two histopathological subtypes: squamous carcinoma found in the superior and upper-two-thirds regions [1], and adenocarcinoma, which develops at deep inferior and junctional mucosal glands. Both have high similarities in their pattern of metastasis [2]. Esophageal cancer is the sixth most common cause of specific deaths worldwide [3]. The peak of incidence is reported in the sixth decade of age, and cancer occurs more frequently in men [4].

Approximatively half of the patients have advanced disease at diagnosis. Three-quarters of resectable disease will relapse, of which more than half will be candidates for

Corresponding author: Anca Zgura
medicanca@gmail.com

[1] Department of Oncology-Radiotherapy, Prof. Dr Alexandru Trestioreanu Institute of Oncology, Bucharest, Romania
[2] Department of Internal Medicine II, Fundeni Clinical Institute, Bucharest, Romania
[3] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[4] Department of Radiotherapy II, Prof. Dr Alexandru Trestioreanu Institute of Oncology, Bucharest, Romania

second-line systemic therapy [5]. Overall five-year survival is less than 10% [3].

Regarding the first line, for adenocarcinoma, the regimen used is similar to those used in gastric cancer, fluoropyrimidine-based chemotherapy while in squamous esophageal cancer the regimen is cisplatin-based and in general, regardless the histology, the median overall survival (OS) does not exceed nine months [6].

Currently, there is no established second-line systemic treatment for esophageal cancer [7]. Subsequent lines of chemotherapy have recently been proposed by NCCN (National Comprehensive Cancer Network) guidelines for locally advanced or metastatic esophageal and oesophagogastric junction cancer [8]. New treatment options include ramucirumab and paclitaxel which give a 2-month benefit in median overall survival (9.6 months versus 7.4 months for paclitaxel only, p = 0.017) [9]. Pembrolizumab is a category 1 recommendation anti-PD1 (programmed cell death protein) antibody for esophageal PD-L1 (programmed death-ligand 1) positive or for any histology displaying MSI-H (microsatellite instability-high) or d-MMR (deficient mismatch repair) status [8] based on a benefit of 1 month (8.2 vs. 7.1 months, HR = 0.78, P = 0.0095) versus classical chemotherapy taxanes or irinotecan in the squamous cell carcinoma subgroup [10]. With a 2B level of recommendation, entreticnib is proposed for a median 10 months' duration of response, 95% CI [7.1 - NE] [11], and larotrectinib is proposed in NTRK (Neurotrophic Tropomyosin-Related Kinase) fusion-positive esophageal tumours [12].

MATERIALS AND METHODS

Medical files from the institutional database of patients diagnosed with metastatic invasive esophageal squamous cell carcinoma (SCC) or adenocarcinoma (AC), referred to our institution for second-line chemotherapy were analysed. The main inclusion criteria were age >18 years, clinical-stage IV according to AJCC 8th edition [15], treatment by at least one regimen of chemotherapy or radiotherapy and assessed for response.

Patients were excluded if they were eligible for salvage surgery or had synchronous cancer or severe comorbidities that might impair our results. The study was approved by Ethycal Committee of Insitute of Oncology "Prof. Dr. Alexandru Trestioreanu", Bucharest, Romania no 1597/17th December 2010.

The primary outcome was time to progression, evaluated between the start of second-line chemotherapy and first progression or death by any cause. Secondarily, treatment benefit was evaluated using CT scan, and, in terms of tolerance, the rate and duration of grade III-IV adverse events (AE) classified according to CTCAE v. 4.03 [16].

Data were analysed using SPPS version 23 (IBM Corporation, Armonk, NY, USA). Non-parametric tests were used to compare subgroups. The chi-squared test determined the correlation between response to treatment and demographic and clinical variables. Fisher's exact test was employed when there were fewer than five cases in any cell of the 2×2 table. The associations between variables and survival parameters were analysed by logistic regression analysis, and survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) for variables were calculated using the Cox proportional hazard model. All statistical tests were two-sided, and a p-value < 0.05 was considered significant.

RESULTS

3.1. Patient characteristics

During the period of analysis, a total of 87 patients were treated in our department by chemotherapy for esophageal cancer, with a mean age 59.5 (range between 41 and 84). Among them, 37 patients were treated for recurrent disease, 29 patients had metastatic disease at initial presentation, and 21 patients received the second-line treatment for a locally advanced disease with no indication of surgery or radiotherapy.

