Efficacy and safety evaluation of fludarabine-based chemotherapy regimen for patients with non-Hodgkin lymphoma
A meta-analysis

Xiaoping Zhang, MD, Zheng Ge, MD, Baoan Chen, MD, Ran Liu, MD, Chong Gao, MM∗

Abstract
This meta-analysis was performed to evaluate the efficacy and safety of fludarabine (F)-based regimen for the treatment of non-Hodgkin lymphoma (NHL) compared with other regimens with no F contained.

PubMed, Embase, Cochrane Library, Wanfang, VIP, and CNKI databases were searched to identify eligible literatures. R software version 3.12 was used for statistical analysis. Odds ratio (OR) with 95% confidence interval (CI) were utilized to express the complete response, overall response and adverse events outcomes. Egger test was carried out to examine the publication bias and sensitivity analysis was performed to evaluate the stability of our results.

Twelve eligible literatures consisting of 1587 patients were included in this study. Greater complete response (OR=1.66, 95% CI: 0.98–2.90) and overall response (OR=1.38, 95% CI: 0.85–2.24) were found for patients who received F-based regimen than those received other regimens, although the results were not statistically significant. In addition, F-based regimen was associated with significantly lower risk of adverse events compared with other regimens (OR=0.46, 95% CI: 0.28–0.74). Results of subgroup analysis showed that significantly lower incidence was presented only for constipation among the 7 specific adverse events (OR=0.03, 95% CI: 0.01–0.14).

F-based chemotherapy regimen was an effective and well-tolerated treatment for patients with NHL.

Abbreviations: BR = bendamustine, rituximab, CdA = cladribine, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone, CHVP = cyclophosphamide, doxorubicin, vindesine, prednisone, CI = confidence interval, CVP = cyclophosphamide, vincristine, prednisone, EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, F = fludarabine, Fl = fludarabine, ilosfamide, FM = fludarabine, mitoxantrone, FMD = fludarabine, mitoxantrone, dexamethasone, FR = fludarabine, rituximab, NHL = non-Hodgkin lymphoma, OR = odds ratio, PFS = progression-free survival, RCTVP = rituximab, cyclophosphamide, pirarubicin, vindesine, prednisone, RFT = rituximab, fludarabine, pirarubicin.

Keywords: adverse events, complete response, fludarabine, meta-analysis, non-Hodgkin lymphoma, overall response

1. Introduction
The non-Hodgkin lymphoma (NHL) is a group of heterogeneous neoplasms which develops usually in lymphoid tissues but can occur in almost any tissue.110 Approximately, 85% to 90% NHL derives from B lymphocytes and the remainder arises from T lymphocytes or NK lymphocytes.12 Under the most recent World Health Organization classification revised in 2016,13 over 60 specific subtypes of NHL are recognized in which diffuse large B cell lymphoma, follicular lymphoma, and mucosa-associated lymphoid tissue lymphoma occur most frequently. NHL makes up about 4.6% of all cancer diagnoses and is the fifth or sixth common cancer in women or men.11 Overall, NHL is a curable tumor that needs effective treatments.

Chemotherapy is one of the effective treatments for NHL in addition to radiation therapy, immunotherapy, and radioimmunotherapy.14–6 Various chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CVP (cyclophosphamide, vincristine, prednisone) have high efficiency but are associated with poor progression-free survival (PFS).17–9 The disease relapses inevitably, and multiple cycles of same regimen are commonly performed to achieve further remission.10 In contrast, fludarabine (F), a purine analog has been reported to have a helpful influence on median PFS10 and also presents a relatively satisfactory clinical efficacy on relapsed and indolent NHL.11,12 Furthermore, F-based regimen is strongly recommended by National Comprehensive Cancer Network as a second-line treatment. However, controversies exist regarding the efficacy and safety of F-based chemotherapy regimen for patients with NHL. Klasa et al19 have reported the superiority of this regimen on median PFS. In addition, it is suggested as a safe regimen with negligible
complications by several clinical trials. However, no significant improvement on PFS is detected in the study of Zinzani et al. and it is accused to be unbearable for the reason of severe toxicity. Therefore, a meta-analysis is urgently needed to achieve a comprehensive conclusion, which is rarely studied by other investigators.

