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Trial Watch
Radioimmunotherapy for oncological indications

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Abbreviations: DC, dendritic cell; EBRT, external-beam radiation therapy; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; ICD, immunogenic cell death; IL, interleukin; mAb, monoclonal antibody; NHL, non-Hodgkin's lymphoma; TLR, Toll-like receptor.

During the past two decades, it has become increasingly clear that the antineoplastic effects of radiation therapy do not simply reflect the ability of X-, β- and γ-rays to damage transformed cells and directly cause their permanent proliferative arrest or demise, but also involve cancer cell-extrinsic mechanisms. Indeed, among other activities, radiotherapy has been shown to favor the establishment of tumor-specific immune responses that operate systemically, underpinning the so-called 'out-of-field' or 'abscopal' effect. Thus, ionizing rays appear to elicit immunogenic cell death, a functionally peculiar variant of apoptosis associated with the emission of a particularly immunostimulatory combination of damage-associated molecular patterns. In line with this notion, radiation therapy fosters, and thus exacerbates, the antineoplastic effects of various treatment modalities, including surgery, chemotherapy and various immunotherapeutic agents. Here, we summarize recent advances in the use of ionizing rays as a means to induce or potentiate therapeutically relevant anticancer immune responses. In addition, we present clinical trials initiated during the past 12 months to test the actual benefit of radioimmunotherapy in cancer patients.

Introduction

Radiation therapy perhaps constitutes the most widely employed antineoplastic intervention of all time.[1,2] Current estimates indicate that more than 50% of cancer patients will undergo radiotherapy at some point in the course of their disease.[3,4] Originally conceived in the early 1900s following the groundbreaking discovery of Wilhelm Conrad Röntgen,[1] the possibility of treating malignant lesions with ionizing rays has transformed into a robust clinical paradigm coincident with the huge technological advances achieved throughout the 20th century.[1,2] Nowadays, ionizing irradiation is frequently administered in combination with other treatment modalities (including surgery and chemotherapy), either with a curative intent (i.e., to eradicate primary tumors or prevent disease recurrence) or as a palliative approach (i.e., to relieve the pain/discomfort provoked by tumors at particular anatomical locations).[3,4] Depending on the specific case, irradiation can be administered as a neo-adjuvant intervention (to limit the esthetic/anatomical impact of the procedure and minimize the risk of recurrence), intra-operatively (granting access to neoplastic lesions with a particularly complicated anatomical localization), or as an adjuvant treatment (constituting an efficient means to prevent disease relapse).[5-7]

For the purpose of this discussion, radiation therapy can be broadly subdivided into 2 large categories: external-beam radiation therapy (EBRT) and internal radiotherapy.[2,8] EBRT generally relies on an external source of collimated X- or γ-rays targeting neoplastic lesions across the intact skin. We have previously discussed in detail the types of EBRT most commonly employed for oncological indications.[7] Internal radiotherapy can be further subdivided into 2 variants: (1) brachytherapy, which involves the seeding of small radioactive pellets within the tumor mass (interstitial brachytherapy) or in an adjacent cavity (intracavitary brachytherapy); and (2) systemic radiation therapy, consisting in the oral or intravenous administration of a radionuclide, often (but not always) coupled to a tumor-targeting monoclonal antibody (mAb).[8,9] EBRT, brachytherapy and systemic radiation therapy are associated with specific advantages

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and drawbacks that render them particularly conducive to the treatment of specific tumors. A detailed discussion of these aspects goes beyond the scope of this Trial Watch and can be found in Refs. 2, 7 and 8

For a long time, the therapeutic potential of ionizing rays has been exclusively ascribed to their ability to mediate robust antiproliferative and cytotoxic effects as they directly damage various macromolecules (including lipids and DNA) and favor the establishment of oxidative stress (which also promotes DNA damage).[10-12] The molecular damage inflicted by radiation therapy can cause: (1) a permanent proliferative arrest known as cellular senescence;[13-16] (2) mitochondrial outer membrane permeabilization, de facto committing cells to die along with the massive activation of caspases;[17-21] or (3) various forms of regulated necrosis, including a receptor-interacting protein kinase 3 (RIPK3)- and mixed lineage kinase domain-like (MLKL)-dependent variant commonly referred to as necroptosis,[22-25] as well as poly(ADP-ribose) polymerase 1 (PARP1)- and apoptosis-inducing factor, mitochondrion-associated, 1 (AIFM1)-dependent subroutine known as parthanatos.[26,27] The induction of regulated cell death by irradiation often, but not always, involves tumor protein p53 (TP53, best known as p53),[28-30] and results from the activation of mitotic catastrophe, an oncosuppressive mechanism for the elimination of cells unable to complete mitosis.[31,32]

