Experience with Sunitinib Treatment for Metastatic Renal Cell Carcinoma in a Large Cohort of Israeli Patients: Outcome and Associated Factors

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ABSTRACT: **Background:** The VEGFR/PDGFR inhibitor sunitinib was approved in Israel in 2008 for the treatment of metastatic renal cell carcinoma (mRCC), based on an international trial. However, the efficacy of sunitinib treatment in Israeli mRCC patients has not been previously reported.

Objectives: To report the outcome and associated factors of sunitinib treatment in a large cohort of Israeli mRCC patients.

Methods: We conducted a retrospective study of an unselected cohort of mRCC patients who were treated with sunitinib during the period 2006–2013 in six Israeli hospitals. Univariate and multivariate analyses were performed to determine the association between treatment outcome and clinicopathologic factors.

Results: We identified 145 patients; the median age was 65 years, 63% were male, 80% had a nephrectomy, and 28% had prior systemic treatment. Seventy-nine percent (n=115) had clinical benefit (complete response 5%, n=7; partial response 33%, n= 48; stable disease 41%, n=60); 21% (n=30) were refractory to treatment. Median progression-free survival (PFS) was 12 months and median overall survival 21 months. Factors associated with clinical benefit were sunitinib-induced hypertension: [odds ratio (OR) 3.6, P = 0.042] and sunitinib dose reduction or treatment interruption (OR 2.4, P = 0.049). Factors associated with PFS were female gender [hazard ratio (HR) 2, P = 0.004], pre-sunitinib treatment neutrophil-to-lymphocyte ratio ≤ 3 (HR 2.19, P = 0.002), and active smoking (HR 0.19, P < 0.0001). Factors associated with overall survival were active smoking (HR 0.25, P < 0.0001) and sunitinib-induced hypertension (HR 0.48, P = 0.005). To minimize toxicity, the dose was reduced or the treatment interrupted in 39% (n=57).

Conclusions: The efficacy of sunitinib treatment for mRCC among Israeli patients is similar to that in international data.

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KEY WORDS: metastatic renal cell carcinoma (mRCC), sunitinib, progression-free survivall (PFS), overall survival (OS)

Renal cell carcinoma is the most common cancer of the kidney [1]: 20%–30% of patients are diagnosed with metastatic disease and 70–80% of patients present with localized or locally advanced disease at diagnosis, which is potentially curable by radical surgical resection alone [2,3]. Among patients who undergo radical resection for localized disease, future metastatic disease develops in 20–40% [3].

Randomized clinical trials as well as recognition of the pathogenesis of RCC at the molecular level have established the standard role of sunitinib – the orally administered vascular endothelial growth factor receptor and platelet-derived growth factor receptor inhibitor – in the treatment of advanced renal cell carcinoma [4,5]. This had a considerable impact on the management of renal cell carcinoma, which a decade ago was considered refractory to systemic therapies [4].

Sunitinib was approved in Israel in 2008 for the treatment of metastatic RCC, based on the results of an international trial that demonstrated the superiority of sunitinib over interferon (the historic standard of care) in terms of response rate (47% vs. 12%), progression-free survival (11 vs. 5 months), and overall survival (26.4 vs. 21.8 months) [5]. However, the efficacy of sunitinib therapy in the Israeli mRCC patient population has not been previously reported. A commonly asked question is whether patient outcome as

RCC = renal cell carcinoma

reported in international clinical trials is representative of standard clinical practice or of different geographic areas [6]. This study describes the outcome and associated factors of sunitinib treatment in a large cohort of unselected Israeli mRCC patients.

PATIENTS AND METHODS

The study population consisted of an unselected cohort of Israeli patients with metastatic RCC who were treated with sunitinib from 2006 to 2013 in six institutes of oncology: Meir Medical Center, Assaf Harofeh Medical Center, Rambam Medical Center, Sheba Medical Center, Wolfson Medical Center, and Soroka Medical Center. Patient data were retrospectively collected from electronic medical records and paper charts. All patients were histologically diagnosed on the basis of histological analysis of specimens obtained by radical nephrectomy or imaging-guided needle biopsy.