Meta-analysis is an analytical technique that combines the results of multiple studies, and it increases the sample size and thus the power to study effects of interest. In this study, a pairwise meta-analysis was performed to evaluate the efficacy and safety of F-based chemotherapy regimen for the treatment of NHL compared with other chemotherapy regimens which did not contain F.

2. Methods

2.1. Data acquisition and search strategy

A systematic literature search was conducted on PubMed, Embase, Cochrane Library, Wanfang, VIP, and CNKI databases. Additionally, reference lists of relevant literatures were also searched manually to identify eligible literatures. Key words included: fludarabine, non-Hodgkin lymphoma, and non-Hodgkin’s lymphoma. Relevant studies were obtained until January 2017, and there was no language restriction.

2.2. Selection criteria

Inclusion criteria were: full-published articles in Chinese or English; patients with NHL; patients in intervention group received single F chemotherapy or F-based chemotherapy regimen, such as FM (fludarabine, mitoxantrone), RFT (rituximab, fludarabine, pirarubicin), FMD (fludarabine, mitoxantrone, dexamethasone), FI (fludarabine, ifosfamide), and FR (fludarabine, rituximab); patients in control group received other chemotherapy regimens with no F contained, such as CHOP, CVP, CHVP (cyclophosphamide, doxorubicin, vindesine, prednisone), BR (bendamustine, rituximab), RCTVP (rituximab, cyclophosphamide, pirarubicin, vindesine, prednisone), CdA (cladribine), and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin); parameters regarding the kind of chemotherapy in control group and 7 reduplicative studies were further excluded. Finally, 12 eligible studies were included in this meta-analysis.

The characteristics of all eligible literatures are listed in Table 1. A total of 1587 patients (804 patients in intervention group and 783 patients in control group) were included in this study. Studies were conducted between 1993 and 2014, and published between 1999 and 2015. Most of the patients suffered from indolent, advanced, or relapsed NHL. Locations of studies included Italy, France, Germany, Canada, and China. Age of patients differed obviously among different literatures, but no significant difference was found between 2 groups in every single literature. Sex distribution between the intervention and control groups was similarly balanced in every eligible literature. Follicular NHL took up a large proportion among all specific subtypes of NHL for patients enrolled in our study. In addition, most of the patients were diagnosed as III or IV stage according to the Ann Arbor staging system.

2.3. Data extraction

Data were extracted by 2 investigators from the eligible literatures independently, such as name of first author, year of publication, location of study, year of study, the specific subtypes of NHL, number of patients, and demographic characteristics (sex ratio, age, etc.). Disagreements were settled by group discussion with a third investigator.

2.4. Statistical analysis

The meta-analysis was performed by using R software version 3.12 (R Foundation for Statistical Computing, Beijing, China, meta package). Odds ratio (OR) with 95% confidence interval (CI) were utilized to evaluate the effect of chemotherapy for all dichotomous outcomes. The potential heterogeneity was assessed by Q statistic and I². A random-effects model was used to pool the effect size if significant heterogeneity was detected (P < .05 or I² > 50%), otherwise, a fixed-effects model was adopted. Egger test and funnel plot were carried out to examine the publication bias, and trim and fill method was applied to recount the effect size if publication bias was detected. Furthermore, the sensitivity analysis was conducted by removing one literature at a time to evaluate the stability of our results.

3. Results

3.1. Eligible literatures

Figure 1 shows the flow diagram of literature selection. A total of 1069 literatures (348 in PubMed, 453 in Embase, 49 in Cochrane Library, 55 in Wanfang, and 62 in CNKI database) were obtained by using the search strategy. After removing 498 duplicates and 463 irrelevant articles, a full-text review was applied to the remaining 108 articles. Ninety-six articles (15 letters, 16 case series or reports, 33 reviews, 11 articles with irrelevant data, 14 articles without clear clarification of the kind of chemotherapy in control group and 7 reduplicative studies) were further excluded. Finally, 12 eligible studies were included in this meta-analysis.