During the past 2 decades, it has become clear that the clinical activity of radiation therapy also involves various cell-extrinsic mechanisms. First, malignant cells exposed to ionizing irradiation die while releasing a wide panel of cytotoxic mediators, including reactive oxygen and nitrogen species,[33-35] as well as several cytokines like interleukin (IL)-6,[36] IL-8,[37] transforming growth factor β1 (TGFβ1)[38] and tumor necrosis factor α (TNFα).[39] These biologically active molecules de facto promote the demise of non-irradiated neighboring cells, underpinning the ability of radiation therapy to mediate local bystander effects.[10,40,41] Second, cancer cells are thought to succumb to radiation therapy by undergoing an immunogenic variant of apoptosis commonly known as immunogenic cell death (ICD).[12,17,42,43] ICD is intimately linked to the emission of various damage-associated molecular patterns in a manner that is spatiotemporally compatible with the recruitment of antigen-presenting cells and the elicitation of adaptive immunity.[42,44-46] Thus, irradiated cancer cells can, at least under some circumstances, prime a tumor-specific immune response that operates systemically, underpinning the long-range bystander effects of radiation therapy commonly known as "out-of-field" or "abscopal" reactions.[47-52] Finally, several types of radiotherapy favor the normalization of the tumor vasculature, a process that inhibits tumor growth while facilitating the access of neoplastic lesions by chemotherapeutic agents and immune effector cells.[53-55]

Radiation therapy causes both acute and chronic side effects.[56-59] The former, which generally resolves in a few days/weeks after interruption, generally reflect the temporary damage inflicted to highly proliferative normal tissues inevitably irradiated along with neoplastic lesions (e.g., the skin in the case of EBRT).[8,60] Conversely, the latter result from the permanent damage of highly proliferating cell compartments, such as the intestinal mucosa. In addition, radiation therapy is associated with a small but quantifiable increase in the risk of developing a secondary, treatment-induced neoplasm later in life.[61-63] Several strategies have been developed throughout the past 50 years to increase the therapeutic index of radiation therapy, that is, to maximize its antineoplastic activity ("radiosensitization") while limiting its cytotoxic effects on non-transformed tissues ("radioprotection").[2,64-66] Fractionation, i.e., the delivery of radiotherapy in multiple sessions (spaced by at least 6 hours) over several weeks, is by far the most common approach to simultaneously achieve this goal.[1] Moreover, several molecules have been shown to mediate bona fide "radiosensitizing" or "radioprotective" effects in preclinical models.[67-82] Nonetheless, the radical scavenger amifostine (also known as Ethyol®) is the only chemical currently approved by the US Food and Drug Administration (FDA) for use as a radioprotector in cancer patients.[83-85]

One year ago, in the September issue of OncoImmunology, we discussed in detail the scientific grounds for the use of ionizing irradiation as a means to elicit or boost tumor-targeting immune responses in cancer patients and presented recent clinical trials investigating the actual therapeutic profile of this approach.[7] In this Trial Watch, we summarize the latest developments in this promising area of clinical investigation, focusing on clinical and preclinical paradigms of radioimmunotherapy, i.e., the combinatorial administration of radiation therapy and one or more immunostimulatory interventions.

Literature Update

Since the submission of our latest Trial Watch dealing with topic (June 2013),[7] the results of some 130 clinical studies evaluating the therapeutic profile of anticancer radioimmunotherapy have been published in the peer-reviewed scientific literature (source http://www.ncbi.nlm.nih.gov/pubmed).

