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Advances in Clinical Toxicology
ISSN: 2577-4328

Radiation/Drug Interactions and the Combinational Effects of Tyrosine Kinase Inhibitors and Radiation Therapy in the Treatment of Cancer

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Research Article
Volume 6 Issue 3
Received Date: August 18, 2021
Published Date: September 03, 2021
DOI: 10.23880/act-16000224

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Abstract

Introduction: Progress in both the development of Tyrosine Kinase Inhibitors (TKIs) and modern radiation therapy (RT) have opened new horizons for the safe and effective treatments of cancer. Combination therapies of TKIs and radiation therapy have been evaluated with variable sequencing and dosing of both agents. Radiation therapy induces cellular damage to cancer and normal tissue DNA by the production of direct and indirect ionization leading to a cascade of biological events. These ultimately lead to potential loss of cellular reproductive capacity, cell death or impotency. Repair mechanisms of RT-induced cell damage require repair pathways dependent on TK. TKIs are key regulators of cellular function and signaling proteins that catalyze phosphorylation reactions of tyrosine molecules. The purpose of this study was to briefly review the basic biology of RT and TKIs and to review the modern literature pertaining to the toxic and therapeutic effects of their combination in the treatment of cancer based on preclinical and clinical data.

Methods: A retrospective review of the basic biology of RT and TKIs with the aim of identifying their combined toxicity and benefit in the treatment of cancer was performed. A systematic search of the standard published radiotherapeutic, radiobiology, chemotherapy and radiotherapy texts, PubMed, Google Scholar, and Clinical Key using the search terms; TKI, RT and combination TKI and RT from 1985-2020 was employed. Data were abstracted from 222 entries from the literature published in English. Issues of toxicity and therapeutic efficacy were defined to evaluate the safe and effective use of combined modality therapy (CMT).

Results: Few randomized studies were available for high-level recommendations. The combined treatment of cancer with TKIs and RT may have benefit for palliation, progression free survival, and potential survival under well-defined circumstances. Any benefit of combined therapy is accompanied by significant potential for enhanced radiation toxicity in addition to the baseline potential toxicities of both agents.

Conclusion: The data reviewed suggest potential benefit from the CMT of TKIs and RT but at a significant risk of toxicity, which may include severe, hematological, cardiac, gastrointestinal, pulmonary and central nervous system toxicity. Further randomized prospective studies are necessary to define their safe and effective combined therapies. New TKI's and radiotherapeutic modalities are constantly under development necessitating ongoing and often long term clinical evaluation to define benefits and risks.

Keywords: Radiation Therapy; Tyrosine Kinase Inhibitors; Radiation/Drug Interactions; Drug/Drug Interactions; Radiation Toxicity; Radiosensitization; Combined Modality Treatment of Cancer

Introduction

The combination of pharmacological agents and radiation therapy represents a significant advance in the treatment of cancer. Multimodality treatment has resulted in both enhanced curative and palliative effects as well as the potential for enhanced toxicity of chemotherapeutic, immunotherapeutic and radiotherapeutic agents. The therapeutic benefit versus the toxicological detriment of combined modality therapy depends on the sequencing of the agents such as whether administration of chemical agent precedes, occurs concurrently, or follows radiation therapy [1,2]. In addition the interactive effects may be synergistic (the combination effect is greater than additive effect of both agents), additive (their effects are summated), sub-additive (the combinational effect is less than the sum of both), or inhibitory/protective (the combinational effect is less than either one alone) [1,3].

The combination of multimodality therapy (CMT) has demonstrated clinical benefits in brain tumors, head and neck cancers, upper gastrointestinal cancers, lung cancer, breast cancer, rectal and anal cancers, bladder cancers, gynecological cancers and a multitude of other cancers. However, those benefits often are accompanied by toxicities and adverse events, which may be early or acute, delayed or subacute or late even up to years after CMT [2].

Tyrosine Kinase Inhibitors (TKIs) represent an expanding class of targeted therapeutic agents that are playing a more frequent role in cancer treatment. As their utilization increases, their interactions with radiotherapeutic applications become more clinically relevant. Radiation therapy has played an active role in cancer treatment of nearly 100 years, and its biology has become more complex due to the interactive pharmacological modalities of treatment with radiobiology. This review will address modern data concerning the toxic and interactive effects of TKIs and radiation therapy, including review of the individual biology's of radiation therapy and TKIs, followed by the current preclinical and clinical analysis of their interactive effects.

