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Treatment-related fatigue with sorafenib, sunitinib and pazopanib in patients with advanced solid tumors: An up-to-date review and meta-analysis of clinical trials

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Mini Review

Fatigue is the most common symptom associated with cancer and cancer treatment. We performed an up-to-date meta-analysis to determine the incidence and relative risk (RR) of fatigue in patients (pts) with cancer treated with sorafenib (SO), sunitinib (SU) and pazopanib (PZ). PubMed databases were searched for articles published till August 2013. Eligible studies were selected according to PRISMA statement. Summary incidence, RR and 95% confidence intervals were calculated using random-effects or fixed-effects models based on the heterogeneity of selected studies. Fifteen studies were included in our analysis. A total of 6,996 pts was enrolled: 2,260 had renal cell carcinomas (RCC), 1,691 non-small cell lung cancers, 1,290 breast cancers, 823 hepatocellular carcinomas, 362 soft tissue sarcomas, 304 gastrointestinal solid tumors, 165 neuroendocrine tumors and 101 melanomas. When stratified by drug, SO registered lower incidence and RR of all and high-grade fatigue when compared to SU, whereas the difference between SO and PZ was significant only for all-grade fatigue ($p < 0.001$). The difference between SU and PZ was significant for high-grade ($p < 0.001$) but not for all-grade fatigue ($p = 0.52$). In RCC pts, PZ showed the lower incidence and RR of all and high-grade fatigue. The differences were significant for SU *vs.* SO ($p < 0.001$), SU *vs.* PZ ($p < 0.001$) and SO *vs.* PZ ($p < 0.001$). Treatment with SO, SU and PZ is associated with an increased incidence of fatigue in pts with cancer. Early and appropriate management is required to avoid unnecessary dose reductions and transitory or definitive treatment discontinuations.

Key words: cancer, fatigue, meta-analysis, pazopanib, renal cell carcinoma, sorafenib, sunitinib, tyrosine kinase inhibitors

Abbreviations: BC: breast cancer; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; GIST: gastrointestinal stromal tumor; HCC: hepatocellular cancer; HRQoL: health-related quality of life; MCV: mean corpuscular volume; NPP: named patient program; NSCLC: non-small cell lung cancer; PNET: pancreatic neuroendocrine tumor; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; pts: patients; PZ: pazopanib; RCC: renal cell carcinoma; RR: relative risk; SO: sorafenib; STS: soft tissue sarcoma; SU: sunitinib; TKI: tyrosine kinase inhibitor; VEGFR: vascular endothelial growth factor receptor

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Fatigue is the most common symptom associated with cancer and cancer treatment. It is a subjective symptom characterized by a pervasive and persistent sense of body tiredness, exhaustion, depression, feeling unwell, loss of motivation and reduced capacity for mental work, which are unrelated to activity or exertion. This condition can negatively impact the functional status and the health-related quality of life (HRQoL) of cancer patients (pts), thus affecting multiple aspects of daily simple physical activities.[1–3]

In the last decade, several small-molecule tyrosine kinase inhibitors (TKIs), such as sunitinib (SU), sorafenib (SO) or pazopanib (PZ), have been developed as angiogenesis inhibitors and have demonstrated their efficacy in a variety of solid tumors.[4–18] Presently, SO is approved for pts with advanced renal cell cancer (RCC) and hepatocellular cancer (HCC), SU is approved for treatment of advanced RCC as well as imatinib-resistant gastrointestinal stromal tumor (GIST), while PZ is approved for advanced RCC and soft tissue sarcoma (STS).

However, the use of VEGFR TKIs is limited by the occurrence of different side effects, such as fatigue. TKI-induced

fatigue is a multifactorial process, and the precise underlying pathophysiology remains often unclear.[19] For this reason, many interventions for managing this symptom remain empirical.[20] Among the potential causes, anemia and hypothyroidism play a major role, together with comorbid conditions such as cachexia, anxiety, depression and sleep disorders.[19] The onset of moderate or severe fatigue can have serious implications for treatment, requiring dose reductions until symptoms have resolved, potentially affecting the outcome of pts treated with VEGFR TKIs.

In our study, we conducted a review of the main causes underlying VEGFR TKI-induced fatigue. Moreover, we performed an up-to-date meta-analysis to determine the incidence and relative risk (RR) of fatigue in pts with advanced solid tumors treated with SO, SU and PZ.

Fatigue as a Consequence of VEGFR TKI-Induced Endocrine Disorders

Fatigue is commonly related to many endocrine disorders. In cancer pts treated with VEGFR TKIs, the overlap of signs and symptoms caused by treatment and tumor itself make difficult to recognize and manage the endocrine-related dysfunctions associated with development of fatigue. These causes include adrenal, thyroid and gonadal alterations, as far as bone and glucose metabolism abnormalities.[21,22]

Adrenal dysfunctions

Patients treated with VEGFR TKIs might develop a persistent primary adrenal insufficiency.[23] Although adrenal necrosis and hemorrhage were frequently observed in *in vivo* studies with SU, in clinical practice adrenal insufficiency was extremely rare.[21,24,25] The symptoms of adrenal insufficiency are variable and nonspecific including fatigue, reduced muscle strength, muscle and joint pain, weight loss, anorexia, abdominal complaints (nausea, vomiting and pain), hypotension, hyponatremia, hyperkalemia and hypoglycemia.

