Tumour flare reaction in cancer treatments: a comprehensive literature review

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In the past decade, tumour flare reaction (TFR) was considered as a new side effect associated with immunomodulatory agents (IMiDs) and as a condition of chronic lymphocytic leukaemia (CLL). However, this phenomenon is also observed with immune checkpoint inhibitors in solid tumours. It is still poorly understood and its incidence is underestimated. TFR has been associated with morbidity, therefore, early recognition and management of patients with TFR is critical. An exhaustive literature research between 1985 and 2016 was performed using *PubMed*; American Society of Clinical Oncology and American Society of Hematology abstracts reporting TFR or pseudoprogression were identified. The incidence of TFR in CLL ranged from 28 to 58%. Tumour response in patients treated beyond progression was reported in 9.7% with ipilimumab, 10% with nivolumab, 6.7 and 12% with pembrolizumab, and in renal cell carcinoma 69% with nivolumab. Rare life-threatening or fatal cases were reported; symptoms were usually mild. Studies showed that treating patients beyond progression yielded tumour responses, considering TFR as predictive of response. Treatment with immunomodulatory agents is associated with TFR, often misinterpreted as progression. Therefore, the identification of appropriate clinical benefit criteria and the use of immune-related response criteria in prospective trials for a better understanding are compulsory. *Anti-Cancer Drugs* 30:953–958 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

In the past decade, tumour flare reaction (TFR) was considered as a new side effect associated with immunomodulatory agents (IMiDs) (thalidomide and lenalidomide) [1,2]. It was believed that TFR is a specific side effect of chronic lymphocytic leukaemia (CLL). However, TFR is also observed in solid tumours treated with immune checkpoint inhibitors (ICIs) [3]. Several cases of flare reaction with hormonotherapy and haematologic malignancies and manifestations of TFR possibly mimicking disease progression have been reported [4,5].

Lenalidomide induces a TFR suggestive of an immune-mediated inflammation in CLL; a concurrent decrease in absolute lymphocyte count in these patients led to the hypothesis that TFR is rather an immune reaction phenomenon instead of a disease progression [6,7].

Several studies have indicated that TFR may predict better responses, although no differences in progression-free survival were shown [8,9].

Method of literature research

A literature research using the following keywords: cancer, chronic lymphocytic leukaemia, haematological malignancies, ICIs, IMiDs, lenalidomide, nivolumab, pseudoprogression, solid tumours, tumour flare reaction, TFR was performed in *PubMed* as well as for the American Society of Clinical Oncology and American Society of Hematology abstracts covering TFR.

Tumour flare reaction definition

TFR corresponds to an increase in a lesion size related to treatment, simulating a progression of the disease (Table 1) [10].

Tumour flare with IMiDs, and immune checkpoint inhibitors

In CLL, TFR resulting from immunomodulatory drugs (1) presents clinically with painful lymph nodes sometimes spleen enlargement, and can be accompanied by fever, rash and clear lymphocytosis and (2) and as an acute inflammatory reaction that primarily involves tumour-bearing sites [2,7].

In solid tumours, tumour flare or pseudoprogression which mimics progression on imaging was observed with ICIs included nivolumab in various tumour types, occasionally associated with tumour flare. It was referred to the apparent increase in tumour burden or the occurrence of new lesions that sometimes may precede antitumour effects, resulting from T-cells infiltrating the tumour site until a sufficient immune response develops [3].

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Clinical evidence for therapy-related TFR: Pseudoprogression has been reported in brain tumour imaging, especially for high-grade gliomas. It has been observed in about 30% of patients after a combination of chemotherapy and radiotherapy; pseudoprogression after radiotherapy was observed in about 15% of patients [11].

In 60% of all cases, pseudoprogression occurred mainly within the first 3 months after completing treatment [12–14].

Patients with methylated O6-methylguanine-DNA-methyltransferase show pseudoprogression more frequently, particularly with temozolomide [12,15,16].

Tumour flare reaction in lymphoid malignancies

An overview of TFR in lymphoid malignancies is provided in Table 2.

Early clinical trials testing thalidomide in patients with pretreated CLL reported a substantial number of patients experiencing tumour flare and other toxicities leading to poor accrual and premature closure [17,18]. Several subsequent small phase II studies showed similar limited benefits of thalidomide with a high incidence of tumour flare [1,17,19].