To accomplish this, a systematic search of the standard published radiotherapeutic, radiobiology, chemotherapy and radiotherapy texts, PubMed, Google Scholar, and Clinical Key using the search terms; TKI, RT and combination TKI and RT from 1985-2020 was employed. Data were abstracted from 222 entries from the literature published in English. Issues of toxicity and therapeutic efficacy were defined to evaluate the safe and effective use of combined modality therapy (CMT).

Radiation Therapy

To appreciate the interactive effects of radiation therapy and TKIs, an understanding of the biology and toxicology of both agents individually is necessary. Radiation therapy (RT) is an essential treatment used in the management of many patients with cancer. Based on statistics from the National Cancer Institute, approximately 50% of cancer patients receive radiation during the course of their treatment. Although the vast majority of these therapies are safe and effective, but when treatment errors occur, they can have serious consequences, as highlighted in a series of popular press articles [1,2].

Radiation therapy owes its efficacy to its differential effects on normal and tumor tissue. X-rays, photons and other varieties of radiation are part of the electromagnetic spectrum. A photon, which is utilized most frequently in radiation therapy, is a packet of energy characterized by the equation E=hv where E is the energy of the photon, h is Planck's constant; and v is the frequency of the photon. High-energy radiation has high frequency and short wave length. Evidence suggests that double-stranded breaks of nuclear DNA is the most significant cellular event of radiation. This damage to DNA leads to potential irreversible loss or cellular reproductive capacity with eventual cell death or biologic impotency. However, in clinical radiation therapy, cellular damage is most frequently induced by indirect ionization via the production of free radical intermediaries, including hydroxyl ions, peroxides, and other reactive oxygen species (ROS), formed from the radiolysis of water. These ROS are related to the oxygen tension of the environment. Similar to chemotherapeutic drugs, a dose response curve can be generated but with a subtle difference. Radiation survival curves have a shoulder that indicate the existence of normal biologic repair mechanisms. Once that shoulder is surpassed dosimetrically, the dose effect curves become logarithmically linear.

Cancer cell survival after radiation therapy is dependent not only on oxygen tension, but also to the position in the cell cycle, as G1 and M are more radiosensitive than G2 and S. In addition to a therapeutic benefit over a period of multiple radiotherapeutic administrations (fractionation), several processes must occur. Repair must occur to a greater extent in normal tissue than in tumor. Redistribution of the cell into a more radiosensitive part of the cell cycle is required to optimize tumoricidal activity of each treatment. Repopulation of normal cells is necessary to maintain normal tissue integrity. Reoxygenation within the tumor to maintain production of ROS develops when tumor shrinkage allows for better diffusion of oxygen. These four processes are referred to, as the four R's of radiation therapy. The addition of Radiosensitivity adds a fifth R.

The normal tissue response to radiation is complex and variable depending on the radiosensitivity of the irradiated

tissue and its ability to repair radiation damage, which in turn depends on complicated biochemical and enzymatic repair cascades. The effects of radiation on tissue and organs may be acute, subacute, or delayed, even years, as tissue-radiation interactions continue to accrue over time [3]. CMT embellishes the complexity of calculating the therapeutic ratio of a treatment delivery [4].

Acute side effects of radiation (0-3 weeks after or during treatment) include, depending on the tissue irradiated, mucositis, loss of taste, dry mouth secondary to diminished saliva, skin tanning, epithelialitis, telangiectasia, ulceration or later fibrosis, diarrhea, urinary irritation, nausea, alopecia, vomiting, weakness, fatigue etc. There is potential injury to any organ depending on dose of radiation and the volume or the area irradiated.

Subacute, chronic, or late effects of radiation may include, microvascular injury, stem cell depletion, organ failure, fibrosis, delayed wound healing, and or impaired organ function of any irradiated tissue. For instance, chronic diarrhea, cystitis, endocrine dysfunction, muscular dysmotility and others may develop. Detrimental cognitive late effects of radiation therapy on central nervous system tissue have been described after radiotherapeutic brain treatment, in spite of its efficacy in treating primary or metastatic brain cancers [5,6].