Considering that adrenal insufficiency is a potentially life-threatening condition, the adrenal function should be carefully evaluated in cancer pts who experience fatigue during treatment with VEGFR TKIs. In general, a morning cortisol value below 100 nmol/L (3.6 mcg/dL) indicates adrenal failure, whereas a serum cortisol greater than 500 mmol/L (20 mcg/dL) is consistent with an intact hypothalamic-pituitary-adrenal axis. For intermediate cortisol values the diagnosis is confirmed by the demonstration of suboptimal cortisol levels following dynamic testing.

In clinical practice, adrenal insufficiency should be suspected and vigilantly managed with appropriate interventions and steroid replacement therapy.[23]

Thyroid alterations

Thyroid dysfunctions are commonly associated with the use of VEGFR TKIs, which may cause *de novo* hypothyroidism or exacerbate preexisting conditions. The incidence of primary hypothyroidism ranges from 20 to 80% in cancer pts treated with TKIs.[21,26,27] However, the mechanisms by which VEGFR TKIs may induce thyroid dysfunctions remain unclear and probably more than one mechanism is involved including a destructive thyroiditis, an impaired iodine uptake, a direct inhibition of thyroid peroxidase activity and a capillary regression induced by VEGF receptor inhibition.[21,26,27]

It is important to remember that hypothyroidism may correlate with a better outcome in these pts but this interesting finding needs to be confirmed in further studies.[28]

Although primary hypothyroidism is the most common thyroid function alteration, thyrotoxicosis has also been described in several pts.[29] In these cases, the hyperthyroidism was relatively mild, self-limiting and rapidly progressed to hypothyroidism, supporting that this endocrine problem is a consequence of a destructive thyroiditis.

The clinical management of VEGFR TKI-associated hypothyroidism remains a major challenge for clinicians. This is partially explained by considering that many adverse events induced by VEGFR TKIs (fatigue, dry skin or hair changes) can mimic hypothyroidism. Some authors recommend measuring thyroid-stimulating hormone (TSH) and free thyroxine (FT4) before treatment and then monitoring TSH on Days 1 and 28 of the first four cycles and then on Day 28 of every third cycle.[30] Other authors recommend routine testing of thyroid function and antibodies at baseline, and measurement of TSH on Day 1 at start of every new treatment cycle.[27] Recently, some authors propose a simplified algorithm suggesting measurement of TSH before treatment, then every 4 weeks for 4 months and then every 2–3 months.[26,27] In any case, although hypothyroidism usually remits with drug discontinuation, it does not require VEGFR TKI withdrawal or reduction. VEGFR TKI-associated hypothyroidism is easily controlled by L-thyroxine replacement, although there is no clear benefit to treat all pts.

Patients with preexisting hypothyroidism may require higher doses of thyroxine replacement therapy to maintain a euthyroid state (up to 30–50% pre-TKI dosage). This is particularly important in pts with thyroid cancer treated with VEGFR TKIs in whom suppression of the plasma TSH concentration is an important component of therapy and development of hypothyroidism may abrogate the beneficial effect of the VEGFR TKIs.[22,31]

On the contrary, the decision to treat pts with subclinical hypothyroidism (TSH ranging from 5 to 10 mIU/mL) is still an unresolved clinical challenge. Some authors suggest to start thyroxine replacement therapy only in pts with persistent TSH $>$ 10 mIU/mL and either low FT4 or normal FT4 but with typical symptoms of hypothyroidism.[30] Other authors suggest treating pts with overt hypothyroidism and subclinical hypothyroidism with antithyroid antibodies and/or high cholesterol levels and/or thyroid nodules and/or thyroid complaints (*e.g.*, fatigue).[27] However, it should be remembered that these latter symptoms may also be the consequence of cancer itself.

Mineral, gonadal and other metabolic alterations

Patients treated with VEGFR TKIs showed bone and mineral metabolism abnormalities, secondary hyperparathyroidism (up to 68% of cases), hypophosphatemia and vitamin D deficiency.[22,32] These effects may be due to nonspecific inhibition of kinases expressed by osteoclasts and osteoblasts and to a reduction in intestinal vitamin D absorption.[33] Given that vitamin D deficiency is a well-recognized cause of fatigue and myopathy, it is suggested to assess bone density, PTH and vitamin D levels in pts on VEGFR TKIs at baseline and during treatment, despite no clear recommendations exist.

All VEGFR TKIs may have similar effects on growth hormone (GH) secretion in both pediatric and adult pts.[34] Even though treatment with GH is not indicated in pts with active malignancy, fatigue is a common complaint in adult GH deficiency and this endocrine disorder could contribute to TKI-related fatigue.