The largest fraction of these studies investigated the safety and efficacy of potentially immunogenic chemoradiotherapy, i.e., combinatorial regimens involving EBRT or internal radiotherapy plus immunostimulatory chemotherapeutics[86-90] including (but not limited to) 5-fluorouracil (a pyrimidine analog generally utilized for the therapy of head and neck carcinoma and colorectal neoplasms) and its precursors (capecitabine and S-1, both of which are currently approved by the US FDA for use in colorectal cancer patients),[91-131] etoposide (a topoisomerase inhibitor currently employed against testicular tumors and small cell lung cancer),[132-136] docetaxel and paclitaxel (two microtubular inhibitors of the taxane family routinely harnessed for the treatment of several carcinomas),[96,97,111,115,127,134,136-153] ifosfamide and cyclophosphamide (two alkylating agents licensed by the US FDA for the therapy of various solid malignancies),[154,155] gemcitabine (a nucleoside analog currently employed in patients affected by various carcinomas),[109,131,150,156,157] bortezomib (a proteasomal inhibitor most commonly utilized in multiple myeloma patients),[158] and various platinum derivatives (i.e., cisplatin, carboplatin and oxaliplatin, which are employed for the treatment of various carcinomas).[91,92,95-104,106-108,111-

[113,115,116,119,121-124,134,138-146,156,157,159-161] In addition, several research groups worldwide assessed the clinical profile of EBRT in combination with naked tumor-targeting mAbs,[162-174] immunostimulatory mAbs,[175,176] dendritic cell (DC)-based or peptide-based anticancer vaccines,[177,178] or multiple immunogenic interventions (most often a tumor-targeting mAbs plus immunostimulatory chemotherapy).[179-195] Finally, a few studies evaluated the therapeutic potential of mAb-based internal radiotherapy, either employed as a stand alone intervention[196-204] or combined with additional immunotherapeutic agents, most often naked tumor-targeting mAbs.[158,205-208]

Most clinical studies on the therapeutic activity of radioimmunotherapy published during the last 13 months enrolled patients bearing solid tumors, including subjects with glioma or glioblastoma,[118,167,168,181] breast carcinoma,[125,130,163] head and neck cancer,[95-97,111,115,116,129,141,142,161,173,174,185,194,195] gastric, esophageal or gastroesophageal carcinoma,[94,112,119-124,138,143,166,184] lung carcinoma,[113,114,134,136,139,140,149,150,160,178,183] endometrial carcinoma,[144-147,153] pancreatic cancer,[109,110,131,156,157,169,170,186-188] colorectal or anal carcinoma,[92,98-108,128,159,162,171,180,189-193,196,200,201,209-211] bladder carcinoma,[126,127] cervical carcinoma,[91,148,151,152,164] prostate carcinoma,[137,176] and others.[93,154,172,175,177,204] In addition, a few groups assessed the safety and efficacy of radiation therapy (most often internal radiotherapy) combined with immunostimulatory interventions in patients affected by various forms of lymphoma.[132,133,135,155,158,165,182,197-199,202,203,205-208] Taken together, these studies corroborate the notion that both EBRT and internal radiotherapy can be combined with a wide panel of immunostimulatory agents in the absence of accrued toxicity. As exceptions to this trend, Vaklavas and colleagues found that the combination of ^{90}Y-ibritumomab tiuxetan, a radiolabelled CD20-targeting mAb approved by the US FDA for use against non-Hodgkin lymphoma (NHL),[212,213] and rituximab, a naked CD20-specific mAb currently employed for the treatment of chronic lymphocytic leukemia and NHL,[214-216] correlates with an increased rate of Grade 3-4 adverse events relative to ^{90}Y-ibritumomab tiuxetan monotherapy among NHL patients.[203] Along similar lines, two independent groups reported that patients with locally advanced anal carcinoma receiving cetuximab, a naked epidermal growth factor receptor (EGFR)-targeting mAb currently licensed for the therapy of head and neck cancer and colorectal carcinoma,[217-220] along with cisplatin- or 5-fluorouracil-based chemoradiotherapy display an elevated rate of severe side effects, including dermatitis, diarrhea, thrombosis/embolism, and infection.[162,180] However, it remains to be determined which components of these combinatorial radioimmunotherapeutic regimens are truly responsible for such an accrued toxicity. Moreover, Olivatto and colleagues observed a high rate of pathological complete responses (95%) and locoregional control at 3-year follow-up (64.2%) among anal carcinoma patients treated with cetuximab plus chemoradiation.[180] These data encourage the evaluation of EGFR-targeting agents other than cetuximab in support of cisplatin- or 5-fluorouracil-based chemoradiotherapy as a treatment for anal carcinoma. Along similar lines, the results of various other studies published in the last 13 months suggest that the combinatorial use of radiation therapy (in several of its variants) and diverse immunostimulatory agents exhibit a superior clinical profile (i.e., improved efficacy, limited incidence and severity of side effects) as compared to either therapeutic paradigm employed alone (at least in a subset of patients).[91,95,96,99,103,104,107,108,111,115,116,125,126,132-135,137,138,141,143,145,147,155,157,159-161,164,168,172,179-183,185,187,192,193,198,200,203,204,206-210]