Despite the potential toxicities of radiation therapy, adverse events have been greatly mitigated by respect for normal tissue tolerance, more accurate tumor localization, new dosiometric computer algorithms and mechanisms for avoiding normal in-field tissues [4]. Radiotherapeutic accommodations with sharper beams for better collimation, avoidance of normal tissue, utilization of dosimetry to modulate intensity of radiation therapy, stereotactic radiotherapy, and planned avoidance of radiosensitive areas have improved the safety of radiotherapy [7-10].

Tyrosine Kinase Inhibitors

Receptor Tyrosine Kinase Inhibitors (TKIs) have revolutionized the practice of oncology and hematology for almost 20 years since the FDA's approval of Imatinib in 2001 for the treatment of chronic myeloid leukemia [11-15]. As of August, 2019, 43 TKIs gained approval for the treatment of a variety of cancers, including lung, breast, urothelial carcinoma, myelofibrosis, polycythemia vera, acute lymphoblastic leukemia, acute myelogenous leukemia, renal cell carcinoma, melanoma, and others [16,11].

Tyrosine Kinases (TKs) are key regulators of cell function signaling proteins that govern cancer cell growth and metastasis. There are approximately twenty subfamilies of receptor TKs with a similar structure. TKs are responsible for catalyzing phosphorylation reactions of the tyrosine molecules that use ATP as their donor. As such, they are critical mediators of signaling cascades [11]. Irregular expression of receptor TKs commonly leads to dysfunction of cell growth, resulting in tumor progression and growth, angiogenesis and metastases. [11,13,17]. TKIs compete with the receptor TK ATP binding site for ATP that reduces TK phosphorylation and hampers growth of tumor cells. TKIs may also be composed of monoclonal antibodies that compete for the extracellular domain or small molecules that inhibit the tyrosine kinase domain and prevent conformational changes that activate receptor TKs. If TKs are aberrant, progression of cells to cancer may occur due to mutation, excessive production or autocrine stimulation [16]. TKIs may also possess both stimulatory and inhibitory activity on tumor immunity. While promoting the ability of dendritic cells to stimulate NK cell activity, they may also simultaneously inhibit the proliferation of T cells. These actions mitigate the expansion of regulatory T cells and myeloid-derived suppressor cells that enhance the number of mature myeloid dendritic cells in tumor sites [12].

Type-I tyrosine kinase inhibitors are ATP-competitive inhibitors that bind to active conformations. Type-II inhibitors bind adjacent to the ATP site of inactive kinases and maintain their inactive conformation. Type-III inhibitors create kinase inhibition by selectively binding to an allosteric site distant from the ATP and the hinge. Type-IV inhibitors target substrate-binding site in a reversible manner (under development). Type-V inhibitors bind to their targets with covalent bonds that include, but are not limited to, ALK: anaplastic lymphoma kinase; BCR-ABL: breakpoint cluster region-Abelson; CDK: cyclin-dependent kinase; CML: chronic myeloïd leukemia; CSFR: colony stimulating factor 1 receptor; DTC: differentiated thyroid carcinoma; ECD: Erdheim-Chester disease; EGFR: Epidermal growth factor receptor; FGFR: fibroblast growth factor receptor; HER or ErbB: human epidermal growth factor receptor; IGF insulin-like growth factor; and others Pottier, et al. [15].

The potential toxicities of TKIs compared to cytotoxic chemotherapy are mild but not without adverse effects. TKIs do not exhibit the same degrees of problematic adversities of myelosuppression, hair loss, kidney damage, or peripheral neuropathy, etc as chemotherapeutic agents. Adverse TKI effects include potential nausea, vomiting, myelosuppression, cardiotoxicity, teratogenesis, skin rash, interstitial lung disease, gynecomastia, suppression of immune function, hepatotoxicity, hypertension, diarrhea, and secondary malignancies. By way of inhibition of cellular function as a mechanism of action, TKIs may inhibit vascular endothelial growth factor, epidermal growth factor, insulin growth factor, and fibroblast growth factor [13,18,19]. Further, TKIs may

be associated with adverse drug-drug interactions since some TKIs are substrates of CYP3A4 and others may inhibit CYP2D6, 2C8, 2C9 and 2D6. Dosing adjustments may be necessary to prevent toxicity [13].