Considering that gynecomastia was reported in up to 18% of male pts, hypogonadism may be another potential cause of TKI-related fatigue.[35] Although data regarding gonadal function are scarce, all pts should be assessed periodically for the risk of hypogonadism measuring testosterone levels.

Finally, diabetic pts on treatment with VEGFR TKIs should be monitored closely for glucose metabolism abnormalities. However, it is important to note that opposite effects on glucose levels have been observed in pts treated with VEGFR TKIs and in several case reports an improvement of glycemic control in diabetic pts was described. Thus, in a retrospective study, 47% of pts treated with TKIs (dasatinib, imatinib, SO and SU) were able to discontinue their antidiabetic medications including insulin.[36] Therefore, clinicians should be aware of the potential hypoglycemic effect in diabetic pts; a periodic assessment of hemoglobin A1c and blood glucose levels in nondiabetic pts during treatment with VEGFR TKIs is a reasonable recommendation.

Fatigue as a Consequence of VEGFR TKI-Induced Anemia

Anemia is a common laboratory abnormality induced by VEGFR TKIs and is considered as one of the most relevant factors contributing to VEGFR TKI-induced fatigue.[37] In the Phase III trials of SU, SO and PZ in pts with RCC, the incidences of any grade and Grades 3 and 4 anemia were 71 and 4% in pts treated with SU and 8 and 3% in those treated with SO, respectively.[5,6,11]

Additional data can be obtained from the results of the noninferiority Phase III COMPARZ trial, comparing the efficacy and safety of PZ and SU in the first-line treatment of RCC[38]; anemia of any grade and Grades 3 and 4 was reported in 31 and 1% of pts treated with PZ and in 60 and 7% of those treated with SU, respectively. The different toxicity profiles of SU and PZ have also been evaluated in the PISCES study.[39] Hematological toxicity was prevalent in the SU arm; particularly, as regard to anemia, all grades and high-grade events were respectively reported in 25% and less than 1% in the SU arm, whereas in the PZ arm the incidence was 11 and 1%, respectively.

A recent meta-analysis about hematologic toxicities of SU, performed on ten clinical trials and regarding 2,667 subjects SU-treated, confirmed the significant increased risk of developing all-grade anemia [RR = 1.15; 95% confidence interval (CI) 1.00–1.31] in the pts treated with SU compared with the controls.[40] Regard to the tolerability profile of the new drugs in the daily clinical practice, expanded access studies or named patient programs (NPPs), permitted usually more reliable subanalyses about tolerability and safety in pts frequently excluded from clinical trials because of inclusion criteria.

Macrocytosis, defined as an increase in the mean corpuscular volume (MCV) of the red cells, with or without decline in hemoglobin levels, has been noted throughout SU therapy.[41,42] The macrocytosis does not appear to impact clinical efficacy or toxicity and usually is completely reversible within 2–3 months after withdrawal of treatment. The mechanism by which SU leads to increase in erythrocytes volume over baseline remains unclear at present; cobalamin deficiency, owing to an absorption interference at the gastrointestinal tract or inhibition of c-kit at the level of red blood cells progenitors in bone marrow seem to be the most likely hypothesis.

Patients and Methods

Selection of studies

Study selection was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. To identify relevant clinical trials, two authors (M.S. and A.C.) did a review of citations from PubMed from January 1966 to August 2013. The search was conducted by using the keywords "Sorafenib" or "Sunitinib" or "Pazopanib" and was limited to human studies and randomized clinical trials published in English that met the following criteria: (*i*) prospective randomized Phase II and III trials of pts with cancer; (*ii*) random assignment of participants to treatment with a VEGFR TKI or control (standard of care, placebo or best supportive care) and (*iii*) available data on treatment-emergent, non-disease-related, event of fatigue. Meeting abstracts were excluded to avoid the inherent publication bias of underreporting low-frequency gastrointestinal adverse events in these brief summaries. All identified abstracts were collected and coded as not relevant (review articles, editorials, letters/commentaries and study designs), non-SO/SU/PZ or potentially relevant. When multiple publications of the same clinical trial were encountered, only the most recent or most complete reporting of that trial was included.

Phase I, nonrandomized Phase II and randomized trials with a VEGFR TKI in both arms were excluded because of interstudy variability in drug dosing as well as lack of sufficient controls, in line with several meta-analyses done in this context.[43–53]

Data extraction, clinical end points and quality assessment

By reading the full texts of the selected citations, two investigators (M.S. and A.C.) independently extracted the following data: name of all authors, year of publication, number of enrolled pts, treatment arms, type of VEGFR TKIs and doses and number of cases of fatigue (all-grade and high-grade) in each arm. Adverse events were defined as per versions 2 or 3 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) criteria. Study quality was assessed by using the Jadad seven-item scale that included randomization, double blinding and withdrawals, a practice in agreement with other meta-analyses done in this context.