Among recent translational studies focusing on radioimmunotherapy in general, we found of particular interest the work of (1) Deng and collaborators (The Ludwig Center for Metastasis Research; Chicago, IL, US), who demonstrated that the immunosuppressive receptor programmed cell death 1 (PDCD1, best known as PD-1)[221,222] is upregulated in the tumor microenvironment in response to EBRT, and that the administration of a mAb targeting the PD-1 ligand CD274 (best known as PD-L1)[223,224] synergize with irradiation to provoke a therapeutically relevant antitumor immune response;[225] (2) Klug and colleagues (German Cancer Research Center; Heidelberg, Germany), who proved that low-dose γ-rays administered in a neoadjuvant setting stimulate the differentiation of M1 macrophages,[226-229] hence promoting the normalization of the tumor vasculature and orchestrating an efficient tumor-targeting immune response;[230] (3) Nam and coworkers (University of Ulsan College of Medicine; Seoul, Korea), who reported that the mechanistic target of rapamycin (MTOR) inhibitor rapamycin (which is currently approved by the US FDA for use as an immunosuppressive agent to prevent the rejection of solid organ transplants and coronary stents),[231] can be employed to promote cellular senescence among radioresistant cancer cells,[16,31] in spite of its ability to potently stimulate autophagy;[232-234] (4) Bos et al. (Memorial Sloan-Kettering Cancer Center; New York, NY, US), who proved that the short-term ablation of $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs)[235-237] significantly ameliorates the therapeutic efficacy of EBRT in a genetically-driven, autochthonous model of tumorigenesis;[238] (5) Liu and collaborators (Chang Gung University; Taoyuan, Taiwan), who demonstrated that leukemia inhibitory factor (LIF), a cytokine of the IL-6 family,[239,240] plays a significant role in the acquisition of radioresistance by nasopharyngeal carcinoma;[241] (6) Zhou and colleagues (University of Michigan School of Dentistry; Ann Arbor, MI, US), who proved that the administration of the recombinant WNT agonist R-spondin 1 (RSPO1)[242-244] combined with the transgene-driven overexpression of slit homolog 2 (SLIT2) mitigates the lethal effects of high-dose irradiation to the intestine but does not compromise its antineoplastic activity;[245] (7) Sharma and collaborators (University Hospital Zurich; Zurich, Switzerland) and Gerber et al. (University of Rochester Medical Center; Rochester, NY, US), who independently showed that radiation therapy induces an intratumoral immune response (characterized by the recruitment of T lymphocytes and the secretion of T_H1 cytokines), whose magnitude correlates with disease outcome;[246,247] (8) Spary and colleagues (Cardiff University; Cardiff, UK), who demonstrated that low-dose irradiation significantly boosts the effector functions of T lymphocytes upon antigenic stimulation;[248] and (9) Eke and co-workers (Dresden University of Technology; Dresden, Germany), who identified the overexpression of fibronectin and the resultant increase in cell-fibronectin interactions as a possible means by which cetuximab promotes radioresistance.[249] It remains to be determined whether this mechanism is also responsible for the accrued toxicity of cetuximab-based radioimmunotherapy observed in recent clinical trials.[162,180]

Update On Ongoing Clinical Trials

When this Trial Watch was being redacted (June 2014), official sources listed no less than 98 clinical trials launched after June 1st, 2013 aiming to evaluate the efficacy and safety of radioimmunotherapy in cancer patients (source http://www.clinicaltrials.gov). Of these studies, (1) 2 trials involve tumor-targeting mAbs, such as cetuximab[89,250] or the vascular endothelial growth factor (VEGF)-targeting mAb bevacizumab (which is currently approved by the US FDA for use in patients affected by colorectal, lung and renal carcinoma);[251-253] (2) 4 studies involve immunostimulatory mAbs, such as the cytotoxic T lymphocyte-associated protein 4 (CTLA4)-specific mAb ipilimumab (which is currently licensed for use in melanoma patients);[254-257] (3) 62 immunostimulatory chemotherapeutics, including ICD-inducing agents as well as compounds that stimulate anticancer immune responses in an ICD-unrelated manner;[86-89] (4) 3 recombinant cytokines, including IL-2;[240,258] (5) 1 experimental Toll-like receptor (TLR) agonists, such as polyinosinic-polycytidylic acid stabilized in carboxymethylcellulose and poly-*L*-lysine;[259-261] (6) 1 experimental RNA-based anticancer vaccines;[262-264] (7) 1 an experimental DC-based tumor-targeting vaccine;[265,266] and (8) 23 combinatorial strategies based on at least 2 distinct immunotherapeutic regimens (**Table 1**).