The complex injury and repair mechanisms of radiation involve similar biochemical pathways as TKIs. For example, TKIs such as bevacizumab inhibit VEGF neoangiogenesis counter intuitively normalizing vascularity rather than inducing radioresistance by impeding oxygen. Cetuximab inhibits EGFR that may co-inhibit repair mechanisms further inducing tumor cell kill [20]. Each TKI expresses its own pharmacokinetic and pharmacodynamic activity, so it is anticipated that the interactive effects of radiation therapy and TKIs will vary. The following preclinical and clinical experiences will document those observations.

Preclinical Interactive Effects

Tyrosine kinase inhibitors (TKIs) are well-characterized for their role in the regulation of multiple cellular functions to include cell proliferation, metabolism, transcription and apoptosis. As such, TKIs are frequently administered in combination with radiation therapy (XRT) to optimize treatment of many cancers, resulting in lower recurrence rates and improved survival. Importantly, based on the mechanism of action of TKIs, they also non-selectively target the growth and development of non-cancerous or normal cells that can lead to off-target effects and/or adverse events. Disruption of normal gastrointestinal function and diarrhea are the most common adverse events observed with TKI therapy [21,22] that is often worsened during combination treatment with chemotherapy [23]. As diarrhea is also the most common toxicity among patients undergoing whole-body, pelvic, and abdominal radiation therapy [24,25], it is speculated that TKI combination therapy may exacerbate this side effect due to reduced tissue healing as a result of growth factor inhibition [26]. Accordingly, various TKIs that target EGFR signaling pathways are associated with mild to severe gastrointestinal side effects. Preclinical research has shown that TKI-induced diarrhea is a consequence of selective inhibition of the EGFR signaling pathway, contributing to mucosal atrophy [27] and excessive chloride secretion in the intestine [28]. Additional *in vivo* studies have provided further insight into the mechanisms underlying TKI-mediated diarrhea and intestinal dysfunction. A rat model of lapatinib-induced diarrhea developed by Bowen, et al. produced symptomology reminiscent of the clinic; however, no intestinal injury was observed in the jejunum or colon [29]. Conversely, treatment with the TKI/EFGR inhibitor gefitinib in an *in vivo* model led to necrotic enterocolitis, [30] whereas other studies with canertinib [31] and erlotinib [32] also showed intestinal disruptions to include decreased villous height and small intestine weight.

Combination XRT and EGFR TKIs are primary treatments for human non-small cell lung cancer (NSCLC); however, their use may be limited due to radiation-induced lung injury and TKI-induced interstitial lung disease [33,34] resulting in pneumonia and pulmonary fibrosis [35,36]. The lung is one of the most sensitive tissues to ionizing radiation that can limit the success of XRT for cancer treatment [37]. Meta-analyses of thousands of patients indicate an increased risk of lung toxicity and interstitial lung disease (ILD) attributed to TKIs to include gefitinib, erlotinib as well as the ErbB inhibitor afatinib [38,39]. Interestingly, although both ertolinib and gefitinib are reversible EGFR-TKIs, adverse reactions have been described to occur earlier with ertolinib [40] as observed by acute onset of dyspnea, rapid progression to respiratory failure and acute respiratory distress syndrome (ARDS) [41]. In a murine model of lung injury, Wang, et al. [42] revealed that inhibition of nuclear factor kappa B (NFκB), a key inflammatory transcription factor upregulated in a number of tumors, could improve sensitivity to TKI and XRT combination therapy as well as reduce associated lung toxicity. Specifically, NFκB inhibition protected animals from lung injury as indicated by reduced monocyte and macrophage activation [43] a more recent preclinical study that aimed to characterize XRT-induced lung toxicity revealed that thoracic-irradiated mice displayed accumulated inflammatory cells in alveolar spaces, intra-alveolar hyaline membrane formation, thickening of bronchiolar epithelium and fibrotic alveolar septum [44].