SUNITINIB TREATMENT

All patients had scans showing objective disease progression before sunitinib treatment was begun. Sunitinib was prescribed as a part of standard treatment or a clinical trial. It was administered orally, usually at a starting dose of 50 mg once daily in 6 week cycles: 4 weeks of treatment followed by 2 weeks without. In patients with significant comorbidities, treatment was initiated at a reduced dose, with subsequent dose escalation if well tolerated. The dose was reduced or the treatment interrupted if adverse events occurred, depending on their type and severity, according to standard guidelines. Treatment was discontinued if there was evidence of disease progression on scans, unacceptable adverse events, or death. Patient follow-up generally consisted of regular physical examinations and laboratory assessments (hematologic and serum chemical measurements) every 4–6 weeks and imaging studies every 12–18 weeks.

This research was approved by the Institutional Review Boards of the six facilities that participated in the study.

STATISTICAL ANALYSIS

Follow-up time was defined as the time from sunitinib treatment initiation to March 2013. For the evaluation of response, RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 was applied [7]. In patients with only bone metastases, only complete response, stable disease, or progressive disease were noted, but not partial response [8]. Progression-free survival was defined as the time from the initiation of sunitinib treatment until evidence of disease progression on scans or death of any cause. Overall survival was defined as the time from the initiation of sunitinib treatment to death of any cause. Patients who did not progress or die by March 2013 were censored in progression-free survival analysis or overall survival analysis, respectively. We analyzed the association between response rate, progression-free survival and overall survival on the one hand, and baseline clinical characteristics and prognostic factors on the other. Previously described prognostic factors in mRCC patients treated with targeted therapies that were analyzed in the present study include past nephrectomy, clear cell versus non-clear cell histology, presence of more than two metastatic sites, lung/liver/bone metastasis, sunitinib-induced hypertension, past cytokines and/or targeted treatments, sunitinib dose reduction or treatment interruption, mean sunitinib dose/cycle, use of angiotensin system inhibitors before or within 1 month after initiation of sunitinib treatment, use of bisphosphonates, risk according to the Heng prognostic model, pre-sunitinib treatment neutrophil-to-lymphocyte ratio, and active smoking [8-16]. Patients without available data on pre-treatment NLR and those with baseline comorbidity (such as chronic lymphocytic leukemia) and recent (≤ 1 month) treatment (surgery, steroids, tyrosine kinase inhibitors, cytokines) known to be associated with a change in blood counts were excluded from the NLR analysis [15]. A univariate analysis (unadjusted) of association between each clinicopathologic factor and clinical outcome was performed using logistic regression for response rate and Cox regression model for survival outcomes (PFS and OS). Factors with significant association in the univariate analysis were included in a multivariate Cox proportional hazards regression model to determine their independent effects. Survival probabilities and median survival times were estimated from Kaplan-Meier curves. Data were analyzed using the SPSS software (SPSS for Windows, version 17.0, USA).

RESULTS

We identified 145 patients (median age 65 years, 63% males) with mRCC who had been treated with sunitinib from 2006 to 2013. Of these, 22% (n=32) had a non-clear cell histology, 80% (n=116) had undergone a nephrectomy, and 28% (n=40) had received prior systemic treatment. The distribution of clinicopathologic and prognostic factors is shown in Table 1.

SUNITINIB TREATMENT OUTCOMES

Median follow-up was 46 months (mean ± SD 49 ± 21, range 12–86 months). Best response to therapy was complete response in 5% (n=7), partial response in 33% (n=48), stable disease in 41% (n=60), and progressive disease in 21% (n=30) (refractory to therapy, with disease progression at first imaging evaluation within the first 3 months of treatment initiation) – indicating a clinical benefit in 79% (n=115). Median progression-free survival was 12 months (mean ± SD 18 ± 18, range 1–86).