Reflecting currently approved therapeutic protocols,[267-274] many of these clinical trials enroll patients with head and neck cancer (15 trials), gastric or gastroesophageal carcinoma (8 trials), colorectal carcinoma (14 trials), pancreatic cancer (11 trials) or non-small cell lung carcinoma (7 trials). In these settings, a variant of EBRT is generally combined with an immunostimulatory chemotherapeutic regimen, most often based on oxaliplatin in the case of individuals with colorectal carcinoma, gemcitabine in the case of pancreatic cancer patients, and a platinum derivative plus a taxane in the case of subjects bearing head and neck, gastric, gastroesophageal or pulmonary neoplasms. Along similar lines, 5 studies have recently been initiated to investigate the safety and efficacy of radiation therapy combined with ipilimumab or high-dose IL-2 in melanoma patients. These observations suggest that most of the recent clinical trials involving EBRT and one or more immunostimulatory agents rely on radiochemotherapeutic protocols developed prior to the recognition of the immunomodulatory potential of some chemotherapeutics (**Table 1**).[275] In line with this notion, only a few such studies are being performed in the context of

Table 1. Current trends in anticancer radioimmunotherapy*

Cancer type	Phase	N°	Notes
Brain tumors	I-III	5	The panel of radioimmunotherapeutic paradigms tested for these oncological indications is relatively heterogeneous
Breast carcinoma	0-III	4	In a majority of cases, EBRT is administered together with immunostimulatory chemotherapy plus a tumor-targeting mAb
Colorectal carcinoma	I-III	14	EBRT is generally employed in combination with oxaliplatin-based chemotherapy
Gastroesophageal carcinoma	I-III	8	Most often, EBRT is administered in combination with one or more immunostimulatory chemotherapeutic agents, including paclitaxel and capecitabine
Head and neck cancer	I-III	15	In the majority of indications, EBRT is combined with paclitaxel, cisplatin and/or an EGFR-targeting mAb
Hematological neoplasms	I-III	8	Internal radiotherapy based on a tumor-targeting mAb is given alone or together with another immunostimulatory agent
Hepatic neoplasms	II-III	2	Radiation therapy is coupled to TACE based on immunostimulatory chemotherapeutics
Melanoma	I-II	6	EBRT is generally given in combination with ipilimumab
Neuroectodermal tumors and sarcomas	II	2	EBRT is combined with immunostimulatory chemotherapy, alone or together with the VEGF-neutralizing mAb bevacizumab
Pancreatic cancer	0-III	11	Most frequently, EBRT in one of its variants is administered in the context of gemcitabine-based chemotherapeutic regimens
Pulmonary carcinomas	I-III	8	EBRT is generally combined with immunostimulatory chemotherapy based on and a platinum derivative plus a taxane
Renal cell carcinoma	I-II	3	SBRT is combined either with high-dose IL-2 or with the adoptive transfer of autologous lymphocytes
Reproductive tract neoplasms	I-III	7	EBRT is often given in combination with immunostimulatory chemotherapeutics including taxanes a platinum derivatives
Others	I-III	5	The radioimmunotherapeutic regimens in these oncological indications are relatively heterogeneous

Abbreviations: EBRT, external body radiation therapy; EGFR, epidermal growth factor receptor; IL-2, interleukin-2; mAb, monoclonal antibody; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; VEGF, vascular endothelial growth factor.
*Based on clinical trials started after 2013 June 1st and not withdrawn, terminated or suspended by the day of manuscript submission (source www.clinicaltrials.gov).

appropriate immunomonitoring procedures,[276-278] allowing investigators to assess not only toxicity and efficacy, but also the actual involvement of the immune system in disease outcome.