Chanan-Khan *et al.* [2] reported that 58% of CLL patients who received 25 mg/day of oral lenalidomide for 21 days through 28-day-cycles developed TFR (50% developed grade 1–2 reactions, and 8% developed grade 3–4 reactions). Ferrajoli *et al.* [20] observed that 28% of 35 CLL patients who were treated with a dose of 10 mg/day of lenalidomide and then with an increased dose of 25 mg/day developed TFR. Andritsos *et al.* [7] described unacceptable toxicities in 4 patients treated with lenalidomide.

TFR developed in 44% (10% G3) of CLL patients [21]; similar results were reported in other CLL studies (Table 2).

Three out of 25 patients with mantle cell lymphoma (MCL) and who were treated with lenalidomide developed TFR. Two had a mild TFR, however, the third patient died [22].

In non-Hodgkin lymphoma (NHL), TFR was observed both in relapsed or refractory indolent NHL and aggressive NHL [23,24]. In Hodgkin lymphoma, TFR was described in three patients [25].

Table 1 Tumour flare definition according to National cancer institute-common toxicity criteria for adverse events v 3.0 grading scale [10]

Tumour flare is characterized by a 'constellation of signs and symptoms in direct relation to initiation of therapy' (e.g., antioestrogens/androgens or additional hormones). The symptoms/signs include tumour pain, inflammation of visible tumour, hypercalcaemia, diffuse bone pain, and other electrolyte disturbances (hypercalcaemia)

Grade 1	Mild pain not interfering with function
Grade 2	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL
Grade 3	Severe pain; pain or analgesics interfering with function and interfering with ADL
Grade 4	Disabling
Grade 5	Death

ADL, activities of daily living.

Tumour flare reaction with Immunotherapy in solid tumours

An overview of TFR reported with immunotherapy in solid tumours is provided in Table 3.

Treatment of various tumour types with ICIs such as nivolumab has sometimes been associated with « tumour flare [26–32].

Table 2 Tumour flare with IMiDs in lymphoid malignancies

Disease	Therapeutic agent	TFR/grade	References
CLL/NHL	Thalidomide	All grades 46% 53% with G3-4:18% 67% 35%	Chanan-Khan *et al.* [1] Kay *et al.* [18] Furman *et al.* [46] Giannopoulos *et al.* [47,48]
CLL relapse or refractory	Lenalidomide Starting dose 25 mg/ day Lenalidomide 5, 10, 15 up to 25 mg/day	58% of 45 Patients G1-2: 50%–G3-4: 8% 29% of 44 Patients G3-4: 8% 4 Patients One death,G4: 3 53% of 31 Patients 23.5% G3: 14.3% 44% G3: 10%	Chanan-Khan *et al.* [2,9] Ferrajoli *et al.* [20] Andritsos *et al.* [7] Aue *et al.* [49] Wendtner *et al.* [21,50]
CLL untreated	Lenalidomide	88% of 25 Patients	Chen *et al.* [36,51]
CLL elderly untreated	Lenalidomide 5 up to 25 mg	52% of 62 Patients	Badoux *et al.* [52]
CLL treated and untreated	Lenalidomide 2.5–5 up to 20 mg	47% of 21 Patients	Lamanna *et al.* [53]
MCL	Lenalidomide	3/25 Patients G3 ≤ 2; one death	Eve and Rule [22]
NHL	Lenalidomide	13/134 Patients G1–2 10% G1–2 14%	Witzig *et al.* [23,24,54]
Hodgkin lymphoma	Lenalidomide	3 Patients	Corazzelli *et al.* [25]

CLL, chronic lymphotic leukaemia; NHL, non-Hodgkin lymphoma; MCL, mantle cell lymphoma; TFR, tumour flare reaction.

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Table 3 Tumour flare with immunotherapy in solid tumours