NLR = neutrophil-to-lymphocyte ratio
PFS = progression-free survival
OS = overall survival

Table 1. Distribution of clinicopathologic and prognostic factors, and univariate and multivariate analysis of their association with progression-free survival and overall survival

Factor (n)	Distribution	Univariate analysis		Multivariate analysis	
		PFS	OS	PFS	OS
Age (yr) (n=145)	65 (63.8 ± 11.2, 22–87) Median (mean ± SD, range)	NS	NS		
Gender (n=145)	Female: 37% (n=53) Male: 63% (n=92)	HR 0.66 $P = 0.026$	NS	HR 2 $P = 0.004$	
Tumor histology (n=145)	Clear cell histology 78% (n=113) Non-clear cell 22% (n=32)	HR 0.56 $P = 0.009$	HR 0.57 $P = 0.018$	NS	NS
Past nephrectomy (n=145)	80% (n=116)	HR 1.62 $P = 0.034$	HR 0.55 $P = 0.015$	NS	NS
Prior systemic treatment (n=145)	28% (n=40)	NS	NS		
Lung metastasis (n=145)	76% (n=110)	NS	NS		
Liver metastasis (n=145)	27% (n=39)	NS	NS		
Bone metastasis (n=145)	43% (n=63)	NS	NS		
≥2 metastatic sites (n=145)	84% (n=122)	NS	NS		
Users of bisphosphonates (n=145)	23% (n=33)	HR 0.4 $P = 0.005$	HR 0.53 P = 0.018	NS	NS
Heng risk stratification (n=145)	Favorable risk 19% (n=28) Intermediate risk 62% (n=90) Poor risk 19% (n=27)	HR 0.27 and 0.45 (good and intermediate risk) $P < 0.001$	HR 1.5 and 3.7 (good and intermediate risk) $P < 0.001$	NS	NS
Smoking status (n=145)	Never 48% (n=69) Past 25% (n=37) Active 27% (n=39)	HR 3.2 $P < 0.0001$	HR 0.3 $P < 0.0001$	HR 0.19 $P < 0.0001$	HR 0.25 $P < 0.0001$
Users of angiotensin system inhibitors (n=145)	41% (n=59)	HR 0.64 P < 0.022	NS	NS	
Pre-treatment NLR › 3 (n=110)	38% (n=42)	HR 0.52 $P < 0.0001$	HR 2.24 $P = 0.001$	2.19 $P = 0.002$	NS
Sunitinib-induced hypertension (n=145)	50% (n=73)	0.18 $P < 0.0001$	0.47 $P = 0.0001$	NS	0.48 $P = 0.005$
Sunitinib dose reduced/ treatment interrupted (n=145)	39% (n=57)	NS	0.62 $P = 0.031$	NS	NS

n = no. of patients with data available

NLR = neutrophil-to-lymphocyte ratio, NS = non significant, PFS = progression-free survival, OS = overall survival

Median overall survival was 21 months (mean ± SD 24 ± 20, range 1–86). The disease progressed in 114 patients (79%) and 92 patients died (63%). A prolonged response to therapy of ≥ 2 years was noted in 30% of the patients (n=44) and ≥ 3 years in 17% (n=24); 24% (n=35) survived for ≥ 3 years and 14% (n=21) for ≥ 4 years. In 39% (n=57) the dose was reduced or treatment was interrupted to minimize toxicity.

UNIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH RESPONSE RATE, PFS AND OS [TABLE 1]

A clinical benefit of sunitinib therapy (i.e., complete response, partial response, or stable disease, versus disease progression at first imaging evaluation within the first 3 months of treatment initiation) was associated with the following: Heng risk (odds ratio 12.9, $P = 0.002$), use of angiotensin system inhibitors (OR 6.7, $P = 0.01$), prior nephrectomy (OR 4.2, $P = 0.04$), use of bisphospnonates (OR 5.6, $P = 0.018$), pre-sunitinib treatment NLR ≤ 3 (OR 7.55, $P = 0.006$), and sunitinib-induced hypertension (OR 13.9, $P < 0.001$).