Statistical analysis

The principal summary measures were incidence, RR and corresponding 95% CIs. For the calculation of incidence, the number of fatigue events and the number of pts receiving VEGFR TKIs were extracted from the safety profiles of all selected studies. Studies that had a comparative arm were used to calculate RRs of fatigue in pts assigned to SO or SU or PZ *vs.* controls in the same trial.

Cochran's Q statistic was used to test for heterogeneity of the samples for each variable and inconsistency was quantified with the I^2 statistic, which is used to describe the percentage of total variation across studies that was due to heterogeneity rather than chance. Assumption of homogeneity was considered invalid for p values less than 0.1. Random- and fixed-effects model were used for each analysis when Q test resulted significant or not, respectively.

For the meta-analyses, both the fixed-effects model (weighted with inverse variance) and the random-effects model were considered. Homogeneous parameters were compared and tested for an overall log-transformed RR using the fixed-effects model, whereas in case of suspect heterogeneity the Der Simonian-Laird procedure for random effects was adopted.[54] Model estimate and null hypothesis of overall nonsignificant difference between study and control groups were tested for each variable. The correlations between RR was evaluated as proposed by Altman and Bland.[55]

Finally, potential publication bias was evaluated using funnel plots (plots of study results against precision) and with the Begg and Mazumdar and Egger *et al.* tests.[56,57] A two-tailed p value of less than 0.05 was considered statistically significant. Data collection was obtained using Microsoft Excel 2007, data analysis with the "R" statistical software version 2.15.2.

Results

Search results

Our search yielded a total of 671 potentially relevant human clinical studies evaluating SO, SU or PZ in PubMed. A total of 388 citations were immediately excluded for at least one of the following reasons: duplicate trials, Phase I trials, non-SO or SU or PZ studies, review articles, observational studies, case reports, editorials, letters or commentaries. Subsequently, 238 were not randomized Phase II trials, 12 had both control and treatment groups who received VEGFR TKIs and 18 trials did not have an adequate safety profile data listing for fatigue due to study drug. At the end of this review process, 15 trials[4–18] were considered to be of adequate quality and relevance for the meta-analysis. Figure 1 shows the selection process of the randomized controlled trials. Twelve of these studies were Phase III trials and three studies were randomized Phase II trials. Table 1 shows the baseline characteristics of each trial.

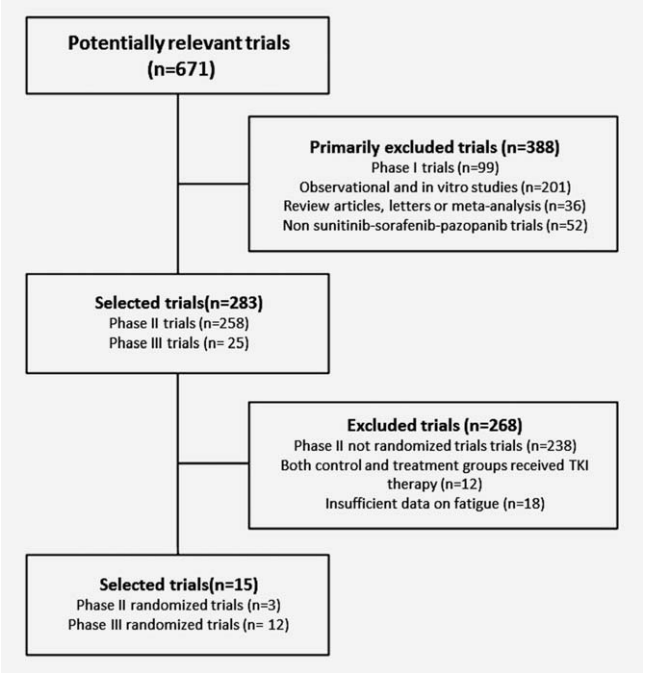

Figure 1. Selection of randomized controlled trials (RCTs) included in the meta-analysis according to PRISMA statement.

Quality of studies

The 15 randomized studies included in the meta-analysis were assessed for study quality using the Jadad scoring system. Seven double-blinded and placebo controlled and eight trials had active treatment as the controls arms. Follow-up time was adequate for each trial. All 15 trials used either CTCAE version 2 or 3 criteria. Jadad scores for each trial are listed in Table 1; the mean score was 4 (range: 2–5), indicating that the overall study quality was fair.

Population characteristics

A total of 6,996 pts were available for the meta-analysis; 2,260 of these pts had RCC[5,6,9,11] and 4,736 had other malignancies (1,691 pts with NSCLC,[12,15] 823 with HCC,[7,10] 1,290 with breast cancer,[13,16,17] 165 with PNET,[14] 304 with GIST,[4] 362 with STS[18] and 101 with melanoma[8]). For the RR analysis, 3,728 pts were assigned to treatment arms (2,006 pts treated with SO,[6–9,10,12,15,17] 1,193 with SU[4,5,13,14,16] and 529

Table 1. Baseline characteristics of randomized trials included in the meta-analysis, and incidence and RR of all-grade fatigue by individual study