The characteristics of all eligible literatures are listed in Table 1. A total of 1587 patients (804 patients in intervention group and 783 patients in control group) were included in this study. Studies were conducted between 1993 and 2014, and published between 1999 and 2015. Most of the patients suffered from indolent, advanced, or relapsed NHL. Locations of studies included Italy, France, Germany, Canada, and China. Age of patients differed obviously among different literatures, but no significant difference was found between 2 groups in every single literature. Sex distribution between the intervention and control groups was similarly balanced in every eligible literature. Follicular NHL took up a large proportion among all specific subtypes of NHL for patients enrolled in our study. In addition, most of the patients were diagnosed as III or IV stage according to the Ann Arbor staging system.

3.2. Complete response

Evidence of heterogeneity was shown (I² = 76.6%, P < .0001) across the 11 studies that reported complete response data, thus a random-effects model was applied to calculate the pooled effect size. Pooled estimates indicated that patients in intervention group obtained greater complete response than those in control group (OR = 1.66, 95% CI: 0.98–2.80), but the results did not reach statistical significance (Fig. 2A). Among
Table 1
Characteristics of eligible studies.

| Author         | Publication year | Location | Style               | Study year | Group N                      | Median age, years (range) | Gender (M/F) | Follicular NHL | Ann Arbor stage (II/III/IV) |
|---------------|------------------|----------|---------------------|------------|-----------------------------|---------------------------|--------------|----------------|-----------------------------|
| Foussard C    | 2005             | France   | Advanced low-grade  | 1995.11–1999.12 | FM 72 | 66 (55–75) | 35/37 | 44          | 3/9/60          |
| Hagenbeek A   | 2006             | NA       | Low-grade malignant | 1993–1997   | CHOP 72 | 65 (55–75) | 38/34 | 42          | 3/7/62          |
| Hou Y         | 2012             | China    | Indolent            | 2002.1–2010.12 | RFT 127 | 62 (21–79) | 69/38 | 106 | 4/43/14 | 12/16/44 |
| Klasa RJ      | 2002             | Canada   | Recurrent low-grade | 1993.10–1996.12 | F 47 | 58 (32–81) | 27/20 | 12 | 1/15/29 |
| Rummel M      | 2016             | Germany  | Relapsed indolent   | 2003.10–2010.8 | RFI 106 | 66.4 (59.3–73.7) | NA | 53 | 0/25/82 |
| Tondini C     | 2000             | Italy    | Low-grade           | 1993.1–1997.7 | CHVP 72 | 65.5 (55–74) | 35/37 | 44          | 3/7/62          |
| Hagenbeek A   | 2006             | NA       | Low-grade malignant | 1993–1997   | CHVP 72 | 65.5 (55–74) | 35/37 | 44          | 3/7/62          |
| Kundaliya J   | 2005             | India    | Indolent B-cell     | 1997–1999   | CHOP 50 | Median age: 62.5 | NA | 24/66 | 3/7/62 |
| Yan-hong H    | 2015             | China    | NA                  | 2011.3–2014.4 | CHOP 68 | 54 (31–70) | 25/33 | 68 | 8/4/74 |
| Xue-dong Y    | 2013             | China    | Relapsed indolent   | 2010.1–2012.9 | RFT 187 | 55 (28–79) | 69/38 | 106 | 4/43/14 |
| Chang-yun Y   | 2009             | China    | Relapsed            | 2007.1–2008.12 | FMD 17 | 40 (36–61) | 21/29 | 18 | 5/43/14 |
| Chun-yan W    | 2007             | China    | Relapsed indolent   | 2003.5–2005.11 | FMD 16 | 53 (32.0–70.0) | NA | 19 | 1/15/29 |

BR = bendamustine, rituximab, CdA = cladribine, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone, CHVP = cyclophosphamide, doxorubicin, vindesine, prednisone, CVP = cyclophosphamide, vincristine, prednisone, EPCH = etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, F = fludarabine, Fl = fludarabine, ifosfamide, FM = fludarabine, mitoxantrone, FMD = fludarabine, mitoxantrone, dexmethasone, FR = fludarabine, rituximab, RFT = fludarabine, mitoxantrone, FMD = fludarabine, mitoxantrone, ifosfamide, RFT = fludarabine, rituximab, RFT = fludarabine, rituximab, FR = fludarabine, rituximab.

