A subclinical condition of lymphedema occurs in all patients with HS in the perineal or buttock areas. In most cases lymphedema cannot be diagnosed until tissue swelling is clinically visible, but, according to the International Society of Lymphology, a 'stage 0 lymphedema' does exist [16,17]. At the beginning, only physiologic changes (increased protein content) with no measurable fluid accumulation occur in the body region which is a candidate for lymphedema. Fluid accumulation supervenes later, and only then the clinician makes the diagnosis of lymphedema. In advanced stages, fibrotic changes and lipid deposition due to stasis of protein-rich extracellular fluid appear, resulting in an overt and difficult to manage condition. Interestingly, a recent study has focused on the role of subclinical lymphedema in the origin of both benign and malignant neoplasia [18].

The concept of ICD in dermatology throws new light on the pathogenesis of cancers, and may possibly pave the way for new therapeutic strategies. The crucial role of cancer prevention in dermatology, as well as in other branches of medicine, is so well known that it requires only a few comments. Knowing how vulnerable a diseased or injured skin site may be for an entire lifespan should alert both the physician and the patient to keep the site under special observation. Any new lesion appearing on that site should promptly be investigated by all means and, when necessary, immediately removed [10,19].

Disclosure statement

No potential conflict of interest was reported by the authors.

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LETTER TO THE EDITOR

Decitabine treatment of multiple extramedullary acute myeloid leukemia involvements after essential thrombocytemia transformation

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Progression of Philadelphia-negative myeloproliferative neoplasm (MPN) to acute myeloid leukemia (AML) is usually associated with a dismal prognosis [1]. Indeed, currently available treatment options for these patients are mostly

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limited to palliative intent. Given that, until now no standard treatments have shown a survival improvement, with few exceptions represented by selected patients suitable for allogeneic hematopoietic stem cell transplantation (HSCT) [2]. In this context, the occurrence of extramedullary sites at the AML transformation may represent a further negative prognostic factor [3]. However, the effectiveness by decitabine in three cases of myeloid sarcoma has been recently reported [4]. Herein, we report the case of a patient who received decitabine to treat AML transformation complicated by several extramedullary blastic localizations in the course of her long-lasting essential thrombocythemia (ET). A 41-year-old woman was diagnosed in November 1987 as having ET JAK2 V617Fpositive, later tested when this analysis became available. At the time of the primary diagnosis of ET, the patient's past history was unremarkable except for thyroidectomy for a nonmalignant euthyroid goiter and mild radiological signs of initially smoking-related chronic obstructive pulmonary disease (COPD). She received acetylsalicylic acid (ASA) followed by pipobroman as her initial cytoreductive treatment for less than two years, later replaced by hydroxycarbamide; the latter agent was administered until May 2013 when, preceded by progressively worsening anemia, the disease transformed in myelofibrosis (MF). Meanwhile, in 2011, she had a cervix carcinoma that was initially managed with neoadjuvant radiotherapy plus chemotherapy followed by surgery (total hysterectomy and bilateral annessiectomy). In addition, COPD exacerbation and the development of type-2 diabetes mellitus, complicated by slight nephropathy, retinopathy, left ventricular hypertrophy and chronic ischemic coronary syndrome have occurred. In November 2014, a progressively worsening cytopenia preceded the overt evolution in AML which was characterized by a 50% of bone marrow (BM) infiltration by myeloperoxidase-negative blasts positive for HLA-DR, CD34, CD117, CD13, CD33, CD123 and atypically expressing CD19 and CyCD79a. Standard cytogenetic and mutational studies, usually performed in the AML diagnostic work-up, were negative. At physical examination, she presented with bilateral inguinal palpable lymphadenopathies. Radiologic examinations, including a total body CT scan, revealed enlarged mediastinal lymph nodes and a small pulmonary mass. Because of her relatively young age (68 years) and in the suspicion of metastatic disease from uterine cancer, excisional inguinal lymphadenectomy and a lung mass biopsy were performed, both resulting as sites of extramedullary AML infiltration. Because of the complex clinical situation, the AML aggressiveness, the previous history of solid tumor and the active comorbidities, the patient was unsuitable to receive intensive chemotherapy and a salvage treatment with decitabine was considered. At that time, she was in poor general conditions presenting with an impaired BM reserve and a heavy transfusion requirement (more than 4 red blood cells (RBC) units per month). After obtaining informed consent, she received 5 days courses of intravenous decitabine at the dosage of 20 mg/m^2 every 4 weeks. Broad spectrum antibacterial and antifungal agents were given according to the duration and the degree of neutropenia. After two decitabine courses, the need for transfusion gradually decreased until a relatively short-term transfusion independence that was achieved after six cycles. At that time, a partial response was observed according to published recommendations from the post–MPN-AML consortium [5]. Indeed, a comprehensive re-evaluation demonstrated a blast clearance higher than 50% alongside with the persistence of MPN features and dysplastic changes. Interestingly, the persistent disappearance of extramedullary involvements, demonstrated by radiological examinations, was in line with a previous report describing the efficacy of decitabine in the treatment of extramedullary sites of AML [4]. Decitabine was well-tolerated; grade 1 to 3 hematological toxicities occurred as the result of expected myelosuppression following early courses of therapy and manageable with standard supportive care. Neither delays nor dose reductions were required and all treatment cycles were administered as an outpatient setting. Unfortunately, the patient was unsuitable for HSCT given her comorbidities burden. Therefore, maintenance therapy with decitabine was continued until the 11th course of treatment, when an overt disease progression occurred leading to patient's death, 14 months after the AML diagnosis. It is noted that there were no detectable signs and/or symptoms compatible with recurrences of extramedullary AML involvements. To our knowledge, this is the first description of a multifactorial therapy-related AML progressed from a Philadelphia-negative MPN and characterized by multiple extramedullary sites. Decitabine therapy allowed achievement of a partial response, including the disappearance of extramedullary sites of AML, and a good quality of life with rapid achievement of the transfusion independency; again, the 14 months survival was similar to other patients responding to this agent [1]. Decitabine is a hypomethylating agent acting as DNA methyltransferases inhibitors; this agent provided effective activity as first-line treatment of AML patients [6], who are unsuitable for standard remission induction chemotherapy, and as salvage treatment, including the setting of refractory disease [7]. In addition, decitabine has shown clinical activity in patients with high-risk primary MF, MPN in accelerated phase and in those transformed in AML [1]. In the latter setting, responses with decitabine were relatively durable and a possible improvement in the survival outcome of these patients has been reported [1]. Our case outlined the tolerability of decitabine in frail patients with aggressive disease, despite some degree of organ dysfunctions, as presented by our patient at the start of HMA treatment: it is important to note that its metabolism does not rely on hepatic and/or renal functions, being its elimination due to cytidine deaminase degradation [8]. The efficacy of decitabine in this difficult to treat setting, although not durable, may represent an useful clinical basis for potential applications of this agent with other synergistic compounds [9] into future clinical trials, which should include molecular profiling tools for an accurate selection of suitable patients [10].