Overall survival was associated with female gender (hazard ratio 0.66, $P = 0.026$), use of angiotensin system inhibitors (HR 0.64, $P = 0.022$), prior nephrectomy (HR 1.62, $P = 0.034$), clear cell histology (HR 0.56, $P = 0.009$), use of bisphosphonates (HR 0.4, $P = 0.005$), pre-sunitinib treatment NLR ≤ 3 (HR 0.52, $P < 0.0001$), sunitinib-induced hypertension (HR 0.18, $P < 0.0001$), Heng risk (HR 0.27 and 0.45 for good and intermediate risk, respectively, $P < 0.001$), and active smoking (HR 3.2, $P < 0.0001$).

Progression-free survival was associated with active smoking (HR 0.3, $P < 0.0001$), prior nephrectomy (HR 0.55, $P =$

OR = odds ratio

HR = hazard ratio

Figure 1. Kaplan-Meier curves showing progression-free survival, stratified by the pre-treatment neutrophil-to-lymphocyte ratio (NLR) and smoking status

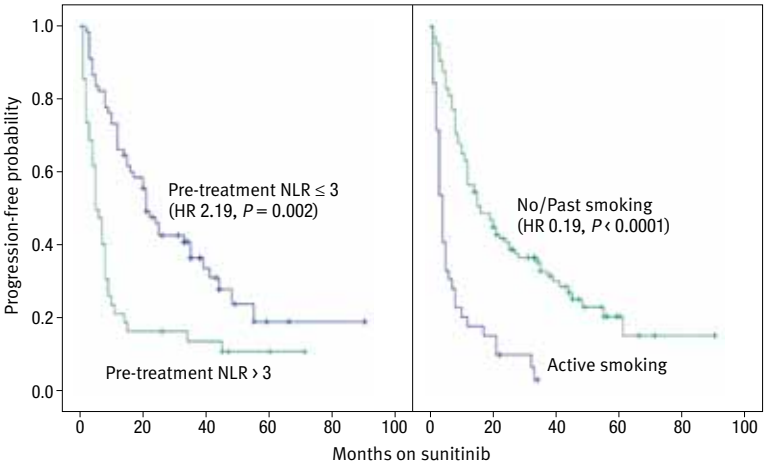
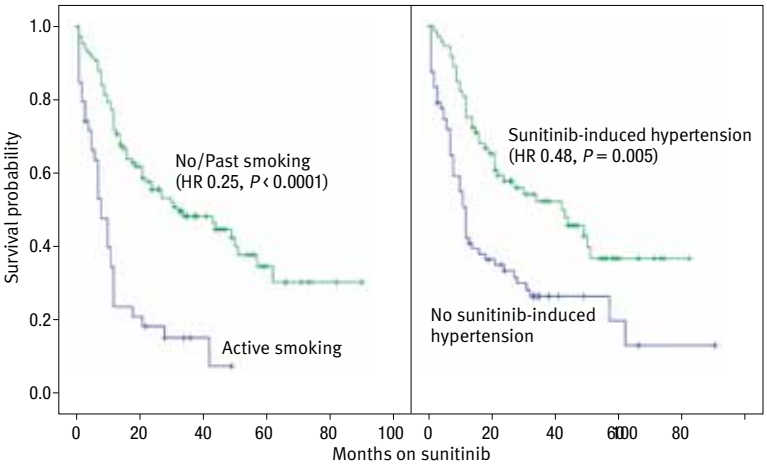


Figure 2. Kaplan-Meier curves showing overall survival, stratified by smoking status and sunitinib-induced hypertension



0.015), clear cell histology (HR 0.57, $P = 0.018$), use of bisphosphonates (HR 0.53, $P = 0.018$), pre-sunitinib treatment NLR ≤ 3 (HR 2.24, $P = 0.001$), sunitinib-induced hypertension (HR 0.47, $P < 0.0001$), sunitinib dose reduction or treatment interruption (HR 0.62, $P = 0.031$), and Heng risk (HR 1.5 and 3.7 for good and intermediate risk, respectively, $P < 0.001$).