Figure 2. Forest plots of treatment effect for (A) complete response and (B) overall response.
these 11 studies, only the study of Rummel et al.\textsuperscript{[27]} exhibited significantly worse response for patients in intervention group than those in control group (OR = 0.31, 95% CI: 0.16–0.57; Fig. 2A). To be noted, significant difference was shown after omitting this study for the parameter of complete response (OR = 2.03, 95% CI: 1.37–2.99; Fig. 3A). No publication bias was detected across the studies (t = 0.38, P = .71). As shown in the funnel plot, no publication bias was existed (Fig. 4A).

3.3. Overall response

According to the WHO criteria, overall response rate was defined as the sum of complete response rate and partial response rate. A random-effects model was used to pool the estimates since heterogeneity was detected (I\textsuperscript{2} = 74.8\%, P < .0001). Pooled estimates suggested that patients in intervention group obtained higher overall response rate than those in control group (OR = 1.38, 95% CI: 0.85–2.24), but the results had no statistically significant (Fig. 2B). Similar to the complete response, significantly decreased overall response rate was found in intervention group in the study of Rummel et al.\textsuperscript{[27]} (OR = 0.23, 95% CI: 0.12–0.42; Fig. 2B), which was unique among the 11 relevant studies.\textsuperscript{[10,15,22–27,29–31]} Significant difference was also exhibited with the omission of this study for the parameter of overall response (OR = 1.66, 95% CI: 1.26–2.18; Fig. 3B). No publication bias was detected across the studies (t = 0.60, P = .56). As shown in the funnel plot, no publication bias was existed (Fig. 4B).

3.4. Adverse events

A random-effects model was used since there was heterogeneity for studies related with adverse events (I\textsuperscript{2} = 80.7\%, P < .0001). Incidence of adverse events was significantly lower for patients in
intervention group than those in control group (OR = 0.46, 95% CI: 0.28–0.74; Fig. 5).

Furthermore, subgroup analysis was performed regarding 7 different adverse events (diarrhea, nausea and vomiting, alopecia, infection, peripheral neurotoxicity, constipation, and fever). Random-effects models were applied to pool estimates for adverse events of alopecia, nausea and vomiting and peripheral neurotoxicity while fixed-effects models were used for other adverse effects. Results of subgroup analysis are listed in Table 2. Significantly decreased incidence was found only in constipation subgroup (OR = 0.03, 95% CI: 0.01–0.14) among the 7 specific adverse events.

Subgroup analysis regarding ages (≥60 group and <60 group) was performed, and the result is shown in Table 3. It showed that there was no statistically significant difference in ≥60 group for complete response and overall response, but statistically significant difference was existed in <60 group for complete response (P < .001) and overall response (P = .0057).

4. Discussion

In the present study, we performed a pairwise meta-analysis to evaluate the efficacy (in terms of complete response and overall response) and safety (in terms of adverse effects) of F-based chemotherapy regimen for the treatment of NHL based on 12 eligible trials. Greater complete response and overall response were found for F-based regimen, but the results were not statistically significant. However, the results reached a statistical significance with the omission of the study of Rummel et al. In addition, patients treated with F-based regimen had significantly decreased incidence of adverse events, but only the outcome of constipation was significant among the 7 specific adverse events according to the subgroup analysis.