Author	Year	Phase	Jadad scale	Malignancy	Treatment		No. of subjects		No. of events		Incidence in the TKI arm (95% CI)	Relative risk[1] (95% CI)
					TKI arm	Control arm	TKI arm	Control arm	TKI arm	Control arm		
Llovet *et al.*[7]	2008	III	5	HCC	Sorafenib	Placebo	297	302	66	49	22.22 (17.87–27.29)	1.36 (0.98–1.92)
McDermott *et al.*[8]	2008	II	5	Melanoma	Sorafenib + dacarbazine	Dacarbazine	51	50	39	35	76.47 (63.24–86.00)	1.09 (0.86–1.39)
Cheng *et al.*[10]	2009	III	5	HCC	Sorafenib	Placebo	149	75	30	6	20.13 (14.48–27.29)	2.51 (1.09–5.75)
Escudier *et al.*[9]	2009	III	3	RCC	Sorafenib	Placebo	452	451	133	74	29.42 (25.41–33.79)	1.79 (1.39–2.32)
Escudier *et al.*[9]	2009	II	2	RCC	Sorafenib	Interferon	97	90	42	39	43.30 (33.88–53.23)	1.00 (0.72–1.39)
Scagliotti *et al.*[12]	2010	III	2	NSCLC	Sorafenib + CBP + PTX	CBP + PTX	463	459	94	97	20.30 (16.88–24.20)	0.96 (0.75–1.23)
Baselga *et al.*[17]	2012	II	5	BC	Sorafenib + capecitabine	Capecitabine	112	112	17	15	15.18 (9.70–22.97)	1.14 (0.59–2.16)
Paz-Ares *et al.*[15]	2012	III	4	NSCLC	Sorafenib + GEM + CDDP	GEM + CDDP	385	384	113	95	29.35 (25.02–34.09)	1.19 (0.94–1.49)
Demetri *et al.*[4]	2006	III	5	GIST	Sunitinib	Placebo	202	102	58	20	28.71 (22.92–35.30)	1.46 (0–2.29)
Motzer *et al.*[5]	2007	III	3	RCC	Sunitinib	Interferon	375	360	203	188	54.13 (49.07–59.11)	1.04 (0.90–1.19)
Barrios *et al.*[13]	2010	III	3	BC	Sunitinib	Capecitabine	238	240	71	49	29.83 (24.38–35.93)	1.46 (1.06–2.01)
Raymond *et al.*[14]	2011	III	4	PNET	Sunitinib	Placebo	83	82	27	22	32.53 (23.42–43.19)	1.21 (0.76–1.95)
Bergh *et al.*[16]	2012	III	2	BC	Sunitinib + DTX	DTX	295	293	136	101	46.10 (40.50–51.80)	1.34 (1.09–1.63)
Sternberg *et al.*[11]	2010	III	5	RCC	Pazopanib	Placebo	290	145	55	11	18.97 (14.87–23.87)	2.51 (1.35–4.62)
van der Graaf *et al.*[18]	2012	III	5	STS	Pazopanib	Placebo	239	123	155	60	64.85 (58.61–70.63)	1.32 (1.08–1.63)
Overall							3,728	3,268	1,239	861	33.23 (31.74–34.76)	1.27 (1.14–1.42)

[1] $Q = 32.23$, $p = 0.004$, $I^2 = 54.67\%$.

Abbreviations: HCC: hepatocellular carcinoma; RCC: renal cell carcinoma; NSCL: non-small cell lung cancer; GIST: gastrointestinal stromal tumor; BC: breast cancer; PNET: pancreatic neuroendocrine tumor; STS: soft-tissue sarcoma; CDDP: cisplatin; CBP: carboplatin; PTX: paclitaxel; DTX: docetaxel; GEM: gemcitabine.

Table 2. Incidence and RR of all- and high-grade fatigue by TKI

TKIs	No. of subjects		All-grade fatigue			High-grade fatigue			
			No. of events			No. of events			
	TKI arm	Control arm	TKI arm	Control arm	Incidence in the TKI arm (95% CI)	TKI arm	Control arm	Incidence in the TKI arm (95% CI)	Relative risk[2] (95% CI)
Sorafenib	2,006	1,923	534	410	26.62 (24.73–28.60)	95	58	4.74 (3.89–5.75)	1.57 (1.14–2.16)
Sunitinib	1,193	1,077	495	380	41.49 (38.73–44.31)	107	86	8.97 (7.48–10.72)	1.13 (0.85–1.48)
Pazopanib	529	268	210	71	39.70 (35.62–43.93)	38	11	7.18 (5.28–9.71)	1.75 (0.90–3.35)
Overall	3,728	3,268	1,239	861	33.23 (31.74–34.76)	240	155	6.44 (5.69–7.27)	1.36 (1.03–1.80)

[1] $Q = 3.69$, $p = 0.16$, $I^2 = 35.62\%$ (for pooled studies).
[2] $Q = 3.19$, $p = 0.02$, $I^2 = 41.2\%$ (for pooled studies).