Disease	Therapeutic agent	Pseudoprogression RECIST/irRECIST	References
Melanoma	Ipilimumab	9.7% Patients (22/227) Response after pseudoprogression	Wolchok *et al.* [3]
Multiple[a]	Anti-PD-L1 BMS-936559	First assessment RECIST:17/135 responses Second assessment irRECIST:4 additional responses	Brahmer *et al.* [55]
Multiple[b]	Nivolumab	First assessment RECIST: 49/236 responses Second assessment irRECIST:8 additional responses	Topalian *et al.* [56]
Melanoma	Nivolumab + ipilimumab	First assessment RECIST: 21/52 responses Second assessment irRECIST:4 additional responses	Wolchok *et al.* [57]
Melanoma	Nivolumab	10% Patients (11/107)	Hodi *et al.* [58]
Melanoma	Pembrolizumab	3.6% Pts (7/192), pseudoprogression first assessment then response second assessment 3.1% Patients (6/192), pseudoprogression first assessment then delayed response Total 6.7% (13/192) pseudoprogression before response 12% Patients (51/411) pseudoprogression RECIST and response irRECIST	Robert *et al.* [59] Hodi *et al.* [60] Hodi *et al.* [38]
Melanoma	Nivolumab	First assessment Recist:33/107 responses Second assessment IrRecist:4 additional responses	Topalian *et al.*[30]
Melanoma	Nivolumab	First assessment RECIST:38/120 responses Second assessment irRECIST:10 additional responses	Weber *et al.* [61]
RCC	Nivolumab	First assessment RECIST:35/168 responses Second assessment irRECIST:3 additional responses	Motzer *et al.* [40]
NSCLC	Nivolumab	First assessment RECIST: 28 pseudoprogression Second assessment IrRecist: 9 responses	Brahmer *et al.* [31]
RCC	Nivolumab	25 (69%) Patients treated beyond first pseudoprogression, with tumour reduction or stabilization	George *et al.* [63]

Incidence TFR NSCLC, HNSCC 2–3% [62,64,65].
NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; TFR, tumour flare reaction.
[a]Melanoma, NSCLC, RCC, and ovarian.
[b]Melanoma, NSCLC, RCC.

In patients receiving immunotherapy, tumour flare or the appearance of new lesions may precede antitumour effects, resulting from T-cells infiltrating the tumour site until a sufficient immune response develops [3]. When assessed by RECIST criteria, TFR occurring with immunotherapy was considered as disease progression and generally led to treatment discontinuation before the potential clinical benefit of the treatment was fully realized [33]. Treatment beyond the first progression was allowed in patients with favourable tolerance and clinical benefit, some of them experienced subsequent tumour response (Table 3).

Tumour flare reaction with endocrine therapies

Flare reactions from tamoxifen are also known in the treatment of metastatic breast and advanced endometrial cancers [4].

During the initial period of treatment with medroxyprogesterone acetate in patients with hormone-resistant prostatic cancer, a marked clinical flare reaction, mainly with bone pain exacerbation was observed [5].

Time to occurrence/management: In CLL, TFR is mostly observed in early therapy phases and it is more common in previously untreated patients with bulky disease, advanced stages and moderate renal impairment. When using high starting doses of lenalidomide, TFR onset has been reported within hours after the first dose, with a median time of 6 days (range 0–56), and a median time to resolution of 14 days [95% confidence interval (CI), 10–26] [9]. This phenomenon was also observed within the first cycle of lenalidomide in relapsed MCL patients [22,34].

In CLL clinical trials with thalidomide, high TFR incidence led to poor accrual and premature closure [17].

TFR is associated with morbidity and may be severe and life-threatening, requiring hospitalization as reported in four patients with relapsed/refractory CLL and who received lenalidomide at a starting dose of 25 mg [7]. Even if rare cases of life-threatening or fatal TFR exist, symptoms were usually mild, and responded to anti-inflammatory therapy.

In a study, using 20 mg prednisone during the first 5 days and 10 mg for another 5 days as prophylaxis decreased severity, but not the incidence [2,35]. In another trial, one third of all patients were treated with lower doses of prednisone (25–50 mg for 5–10 days); in these patients, TFR was common, but mild in severity [36].

In clinical trials, TFR was monitored early after treatment initiation, during the first cycle and at each dose escalation. Adequate management of TFR relies on analgesics, nonsteroidal anti-inflammatory drugs, antihistamines and corticosteroids [20].

Although steroids modulate the timing and severity of TFR, CLL chemotherapy-naive patients demonstrate a high frequency of TFR compared with pretreated patients. The frequency of TFR appears to be lower when lenalidomide was used in combination. Furthermore, rituximab administered prior to lenalidomide may act as a debulking agent, thus reducing the rate and severity of TFR [37].

Biological implications of tumour flare reaction and challenges with therapeutic evaluation

In CLL, studies have shown that lenalidomide induces a TFR suggestive of immune-mediated inflammation [6,7]. Andritsos *et al.* [7] reported laboratory evidence that B-cell activation of the tumour cells may contribute

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to the development of tumour flare *in vivo*. Pretreatment and posttreatment evaluation of lymph nodes, infiltration of Ki67 and CD3-positive, CD8-positive, granzyme B-positive T cells increases.

This reaction has been reported in other B-cell malignancies, such as MCL, and Hodgkin lymphoma illustrating the contribution of upregulation by B-cell activation, T-cell activation and other innate immune effector cells to the mechanism of action of lenalidomide [22,25].