F is a member of purine analog family. It yields a metabolite of 2F-ara-ATP under the function of DNA cytosine kinase which interferes the duplication of DNA subsequently by suppressing the activity of DNA polymerase, DNA ligase, and ribonucleotide reductase.[32] Other agents contained in the regimens had different mechanisms of action, such as cyclophosphamide working as alkylating agent and doxorubicin working as intercalating agent.[33] Our results showed that F-based regimen performed better on complete response and overall response compared with other regimens, which was in line with a number of clinical trials. Single administration of F was reported to present better complete response and overall response in...
untreated NHL patients, and it showed greater PFS in recurrent NHL patients compared with CVP chemotherapy regimen. Similar improvement was also shown for combined administration of F-based regimen.

Among the 7 specific adverse events, only constipation showed a significantly lower incidence of patients treated with F-based chemotherapy regimen in our study. Constipation was a common adverse event for patients treated with various chemotherapy regimens. Two relevant clinical trials provided a support for our analysis, which reached an exact consensus of lower risk of constipation for single and combined F chemotherapy.

Subgroup analysis for ages showed that there was no statistically significant difference in ≥60 group, but statistically
In conclusion, F-based chemotherapy regimen was an effective and well-tolerated treatment for patients with NHL, especially for patients <60 years old. Thus, other things being equal, F-based chemotherapy regimen may be the preferred choice for the treatment of NHL in clinical practice. However, large scale of randomized controlled trials is needed to confirm the conclusion.

References

[1] Evans LS, Hancock BW. Non-Hodgkin lymphoma. Lancet 2003;362:139–46.
[2] Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. Lancet 2012;380:848–57.
[3] Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375–90.
[4] Ansell SM, Armitage J. Non-Hodgkin lymphoma: diagnosis and treatment. Mayo Clin Proc 2005;80:1087–97.
[5] Till BG, Jensen MC, Wang J, et al. Adoptive immunotherapy for indolent non-Hodgkin lymphoma and mantle cell lymphoma using genetically modified autologous CD20-specific T cells. Blood 2008;112:2261–71.
[6] Wiseman GA, Gordon LL, Multani PS, et al. Ibritumomab tiuxetan radioimmunotherapy for patients with relapsed or refractory non-Hodgkin lymphoma and mild thrombocytopenia: a phase II multicenter trial. Blood 2002;99:4336–42.
[7] Hunsault-Berger M, Itrah N, Solal-Celigny P, et al. Intensive therapies in follicular non-Hodgkin lymphomas. Blood 2002;100:1141–52.
[8] Heinzelmann F, Ottinger H, Engelhard M, et al. Advanced-stage III/IV follicular lymphoma: treatment strategies for individual patients. Strahlenther Onkol 2010;186:247–54.
[9] Foussard C, Desablens B, Sensebe L, et al. Is the International Prognostic Index for aggressive lymphomas useful for low-grade lymphoma patients? Applicability to stage III-IV patients. Ann Oncol 1997;8(suppl 1):S49–52.
[10] Klaas RJ, Meyer RM, Shustik C, et al. Randomized phase III study of fludarabine phosphate versus cyclophosphamide, vincristine, and prednisone in patients with recurrent low-grade non-Hodgkin’s lymphoma previously treated with an alkylating agent or alkylator-containing regimen. J Clin Oncol 2002;20:4649–54.
[11] Rao R, Shammo JM, Enschede SH, et al. The combination of fludarabine, cyclophosphamide, and granulocyte-macrophage colony-stimulating factor in the treatment of patients with relapsed chronic lymphocytic leukemia and low-grade non-Hodgkin’s lymphoma. Clin Lymphoma 2003;6:26–30.

[12] Pigatello A, Rohatiner AZ, Whelan JS, et al. Fludarabine in low-grade lymphoma. Semin Oncol; 1993, 20, 24–27.

[13] Velasquez WS, Lew D, Grogan TM, et al. Combination of fludarabine and mitoxantrone in untreated stages III and IV low-grade lymphoma: S9501. J Clin Oncol 2003;21:1996–2003.

[14] Bordonaro R, Petrulis G, Restuccia N, et al. Fludarabine, mitoxantrone and dexamethasone as front-line therapy in elderly patients affected by newly-diagnosed, low-grade non-Hodgkin’s lymphomas with unfavorable prognostic factors: results of a phase II study. Leuk Lymphoma 2004;45:93–100.