with PZ[11,18]); 3,268 were assigned to placebo or control arms (1,923 from SO, 1,077 from SU and 268 from PZ trials). In SO studies, all pts were given 400 mg twice daily. SU was administered at a starting dose of 50 mg in 6-week cycles with 4 weeks on and 2 weeks off treatment in two studies[4,5]; 37.5 mg/daily continuously in other two trials[13,14] and Days 2–15 every 3 weeks in one trial.[16] PZ was given continuously at 800 mg daily in both studies.[11,18]

Incidence of fatigue

A total of 1,239 fatigue events were reported in the 3,728 pts treated with SO, SU or PZ, compared with the 861 events in the 3,268 pts assigned to placebo or control arms; 240 high-grade fatigue events were registered in the treatment groups compared to 155 in the controls. Incidence of fatigue was 26.62 (95% CI 24.73–28.60) for SO, 41.49 (95% CI 38.73–44.31) for SU and 39.70 (95% CI 35.62–43.93) for PZ. Incidences of all-grade and high-grade fatigue are summarized in Tables 1 and 2.

Overall RR of fatigue

Fifteen randomized studies were available to calculate the RR of fatigue in pts assigned to SO or SU or PZ *vs*. controls. The summary RR of developing all-grade and high-grade fatigue with VEGFR TKIs *vs*. controls was 1.23 (95% CI 1.15–1.34) and 1.36 (1.03–1.80), respectively. The RRs of fatigue across selected trials are shown in Table 1 and Figure 2.

RR of fatigue by TKI

When stratified by TKI, pts treated with SO showed a RR of fatigue of 1.25 (95% CI 1.12–1.39), whereas the RR was 1.17 (95% CI 1.06–1.31) for SU and 1.49 (95% CI 1.20–1.88) for PZ. Comparing the different RRs of fatigue, we did not find significant differences among the three agents (SO *vs*. SU trials: $z = 0.86$, $p = 0.39$, RRR<<?3>> = 1.07, 95% CI 0.92–1.24; SO *vs*. PZ trials: $z = -1.38$, $p = 0.17$, RRR = 0.84, 95% CI 0.65–1.07; SU *vs*. PZ trials: $z = -1.91$, $p = 0.06$, RRR = 0.79, 95% CI 0.61–1.01).

As for the RR of high-grade fatigue, no significant heterogeneity was observed ($Q = 3.09$, $p = 0.20$; $I^2 = 41\%$). In addition, no significant differences were observed among the RRs of high-grade fatigue among the three VEGFR TKIs (SO *vs*. SU trials: $z = 1.52$, $p = 0.13$, RRR = 1.39, 95% CI 0.91–2.12; SO *vs*. PZ trials: $z = -0.29$, $p = 0.29$, RRR = 0.897, 95% CI 0.43–1.86; SU *vs*. PZ trials: $z = -1.20$, $p = 0.23$, RRR = 0.65, 95% CI 0.31–1.32). Incidence and RRs of fatigue by TKI are summarized in Table 2 and represented in Figure 3.

When stratified by TKI, the incidence of fatigue was significantly higher in SU *vs*. SO studies (RR 1.55, 95% CI 1.4–1.72, $p < 0.001$). A significantly lower incidence was found for SO *vs*. PZ (RR 0.67, 95% CI 0.59–0.76, $p < 0.001$). No significant difference was found between SU and PZ (RR 1.04, 95% CI 0.92–1.19, $p = 0.52$).

As for high-grade fatigue, the incidence resulted significantly higher with SU when compared to SO (RR 3.72, 95%