In-vitro findings indicate that the in-vivo antileukaemic activity of lenalidomide is not likely to be due to direct cytotoxicity on B-CLL cells [2].

Lenalidomide induced the expression of costimulatory ligands (CD86, CD80 and CD40) on B-CLL cells both *in vitro* and *in vivo* [7]. Upregulation of these ligands is a critical step in engaging an immune response. This rapid, robust and inflammatory nature of TFR suggests the involvement of the immune system dependent on natural killer cell function and then maintained by the rapid recruitment and proliferation of T cells [6].

Treatment with ICIs such as nivolumab in various solid tumours has been associated with TFR [26,27,30-32,38. With ICIs, TFR is believed to be an immune activation into the tumour, potentially causing tumour growth or new lesions to appear upon imaging, while the immune system is priming for an antitumour response [3].

Immunologic treatment may induce the infiltration of immune cells and inflammation of the tumour, which results in increased tumour size by objective measures [3,33]. Alternately, the growth of pre-existing lesions or the appearance of new lesions can occur after administration of immunotherapy, as the process of immune activation may potentially be delayed. The tumour may grow transiently during the period of immune activation and before an effective antitumour response occurs [33].

Di Giacomo *et al.* [39] reported that some patients with melanoma treated with ipilimumab, a mAb against cytotoxic T-lymphocyte–-associated antigen-4, experienced initial increased size of tumour lesions, confirmed by biopsy as inflammatory cell infiltrates or necrosis, with subsequent tumour burden decrease.

Treatment beyond first RECIST-defined progression was investigated in a phase 2 of nivolumab in patients with metastatic renal cell carcinoma who tolerated nivolumab and exhibited clinical benefit [40]. Half of these patients treated beyond first progression experienced subsequent tumour reduction in target lesions.

Other studies assessing nivolumab in melanoma and non-small cell lung cancer, showed a response in a subset of patients treated beyond first progression [30-32]. Similar findings were reported in patients with melanoma treated with ipilimumab and with pembrolizumab [28,38].

Therefore, pseudoprogression represents a real challenge for clinicians, because it is not captured by conventional imaging and RECIST criteria.

These findings have prompted the development of immune-related response criteria to capture these unconventional response patterns, including requirement of confirmation of progression on two consecutive scans at least 4 weeks apart, and inclusion of new lesion measurements to the total tumour burden [3,41,42].

Discussion

Both solid tumours and haematologic malignancies are able to induce an immune response that can regulate their growth; this is known as tumour immunogenicity [43,44].

A new concept called ‘pseudoprogression’ has emerged, making response evaluation difficult. Using RECIST, tumour flare with immunotherapy may be considered as disease progression and may lead to treatment discontinuation before the clinical benefit of treatment is fully realized [33]. Therefore, initial progression may not indicate therapeutic failure.

Radiological features of TFR have proven to be challenging in clinical trials and in clinical practice setting, because it is difficult to differentiate between pseudoprogression and true progression, with imaging largely relying on the tumour size. Furthermore, conventional imaging and RECIST criteria may underestimate the benefit in a subgroup of treated patients, because immunotherapy works differently as compared with cytotoxics.

When evaluating the response to immunotherapy, even if uncommon, pseudoprogression should be considered until disease progression can be confirmed [27]. Histologic confirmation is not always possible. However, close monitoring using performance status, cancer-related symptoms and tumour burden at the time of progression may allow to differentiate between symptomatic and asymptomatic progression [3,45].

While being asymptomatic in most patients, TFR can be observed in a context with or without clinical deterioration. In many trials, to avoid discontinuing effective therapy, patients who presented with a clinically good performance status were allowed to remain on treatment in the case of a new or growing area of disease.

Conclusion

In conclusion, treatment with immunomodulatory agents is associated with TFR, more frequent with haematologic malignancies; TFR is less common in solid tumours.

TFR is poorly understood and as it is not captured by RECIST, its incidence is still underestimated. Thus, it is likely to be misinterpreted as progression. For this reason, after a first radiologic progression, the use of clinical symptoms may be a helpful indicator. Treatment

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continuation may be supported in patients with clinical benefit, unless progressive disease is confirmed by subsequent evaluations.

To avoid a discontinuation of a potentially effective therapy, assessments should be based on clinical symptoms, imaging and biomarkers. The use of irRECIST in prospective trials is needed for a better diagnostic and understanding of TFR while data should be collected through prospective clinical trials, to characterize this phenomenon more effectively.

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Conflicts of interest

There are no conflicts of interest.

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