The principal histology was adenocarcinoma (63.2%, 55 patients), and the primary lesion was typically situated in the lower and junction of the esophagus (48.9%, 51 patients). One-third of patients had liver metastasis, but almost all had no more than two sites of secondary lesions (96.6%, 84 patients) and were in generally good condition, with ECOG 0–1 in 85.1% (74 patients) (Table 1).

Table 1: Patients characteristics in target population

Characteristics	n	%
Age (years): median 59.5; range [41–84]		
40–50	14	16.1
51–70	63	72.4
>70	10	11.5
Gender		
Male	58	66.7
Female	29	33.3
Location of primary lesion		
Upper	14	16.1
Middle	22	11.5
Lower	25	35.6
Junction	26	33.3

Characteristics	n	%
Histopathological sub-type		
Squamous cell carcinoma	32	36.8
Adenocarcinoma	55	63.2
The initial stage of disease		
I	17	19.5
II	10	11.5
III	31	35.6
IV	29	33.3
Metastatic site		
Lymph node	18	20.7
Lung	18	20.7
Liver	30	34.5
Bone	12	13.8
Other	9	10.3
Number of metastatic sites		
1	50	57.5
2	34	39.1
3 and more	3	3.4
ECOG		
0	44	50.6
1	30	34.5
2	13	14.9

Abbreviations: CHT = chemotherapy, ECOG = Eastern Cooperative Oncology Group Performance Status, FU-PI: 5-fluorouracil–platinum regimen, LV5FU2CDDP =5-fluorouracil 1600 mg/m2 + leucovorin 200 mg/m2 + cisplatin 50 mg/m2q2w, 5FU-CDDP=5-fluorouracil 1000 mg/m² day 1-4 + cisplatin 100 mg/m² day 1 q3w, PR = partial remission , PD = progressive disease, SD = stable disease.

3.2. Treatment characteristics

The first-line combination of cisplatin plus 5-FU (5-fluorouracil) was most typical in localized and metastatic esophageal cancer (40.2%, 35 patients). This combination involves 5-fluorouracil 1000 mg/m² per day for 4 days and cisplatin 100 mg/m² on day 1 every 21 days (17) or, in the so-called LV5-FU2 – cisplatin two-week regimen, cisplatin 50 mg/m², calcium folinate 200 mg/m², 5-FU 400 mg/m² on day 1 and 5-FU 1200 mg/m² over a 46-hour continuous infusion (18). Other protocols used were FOLFIRI (39 pts, 44.8%) vinorelbine-cisplatine based (10 pts, 11.5%) and taxane based (3 pts, 3.4%).

Patients who received FOLFOX regimen, as second line treatment modified they represented 20.7% (18 patients), 46% (40 patients) received a docetaxel regimen, 20.7% (18 patients) received a FOLFIRI regimen, and 12.6% (11 patients) received a vinorelbine–cisplatin regimen. Details regarding the protocols used in second line are listed in the Table 2.

Table 2: Second line chemotherapy protocols summary.

Second line regimen	Protocol summary	Number patients	Response rate	Reference
FOLFOX6	oxaliplatin 85 mg/m², leucovorin 200 mg/m², 5-FU push 400 mg/m², 5FU 2400 mg/m² for 46 hours, q2w	18 (20.7%)	83.3% (15 pts)	(19)
NVB-CDDP	vinorelbine 25 mg/m² day 1+ 8, cisplatin 80 mg/m² q3w	11 (12.6)	45.5% (5 pts)	(20)
FOLFIRI	irinotecan 150–180 mg/m², 5-FU 400 mg/m² push, leucovorin/ calcium folinate acid, 125mg/m², 5-FU 2400 mg/m²/46 hours, q2w	18 (20.7%)	50% (9 pts)	(21)
DTX	docetaxel 75mg/m², q3w	40 (46%)	12 (30%)	(22)

Abbreviations: FOLFOX6 = Oxaliplatin 85 mg/m²+ leucovorin 200 mg/m² + 5 FU 2800 mg/m² q2w, FOLFIRI = Irinotecan 150–180 mg/m² + leucovorin 125 mg/m² + 5-FU 1600 mg/m² q2w, NVB-CDDP = Vinorelbine 25 mg/m² day 1 + 8 + cisplatin 80mg/m² q3w, DTX = docetaxel 75 mg/m² q3w.

The median time of chemotherapy was 7.74 weeks, with a range between one and twelve weeks. The mean number of cycles was 2.36, with a range between one and seven cycles and no significant differences was registered between the medians of any regimen (p = 0.065). Choice of chemotherapy regimen was correlated with the initial stage of disease, histological subtype, the number of metastatic sites, site of metastasis and performance status (p < 0.0001). More than half of the patients included in the study were able to benefit from the third line of treatment (55 pts, 63.2%) (Table 3).