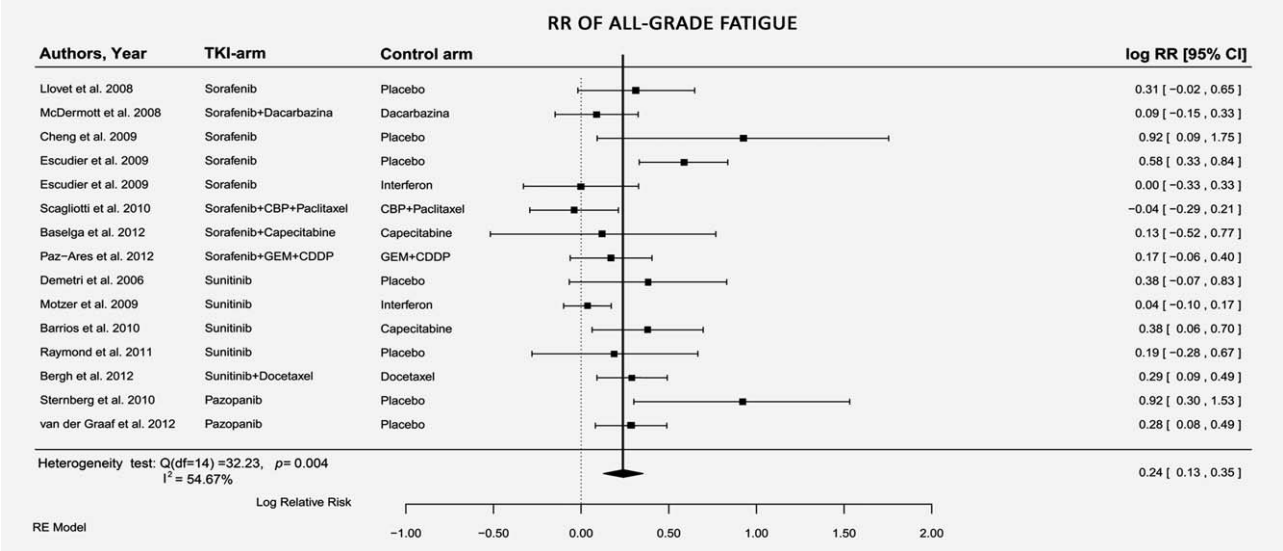

Figure 2. Relative risk (RR) of all-grade fatigue associated with VEGFR-TKIs by individual study.

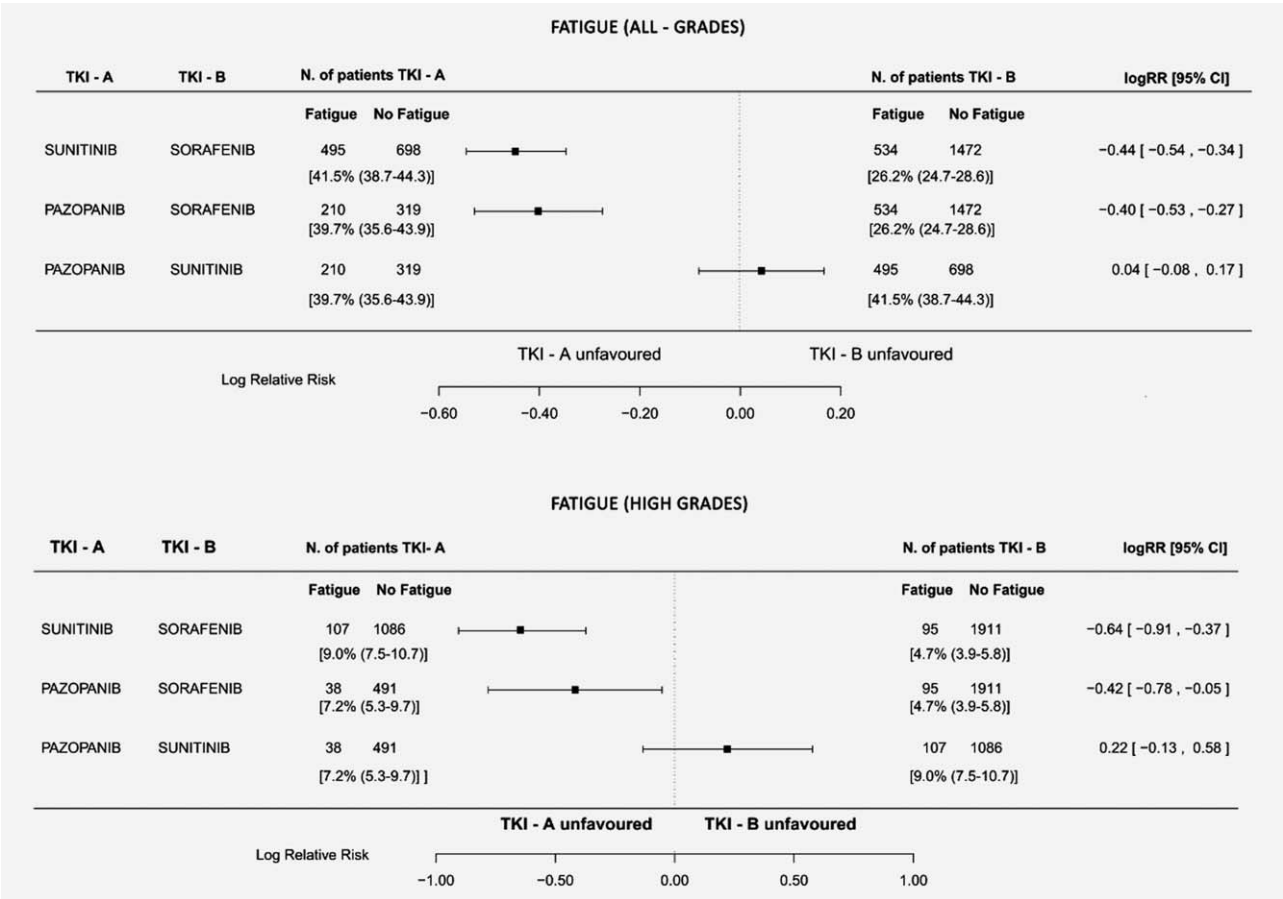

Figure 3. Relative risk (RR) of all- and high-grade fatigue by VEGFR-TKIs.

CI 1.92–5.47, $p < 0.001$) and PZ (RR 4.62, 95% CI 2.12–10.18, $p < 0.001$), whereas the difference between PZ *vs.* SO was not significant (RR 1.43, 95% CI 0.61–3.39, $p = 0.53$).