As for the clinical trials listed in our previous Trial Watch dealing with this topic,[7] the following studies have changed status during the past 12 months: (1) NCT01730157 and NCT-01769222, which have been "suspended"; (2) NCT01326923 and NCT01790516, which have been "terminated"; (3) NCT01634880, NCT01652261 and NCT01728480, which have been "withdrawn"; (4) NCT01290120, NCT01468740, NCT01567202, NCT01569984, NCT01612247, and NCT01-653301, whose status is now "unknown"; (5) NCT01760811, which is listed as "not yet recruiting"; (6) NCT01362127, which appears to be "enrolling by invitation"; (7) NCT01347034, NCT01440270, NCT01497275, NCT01507103, NCT0153-9824, NCT01566435, and NCT01740258, which are indicated as "active, not recruiting"; (8) NCT01557114, NCT01749956, NCT01769508, NCT01795430, NCT01798004, NCT01807-065, NCT01818986, NCT01821729, NCT01833208, NCT0-1843829, NCT01850888, NCT01857934, which are now "recruiting" participants; and (9) NCT01249352, NCT012-71439, NCT01298401, NCT01332929, NCT01434147 and NCT01523847, which are listed as "completed" (source http://www.clinicaltrials.gov). NCT01730157, testing radioembolization plus ipilimumab in patients with metastatic uveal melanoma, has been suspended owing to administrative issues, whereas NCT01769222, investigating the clinical profile of radiation therapy plus ipilimumab in patients with melanoma, colorectal carcinoma or NHL, has been suspended following the decision of the local Data and Safety Monitoring Committee. NCT01326923 and NCT01790516, both assessing the therapeutic profile of cisplatin-based chemoradiation plus cetuximab in patients with locally advanced head and neck squamous cell carcinoma, have been terminated either because the principal investigator left the institution or owing to an excessively low accrual rate, respectively. Along similar lines, NCT01634880, testing adjuvant irradiation plus an experimental EGFR-targeting mAb in subjects with high-risk salivary gland malignancies, and NCT01652261, investigating the clinical profile of radiation therapy plus multimodal immunostimulatory chemotherapy in Hodgkin's lymphoma patients, have been withdrawn prior to enrollment for lack of accrual. Conversely, NCT01728480, which aimed at assessing the safety and efficacy of cisplatin-based chemoradiation plus a recombinant TLR5 agonist (i.e., entolimod),[279] has been withdrawn as per the request of the sponsoring agency. Finally, to the best of our knowledge, the results of NCT01249352 (testing chemoradiation plus an EGFR-specific mAb in subjects with locally advanced esophageal carcinoma), NCT01271439 (assessing the clinical profile chemoradiation plus cetuximab in nasopharyngeal carcinoma patients), NCT01298401 (investigating the safety and efficacy of EBRT plus immunostimulatory chemotherapy and/or a mAb targeting the insulin-like growth 1 factor receptor in individuals with pancreatic cancer), NCT01332929 (testing radiation therapy in combination with bevacizumab for the treatment of brain metastases), NCT01434147 (evaluating whether immunostimulatory chemotherapy, bevacizumab and EBRT can be safely and effectively combined for use in colorectal cancer patients) and NCT01523847 (assessing the clinical profile of an immunostimulatory chemotherapeutic regimen optionally administered together with EBRT in cardiopathic subjects with Hodgkin's lymphoma) have not yet been released (source: http://www.clinicaltrials.gov).

Concluding Remarks

Similar to the action of some chemotherapeutic agents, such as the nucleoside analog gemcitabine[280,281] and the DNA alkylating agent cyclophosphamide,[282,283] radiotherapy per se mediates direct antineoplastic effects while stimulating the insurgence of a tumor-specific adaptive immune response.[88,89] Besides accounting for the so-called abscopal effect, i.e., the ability of ionizing irradiation to induce the regression of distant, non-irradiated lesions, such a dual activity may explain the relative success of this widely employed therapeutic option.[1,2] If this were the case, X- or γ-rays would improve the clinical profile of immunotherapeutic agents including DNA-based, peptide-based or DC-based vaccines,[262,266,284] immunomodulatory cytokines,[239] TLR agonists,[259,260] and immunostimulatory antibodies.[285] One of the major impediments against the development of radioimmunotherapeutic paradigms of this type is the identification of the doses and administration schedules that maximize the immunostimulatory potential of ionizing irradiation while preserving its ability to directly inhibit tumor growth.[248] The results of large, randomized and properly monitored trials are urgently awaited to facilitate the design of novel radioimmunotherapeutic regimens with improved clinical activity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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