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LETTER TO THE EDITOR

Hunting for abscopal and bystander effects: clinical exploitation of non-targeted effects induced by partial high-single-dose irradiation of the hypoxic tumour segment in oligometastatic patients

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Introduction

Until recently, traditional radiobiology was based on the theory that the effects of radiotherapy present themselves only locally, through direct and indirect DNA damage [1]. Recently, after reports on radiation effects outside the irradiated volume, the local effects were denominated as targeted effects, and the distant ones as non-targeted effects [2]. There are two types of non-targeted effects, depending on the site of their occurrence and the relationship between the irradiated and non-irradiated tumor:

- The *Radiation-Induced Abscopal Effect* (RIAE) is a systemic effect of local radiation extended outside the treated volume. Basically, this means that tumor regression is observed at distant untreated sites.
- The *Radiation-Induced Bystander Effect* (RIBE) is a radiobiological effect-transmission that happens when irradiation of only a part of the tumor induces regression of the whole tumor.

Both phenomena have only been sporadically clinically observed, as they were occasional and unintentional. That said, is it possible to induce them intentionally, whenever needed? We have spent the past 7 years testing new ideas in attempts to induce an intentional induction of non-targeted effects from ionizing radiation.

In this letter, we describe the first clinical experience of inducing bystander and abscopal effects by exclusively targeting the hypoxic segment of the tumor with a high, single dose of radiation. The experience confirms the validity of this strategy, and could be the start of a new era in radiotherapy.

Translation of riae/ribe results from pre-clinic to clinic

In vitro, radiation-conditioned medium-transfer experiments using the A-549, H-460 human lung cancer cells, and their hypoxic clones, created for this purpose were behind the clinical studies [3]. Cells were irradiated in normoxic or hypoxic conditions with 10 Gy single doses and the cell growth and survival were monitored by a real time cell electronic sensing system and a colony forming assay, respectively. The studies showed strong correlations between the tumor oxygen status and the RIAE/RIBE-intensity, indicating that the hypoxic tumor segment could be a key-factor for the

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Supplemental data for this article can be accessed here.