Multivariate analysis of factors associated with response rate, PFS and OS [Table 1, Figures 1 & 2] sunitinib-induced hypertension (OR 3.6, $P = 0.042$) and sunitinib dose reduction or treatment interruption (OR 2.4, $P = 0.049$) were associated with a clinical benefit of sunitinib therapy (i.e., complete response, partial response, or stable disease, versus disease progression at first imaging evaluation within the first 3 months of treatment initiation). Female gender (HR 2, $P = 0.004$), pre-sunitinib treatment NLR ≤ 3 (HR 2.19, $P = 0.002$) and active smoking (HR 0.19, $P < 0.0001$) were associated with progression-free survival. Active smoking (HR 0.25, $P < 0.0001$) and sunitinib-induced hypertension (HR 0.48, $P = 0.005$) were associated with overall survival.

TREATMENT-ASSOCIATED TOXICITY

The distribution and grading of adverse events is shown in Table 2. The most common adverse events were fatigue (61%, n=88), diarrhea (53%, n=77), mucositis (43%, n=62), thrombocytopenia (39%, n=56), nausea and vomiting (34%, n=49), anemia (34%, n=49), neutropenia (30%, n=44), and hand-foot syndrome (28%, n=40). Grade 3/4 toxicity events occurred in 26% (n=37). In 39% of the patients (n=57) the dose was reduced and/or treatment interrupted because of adverse events.

DISCUSSION

Until a decade ago, metastatic renal cell carcinoma was considered refractory to systemic therapies [4]. Randomized clinical trials as well as recognition of the pathogenesis of renal cell carcinoma at the molecular level have established the standard role of sunitinib – the orally administered VEGFR/PDGFR inhibitor – in the treatment of advanced RCC [4,5]. This had a considerable impact on the clinical course and prognosis of patients [4]. A pivotal international randomized trial demonstrated the superiority of sunitinib over interferon (the historic standard of care) in terms of response rate (47% vs. 12%), progression-free survival (11 vs. 5 months) and overall survival (26.4 vs. 21.8 months) [5]. Subsequent clinical trials with targeted therapies in patients with mRCC [17] demonstrated a similar triumphant result for these new treatments, with median survivals double the historical median survival rate before the development of the anti-angiogenic targeted therapies [17].

Sunitinib was approved in Israel in 2008 for the treatment for mRCC, based on the results of the pivotal international trial [5]. However, its efficacy in Israeli mRCC patients has not been previously reported. A commonly asked question is whether patient outcome as reported in international clinical trials is representative of standard clinical practice or of different geographic areas [6].

The present study suggests that the efficacy and associated toxicity of sunitinib treatment for mRCC in a large cohort of unselected Israeli patients is similar to international data [5]. It was associated with a clinical benefit in 79%, median PFS of 12 months, and median OS of 21 months. Factors associated with a clinical benefit were sunitinib-induced hypertension and sunitinib dose reduction or treatment interruption; factors associated with PFS were female gender, pre-sunitinib treatment NLR ≤ 3, and active smoking; and factors asso-

PDGFR = platelet-derived growth factor receptor
VEGFR = vascular endothelial growth factor receptor

Table 2. Sunitinib treatment-associated adverse events

Adverse event	All grades	Grades 3/4
Abdominal discomfort	10% (n=15)	0%
Anemia	34% (n=49)	3% (n=5)
Bleeding (epistaxis, gastrointestinal, hematuria)	18% (n=26)	6% (n=8)
Change of taste	24% (n=35)	0%
Decrease in appetite	14% (n=20)	0%
Constipation	5% (n=7)	0%
Cough	5% (n=7)	0%
Diarrhea	53% (n=77)	8 % (n=11)
Edema	10% (n=15)	0%
Fatigue	61% (n=88)	8% (n=12)
Hand-foot syndrome	28% (n=40)	4% (n=6)
Increased bilirubin	8% (n=11)	0%
Increased creatinine	21% (n=31)	4% (n=6)
Mucositis	43% (n=62)	5 % (n=7)
Nausea/Vomiting	34% (n=49)	3% (n=5)
Neutropenia	30% (n=44)	12% (n=18)
Skin toxicity	20% (n=29)	0%
Thrombocytopenia	39% (n=56)	4% (n=6)
Venous thromboembolism	2% (n=3)	2% (n=3)

ciated with OS were active smoking and sunitinib-induced hypertension. In 39% the dose was reduced or treatment interrupted to minimize toxicity.