3.3. Benefit

The response rates that were obtained were as follows: 28.7% (25 patients) had partial remission, 18.4% (16 patients) stable disease and 52.9% (46 patients) recorded either clinical or radiological progression.

Table 3: Second line chemotherapy protocols characteristics and toxicity.

Characteristics	n	%
Number of cycles: median 2.87, range [1–7]		
< 2	28	32.2
2–4	45	51.7
> 4	14	16.1
CHT duration (weeks): median 7.74, range [1–12]		
< 6	20	22.9
6–8	52	59.7
> 8	15	17.3
Grade 3–4 toxicities		
Without	44	50.6
Haematological	30	34.5
Gastrointestinal	10	11.5
Metabolic disorders	3	3.4

The difference between the response to different second line regimen of chemotherapy were not statistically significant (p=0.042).

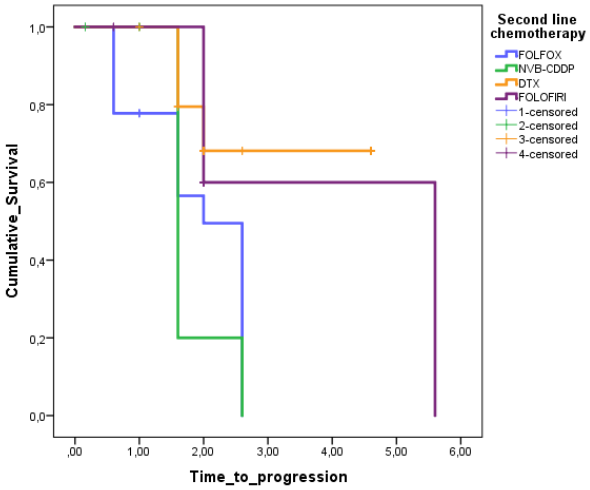
We estimated that the median OS on the basis of the results of several studies of second-line chemotherapy [26-29].

Response was directly correlated with primary tumour location (p = 0.022) and histopathological subtype (p = 0.017) and with tumour burden and type of chemotherapy regimen (p < 0.0001).

The median time to progression was 7.61 weeks, ranging between 1.6 and 8.6 weeks, with no statistical difference between the fourth type of treatment received (p = 0.170).

Time to progression was associated with the number of metastatic sites (HR 2.886, p = 0.004) but not with the type of chemotherapy regimen (p = 0.373). By contrast, the log-rank test showed significant differences in time to progression by type of chemotherapy (chi-square 22.1852, p < 0.0001) (Figure 1).

Figure 1: Kaplan–Meier curves in locally advanced or metastatic oesophageal cancer patients according to the second-line chemotherapy regimen.



Fifty-five patients (63.2%) could benefit from a subsequent, third line of chemotherapy.

The median event-free survival for all patients was two months, with a range between 1 and 6.3 months.

3.4 Toxicity

Forty-four patients (50.6%) displayed no grade III-IV toxicities. Seven patients displayed haematological and gastrointestinal disorder together, and all patients presenting metabolic disorder also had febrile neutropenia.

DISCUSSION

Esophageal cancer are a challenging disease for which there are limited treatment effective options. Despite research, the only treatment with clinical benefit and more accessible in the second-line setting remains chemotherapy.

The population in our study was in relatively good clinical condition: 85.1% with ECOG 0 or 1, almost all without more than two sites of metastasis (96.6%), younger than 70 and, in more than 60%, bearing adenocarcinoma as histological subtype. In this analysis, the most-used (53.9% of cases, 47 patients) were two-agent regimens: FOLFIRI, or cisplatin–vinorelbine, and FOLFOX. The median treatment duration was 7.74 weeks, and most had received 5-fluoropyrimidine in the first line (85.1%, 74 patients).

The general benefit was reflected by a 47.1% (41 patients) response rate, including cases with disease stabilisation, the median time to progression of 7.61 weeks (range 1.6 to 5.6 weeks) and a median time to death of 2 months (range 1 to 6.3 months). Chemotherapy was generally tolerated, though almost half of patients developed grade III-IV toxicities; one-third of these were mostly non-complicated grade III anaemia or thrombopenia.

Several earlier retrospective or phase II studies have evaluated whether second-line chemotherapy might be useful for oesophageal cancer patients.