[15] Zinzani PL, Pulsoni A, Perrotti A, et al. Fludarabine plus mitoxantrone with and without rituximab versus CHOP with and without rituximab as front-line treatment for patients with follicular lymphoma. J Clin Oncol 2004;22:2619–61.

[16] Frewn R, Turner D, Tighe M, et al. Combination therapy with fludarabine and cyclophosphamide as salvage treatment in lymphoproliferative disorders. Br J Haematol 1999;104:612–3.

[17] Walker E, Hernandez AV, Kattan MW. Meta-analysis: its strengths and limitations. Cleve Clin J Med 2008;75:431–9.

[18] Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;127:820–6.

[19] Feng R-N, Zhao C, Sun C-H, et al. Meta-analysis of TNF 308 G/A polymorphism and type 2 diabetes mellitus. PLoS ONE 2011;6:e18480.

[20] Kondo N, Bessho H, Negi A. Complement factor H Y402H variant and risk of age-related macular degeneration in Asians: a systematic review and meta-analysis. Ophthalmology 2011;118:339–44.

[21] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.

[22] Chang-yun Y, Shao-yi C, Zhi-min C. Clinical study on lymphocytic leukemia and low-grade non-Hodgkin’s lymphoma before the era of monoclonal antibodies. Ann Oncol 2005;16:466–72.

[23] Hagenbeek A. Phase III Intergroup study of fludarabine phosphate compared with cyclophosphamide, vincristine, and prednisone chemotherapy in newly diagnosed patients with stage III and IV low-grade malignant non-Hodgkin’s lymphoma. J Clin Oncol 2006;24:1590–6.

[24] Hou Y, Wang HQ, Ba Y. Comparison on therapeutic effects of RFT and RCTVP regimen in the treatment of patients with indolent B-cell lymphoma in China. Med Oncol 2012;29:2372–8.

[25] Rummel M, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. Lancet Oncol 2016;17:57–66.

[26] Sweetenham J, Heike K, Kerrigan M, et al. Fludarabine plus rituximab for patienetreatment of relapsed indolent B-cell non-Hodgkin’s lymphoma in the UK. Br J Haematol 1999;106:47–54.

[27] Tondini C, Balzarotti M, Rampinelli I, et al. Fludarabine and cladribine in relapsed/refractory low-grade non-Hodgkin’s lymphoma: a phase II randomized study. Ann Oncol 2000;11:231–3.

[28] Xue-dong Y, Qiang L, Jian-xin Y. Observation of clinical effect on fludarabine-based combined chemotherapy in patients with relapsed and refractory non-Hodgkin’s lymphoma. Med Inf 2013;26:338–9.

[29] Yan-hong H. Curative effect and feasible analysis on FND in patients with relapsed non-Hodgkin’s lymphoma. Chin J Trauma Disabil Med 2015;23:145–6.

[30] Zinzani PL, Tani M, Fanti S, et al. A phase 2 trial of fludarabine and mitoxantrone chemotherapy followed by yttrium-90 ibritumomab tiuxetan for patients with previously untreated, indolent, nonfollicular, non-Hodgkin lymphoma. Cancer 2008;112:856–62.

[31] Di GN, Xiao Y, Erba E, et al. Synergism between fludarabine and rituximab revealed in a follicular lymphoma cell line resistant to the cytotoxic activity of either drug alone. Br J Haematol 2001;114:800–9.

[32] Gregory SA, Vose J, Modiano M, et al. Mitoxantrone and fludarabine in the treatment of patients with non-Hodgkin’s lymphoma failing primary therapy with a doxorubicinor mitoxantrone-containing regimen. Leuk Lymphoma 2001;40:315–24.

[33] Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin’s lymphoma: results from a phase II multicenter, single-agent study. J Clin Oncol 2008;26:204–10.

[34] Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin’s lymphoma. J Clin Oncol 2008;26:4473–9.

[35] Kuo Y, Koag M-C, Lee S. N7 methylation alters hydrogen-bonding patterns of guanine in duplex DNA. J Am Chem Soc 2015;137:14067–70.