Our study has some limitations. First, it was a retrospective study of a widely varied patient population. We are unable to exclude the possibility that unequal distribution of unidentified clinicopathologic parameters in our patient cohort may have biased the observed results. Second, the total number of 145 patients analyzed is relatively small. Other clinicopathologic factors that were not found to be significantly associated with outcome in the present study might have been important in a larger patient cohort. Finally, whether our findings are specific to sunitinib or generalizable to other tyrosine kinase inhibitors is not known.

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References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55: 74-108.
2. Massari F, Bria E, Maines F, et al. Adjuvant treatment for resected renal cell carcinoma: are all strategies equally negative? Potential implications for trial design with targeted agents. *Clin Genitourin Cancer* 2013; 11: 471-6.
3. Herrmann E, Weishaupt C, Pöppelmann B, et al. New tools for assessing the individual risk of metastasis in renal cell carcinoma. *Clin Exp Metastasis* 2013; 30: 215-24.
4. Sulkes A. Novel multitargeted anticancer oral therapies: sunitinib and sorafenib as a paradigm. *IMAJ* 2010; 12: 628-32.
5. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; 356: 115-24.
6. Yuasa T, Tsuchiya N, Urakami S, et al. Clinical efficacy and prognostic factors for overall survival in Japanese patients with metastatic renal cell cancer treated with sunitinib. *BJU Int* 2012; 109: 1349-54.
7. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228-47.
8. Keizman D, Ish-Shalom M, Pili R, et al. Bisphosphonates combined with sunitinib may improve the response rate, progression free survival and overall survival of patients with bone metastases from renal cell carcinoma. *Eur J Cancer* 2012; 48: 1031-7.
9. Patil S, Figlin RA, Hutson TE, et al. Prognostic factors for progression-free and overall survival with sunitinib targeted therapy and with cytokine as first-line therapy in patients with metastatic renal cell carcinoma. *Ann Oncol* 2011; 22: 295-300.
10. Motzer RJ, Bukowski RM, Figlin RA, et al. Prognostic nomogram for sunitinib in patients with metastatic renal cell carcinoma. *Cancer* 2008; 113: 1552-8.
11. Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol* 2008; 26: 127-31.
12. Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst* 2011; 103: 763-73.
13. Heng DY, Xie W, Regan M, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009; 27: 5794-9.
14. Keizman D, Huang P, Eisenberger MA, et al. Angiotensin system inhibitors and outcome of sunitinib treatment in patients with metastatic renal cell carcinoma: a retrospective examination. *Eur J Cancer* 2011; 47 (13): 1955-61.
15. Keizman D, Ish-Shalom M, Huang P, et al. The association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma. *Eur J Cancer* 2012; 48: 202-8.
16. Keizman D, Ish-Shalom M, Taksey J, et al. Influence of risk factors for renal cell carcinoma (RCC) on outcome of patients with metastatic disease treated with sunitinib. *J Clin Oncol* 2012; 30 (Suppl 5, abstract 437).
17. Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomized phase 3 trial. *Lancet Oncol* 2013; 14: 552-62.

"There is nothing like returning to a place that remains unchanged to find the ways in which you yourself have altered"

Nelson Mandela (1918-2013), South African anti-apartheid revolutionary, politician and philanthropist who served as President of South Africa from 1994 to 1999. He was South Africa's first black chief executive, and the first elected in a fully representative democratic election. His government focused on dismantling the legacy of apartheid through tackling institutionalized racism, poverty and inequality, and fostering racial reconciliation