Regarding irinotecan, in a small phase II study, 29 patients (27 with adenocarcinoma) were given capecitabine 2,000 mg/m2 day on days 1–14 and irinotecan 250 mg/m2 every 3-week cycle. The study showed an objective response of 17% (five patients) and median progression-free survival of 3.1 months 95% CI [2.2–4.1] and median OS of 6.5 months 95% CI [6–7.1] with a 10% rate of febrile neutropenia [24].

In another phase II study, irinotecan combined with cetuximab in 63 cases of platinum-refractory gastro-esophageal carcinoma, led to an 11% (6 patients) partial response rate and 37% (23 patients) rate of stabilization, with median progression-free survival of 2.8 months, median overall survival of 7.1 months and a 32% rate of grade III-IV toxicities [25].

Even as a single agent, irinotecan showed a survival advantage, compared to best supportive care, in 40 patients with metastatic or locally advanced adenocarcinoma gastro-esophageal of the junction. Irinotecan given of 250 mg/m2 with the possibility of an increase to 350 mg/m2 if well-tolerated, gave a 53% rate of stable disease and 50% clinical benefit versus 7% and a median survival of 4 months 95% CI (3.6–7.5) versus 2.4 months 95% CI (1.7–4.9) and 0.48 HR for death 95% CI (0.25-0.92) [26].

In untreated metastatic gastro-esophageal adenocarcinoma (N = 220 patients), by substituting oxaliplatin for cisplatin in a FOLFOX-like regimen (fluorouracil 2,600 mg/m^2 over 24-hour infusion, leucovorin 200 mg/m^2 and oxaliplatin 85 mg/m^2 every 2 weeks) there was no statistically difference in terms of progression-free survival (5.7 vs. 3.9 months, p = 0.077), response rate (35% versus 20%) or median overall survival (10.7 vs. 9.8 months). Adverse events were significantly fewer (9% vs. 19%) and treatment showed better responses in patients aged over 65 years old compared to cisplatin: 41.3% response rate versus 16.7% (p = 0.012), time to treatment failure of 5.4 versus 2.3 months (p < 0.001) and progression-free survival of 6.0 versus 3.1 months (p = 0.029) [19]. A later meta-analysis (N =1294 patients in three randomized trials), regarding the meme subject, showed improved progression-free survival (HR = 0.88, p = 0.02) and overall survival (HR 0.88, p = 0.04) in advanced, unresectable gastric cancer [27].

In a monocentric retrospective study of 94 patients with metastatic esophageal cancer, a modified FOLFOX 6 regimen comprising fluorouracil 2400 mg/m^2 over 48 hours after a bolus of 400 mg/m^2, leucovorin 400 mg/m^2 and oxaliplatin 85 mg/m^2 gave an objective response rate of 41.4% (39 patients), of whom 6.3% (6 patients) with a complete response and 21.3% (20 patients) with stable disease. Any grade of hematologic toxicity was found in 69.1% of cases [28].

Regarding taxane-based chemotherapy, the UK COUGAR-2 phase III study(N=168) confirmed the benefit of second-line chemotherapy by docetaxel 75 mg/m^2 every 3 weeks compared to best supportive care by a median OS of 5.2 versus 3.6 months (HR 0.67, 95% CI [0.49–0.92]; p = 0.01) in patients with a good performance status [22].

In a retrospective study which assessed in 163 patients the clinical benefit of second-line taxane therapies, docetaxel at 70 mg/m^2 every 3 weeks versus paclitaxel 100 mg/m^2 weekly for 6 weeks of 8 weeks cycle, survival without progression was identical (2.3 months) for both regimens the overall survival was 6.1 versus 5.3 months, with 32.6% and 16.1% rates, respectively, of grade III-IV toxicities [29].

Only a few randomized studies have compared the benefits of different second-line chemotherapy regimens, mainly in gastric cancer and in Asian patients.

In 202 Korean patients with less than two prior lines of chemotherapy, randomized in a 2:1 ratio treated with docetaxel or irinotecan compared with supportive treatment,was recorded a superior overall survival (5.3 vs. 3.8 months; HR 0.66, p = 0.007) while no survival difference was recorded between docetaxel and irinotecan. The tolerance was good, the hematologic toxicities manageable and the rates of non-haematologic toxicities were comparable in both groups but there was with no significant differences in terms of survival between two regimens of chemotherapy [30].

In another Asian study, in 223 Japanese patients randomized to received paclitaxel alone or irinotecan alone as second line treament, the median overall survival was comparable (9.5 vs. 8.4 months, p = 0.38), although less toxicity appeared in the paclitaxel arm and more of those patients went on to receive third-line chemotherapy [31].