RR of fatigue by tumor type

A further analysis of fatigue was conducted comparing RCC *vs.* non-RCC pts treated with the three agents. The RR was

1.2 (95% CI 1.06–1.35) in RCC pts and 1.13 (95% CI 1.11–1.16) in non-RCC pts. No significant differences were observed when comparing the two groups ($z = 0.96$, $p = 0.168$, RRR = 1.06, 95% CI 0.94–1.2).

Incidence and RR of fatigue by TKI in the RCC group

We further analyzed the incidence and RR of fatigue by VEGFR TKI in RCC pts. Incidence of all-grade fatigue was highest with SU (54.13%, 95% CI 49.07–59.11), followed by SO (31.87%, 95% CI 28.12–35.89) and PZ (18.97%, 95% CI 14.87–23.87). The difference between incidences was highly significant for SU *vs.* SO (RR 1.7, 95% CI 1.46–1.97, $p < 0.001$), SU *vs.* PZ (RR 2.86, 95% CI 2.2–3.67, $p < 0.001$) and SO *vs.* PZ (RR 1.68, 95% CI 1.28–2.2, $p < 0.001$).

As for high-grade fatigue, the incidence was 11.2% (95% CI 8.39–14.79%) for SU, 3.46% (95% CI 2.23–5.34%) for SO and 2.41% (95% CI 1.17–4.9%) for PZ. Significant differences were found between SU *vs.* SO (RR 3.22, 95% CI 1.92–5.47, $p < 0.001$) and SU *vs.* PZ (RR 4.62, 95% CI 2.12–10.18, $p = 0.01$), whereas the difference between PZ and SO was not significant (RR 1.43, 95% CI 0.61–3.39, $p = 0.53$).

Publication bias

No evidence of publication bias was detected for the incidence or RR of fatigue (all and high grade) (incidence: Begg test, $p = 0.87$ and Egger test, $p = 0.53$; RR: Begg test, $p = 0.61$ and Egger test, $p = 0.77$).

Discussion

In clinical practice, cancer-related fatigue is a distressing and disabling condition that is often underreported, underdiagnosed and undermanaged. This is especially true for elderly and/or frail pts who are more vulnerable to toxicities, due to a higher burden of comorbidities and reduced hematological reserve.[58,59]<<?4>> At this regard, a recent retrospective study in RCC elderly pts has shown that fatigue is the most common reported side effect that led to dose reduction and/or treatment discontinuation.[60]

The range of empirically supported treatment options for fatigue should expand, ultimately leading to enhanced HRQOL of cancer pts. There is a critical need for basic research on mechanisms underlying fatigue onset and persistence that will guide the development of patient-tailored approaches and reduce the risk of fatigue-related dose reductions or treatment interruptions. Then, the determination of risk factors for fatigue may allow an early management of most susceptible pts.

To our knowledge, this is the first meta-analysis focusing on fatigue associated with VEGFR TKIs. We were able to demonstrate that treatment with SO, SU and PZ is associated with a significant increase of the risk of fatigue in pts with advanced solid tumors. In our analysis, SO registered the lower incidence and RR of all- and high-grade fatigue when compared to both SU and PZ in the overall population, whereas the difference between SU and PZ was significant only for high-grade fatigue. We further analyzed data from pts with RCC. In this population, PZ showed the lower incidence and RR of all- and high-grade fatigue when compared to SO and SU. Further studies are strongly needed to understand how to correlate different toxicity profiles with dose reductions and transitory or definitive treatment discontinuations.

Recently, a double-blind, randomized, crossover study has been performed to assess pts' preference between SU and PZ as first-line therapy for pts with metastatic RCC.[39] Diarrhea, fatigue and nausea were the most common adverse events. For most of adverse events, especially fatigue, pts preferred PZ over SU. However, the discrepancy between physicians' reported grading and patient perception of tolerability concerning fatigue in our study suggests the necessity of improving current assessing of adverse events in cancer pts.[61,62] Interestingly, grading of fatigue is based either on the Eastern Cooperative Oncology Group (ECOG) scale or on the Karnofsky performance status scale. The differences between these two scales are partially responsible for the different incidence of fatigue reported among clinical trials.

Our study has several limitations. First, it is a meta-analysis based on studies and not on the pts' data, then confounding variables such as patient comorbidities, previous chemotherapeutic exposure and concomitant treatments were not evaluated into the analysis. Second, all the included studies were conducted in pts with generally adequate organ function at study entry, so the incidence and severity of fatigue could be higher in daily clinical practice. Third, we were not able to correlate our data with dose delays/interruptions or discontinuations secondary to fatigue in the analysis.

In conclusion, our study showed that VEGFR TKIs are associated with a significantly increased risk of all- and high-grade fatigue. Physicians and pts should be aware of these risks and frequent clinical monitoring should be emphasized when managing these three and newer VEGFR-TKIs. An early and careful management of this event is strongly required to reduce its impact on patient outcome and HRQOL and to optimize medical resource utilization.

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