In a meta-analysis of 28 studies (N = 4810 patients), mostly retrospective, the second line showed no difference between taxane- and irinotecan-based regimens in terms of overall survival (HR 0.94, CI [0.78–1.13]) or survival without progression (HR 0.84, CI [0.69–1.03]), nor was there any difference for any single-agent regimen compared to best supportive care (HR 0.65, 95% CI [0.53–0.79]. Median survival gain ranged from 1.4 to 2.7 months among the individual studies considered. Doublet chemotherapy based on taxane or irinotecan plus platinum and fluoropyrimidine did not display different survival but showed increased toxicity compared to taxane or irinotecan monotherapy [6].

As far as new agents, despite the failures of several clinical trials involving molecularly targeted agents, several have shown some benefits worth mentioning that represent the basis of NCCN recommendations [8].

Ramucirumab, an antibody that targets the vascular endothelial growth factor receptor 2, the expression of which might be a mechanism of the aggressiveness of gastric and gastro-esophageal junction adenocarcinoma, led in pre-treated patients with esophagogastric cancer significant survival benefit, 5.8 months compared with 3.8 months for placebo (HR 0.776, 95% CI [0.603–0.998]), a similar benefit were seen in the COUGAR-02 trial assessing the benefit of docetaxel [32].

By adding paclitaxel to ramucirumab, in another phase III trial, it was reported a significant benefit in terms of median OS 9.6 months versus 7.4 months, HR 0.807, 95% CI [0.678–0.962] (p = 0.017). In terms of adverse events, the association was mainly marked by hypertension (14%, 46 patients vs. 2%, 8 patients), fatigue (12%, 39 patients vs. 5%, 18 patients) and abdominal pain (6%, 20 patients vs. 3%, 11 patients) [9].

Regarding the role of immune checkpoint inhibitors, in the KEYNOTE 181 trial (N = 628 patients), the response rates with pembrolizumab were double or even triple those achieved with chemotherapy at the investigator's choice (paclitaxel,

docetaxel, or irinotecan), though the median duration of response was longer in the group with PD-L1 CPS (Combined Positive Score) equal or higher than 10 (9.3 vs 7.7 months with chemotherapy HR 0.69; 95% CI [0.52–0.93]; p = 0.0074); 12-month overall survival rate in CPS ≥10 patients was 43% compared to 20%. With pembrolizumab, fewer patients had drug-related adverse events of any grade (64% vs. 86%) or grades 3 to 5 (18% vs. 41%) compared with chemotherapy. The most common events were fatigue (11.8%), hypothyroidism (10.5%), loss of appetite (8.6%), nausea (7.0%) and diarrhoea (5.4%) [10]. The phase III KEYNOTE-590 study (ClinicalTrials.gov identifier NCT03189719), assessing the efficacy and tolerance of pembrolizumab plus chemotherapy as first-line therapy for locally advanced or metastatic esophageal carcinoma, is ongoing [33].

HER 2 (human epidermal growth factor receptor) expression was not considered in the study due to the fact that it was not frequently found in the study population, and Trastuzumab treatment is not approved in Romania for second-line treatment [23, 34].

The time to disease progression was quite difficult to track due to the fact that several patients have continued their treatment at other institutions or have been transferred to a palliative care unit without the possibility to obtain their date of death, because in Romania there is not a computerized death reporting system and this is a limitation of the study.

The limitations of our study were the retrospective character, small number by each subgroup of treatment patients and lack of the subgroup of patients treated with both active and passive immunotherapy.

CONCLUSIONS

Immunotherapy using immune checkpoint inhibitors has revolutionized the cancer treatment and becomes the new standard of second line treatment in non-operable advanced or metastatic esophageal cancer.

Moreover, the new agents seem to be efficacious only in cases where the expression PD-L1 is positive or high microsatellite instability is present.

The old chemotherapy regimen has a similar efficacy and relatively good tolerance and still might the first-choice recommendation in fit patients

This analysis showed a generally good response to systemic treatment, comparable to the responses reported in other studies.

Our study did not show a difference in clinical benefit depending on the treatment regimen.

Moreover, the incidences of adverse events such as grade 3 or higher leukopenia and febrile neutropenia was observed in all patients. Forty-four patients (50.6%) displayed no grade III-IV toxicities. Seven patients displayed haematological and gastrointestinal disorder together.

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All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Patient consent for publication: Not applicable.

Competing interests:

The authors declare that they have no competing interests.

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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