Overall, clinical treatment with TKIs is typically well tolerated but can be associated with the development of additional mild to moderate side effects, such as edema, rash, and nausea. Severe side effects in cardiac tissue, which can be exacerbated by XRT combination treatment, is suggested to occur in patients with pre-existing cardiac disease [45]. Albeit a rare side effect, cardiotoxicity is associated with a number of TKIs that has prompted the need for careful cardiac monitoring and clinical assessment [46]. Although preclinical studies have provided some understanding of the mechanisms contributing to TKI-mediated cardiotoxicity, adverse cardiac events associated with TKIs are not particularly predictive by *in vivo* and *in vitro* models. Imatinib, a first-line treatment for chronic myeloid leukemia (CML), is known to potentiate the effects of XRT via a variety of mechanisms to include reduction in cell proliferation [47] and inhibition of platelet-derived growth factor (PDGF) receptor [48]. Findings from preclinical studies have suggested that imatinib exerts on-target cardiotoxicity by inducing endoplasmic reticulum stress [49] and increasing protein kinase C S (PKCS) [50]. Additional *in vivo* and *in vitro* analyses have indicated that imatinib leads to severe

left ventricular dysfunction and heart failure, attributed to pathological changes in cardiac tissue as well as increased apoptotic and necrotic cell death [51]. Importantly, a recent study by Wolf, et. al cautioned on the use of clinical doses of imatinib used in animals as well as the lack the appropriate dose translational and/or conversion within preclinical studies. Data presented in this study emphasized that imatinib concentrations, associated with cardiotoxic events *in vitro* and *in vivo*, are substantially greater than that needed or utilized for clinical efficacy [52,53].

PDGF and vascular endothelial growth factor (VEGF) overexpression in a number of cancers is associated with increased resistance to XRT and ultimately poor prognosis. Sunitinib, a potent TKI that targets a variety of receptors, to include PDGF and VEGF, is commonly used with XRT to improve clinical outcomes. *In vitro* studies conducted with DU45 and PC3 hormone, independent human prostate cell lines, revealed that sunitinib enhanced radiosensitivity, while *in* vivo analyses showed sunitinib inhibitory effects on tumor growth only after XRT [54]. These findings corroborate other *in vitro* studies that show sunitinib and XRT combination treatment enhances apoptosis and reduces tumor cell survival [55,56]. Though sunitinib elicits potent anti-tumor and anti-angiogenic activity, treatment has yielded off-target toxic effects in healthy, non-cancerous cells. Namely, a myriad of cardiovascular side effects (i.e. hypertension, QT prolongation, heart failure) that can be attributed to sunitinib, prompting numerous preclinical studies to elucidate mechanisms underlying sunitinib-mediated cardiac injury. *In vitro* experiments with cultured cardiomyocytes have demonstrated sunitinib-mediated cardiotoxicity occurs because of loss in mitochondrial membrane potential and energy rundown via inhibition of AMP-activated protein kinase (AMPK) [57]. Moreover, *in vitro* studies conducted with sunitinib-treated neonatal rat ventricle myocytes revealed cardiotoxicity due to cytochrome *c* release, caspase-9 activation and apoptotic cell death [58]. Recently, a study by Cooper, et al. showed treatment of animals with a clinical dose of sunitinib (1μM) led to myocardial injury via a 41% increase in infarct size via the ASK1 / MKK7 / JNK intracellular signaling pathway [59]. Moreover, dasatinib, the current treatment of choice for imatinib-resistant mutations, enhanced radiosensitivity to head and neck squamous cell carcinomas (HNSCC); [60] however, treatment led to off-target cardiotoxic effects, [61] which can be difficult to diagnose at early stages.

The ability of TKIs to transverse the blood brain barrier (BBB) and access the brain parenchyma has led to increased survival rates for patients with non-small cell lung cancer (NSCLC) with brain metastases [62], while also giving rise to concerns of the neurotoxic effects associated with TKIs. Accordingly, cognitive dysfunction during and after cancer treatment has been largely reported in patients, with variable reversibility. Clinical findings have identified memory, processing speed, attention and executive functions as the cognitive domains most impaired because of cancer treatment [63]. Accumulating evidence in animal models has also suggested that XRT-induced cognitive decline involves damage to multiple neural cell types [64] of particular relevance, a recent study demonstrated that animals administered clinical doses of sunitinib displayed impaired memory processing via various behavioral cognitive assessments. Specifically, decreases in cognitive function were observed in conjunction with increased neurodegeneration in the cerebral cortex and hippocampus, brain regions critical for proper learning and memory functions [65]. Collectively, these data indicate that sunitinib preferentially impairs spatial cognition as a result of inhibition of VEGFR2 signaling and hyperactivation of apoptotic processes. In 2012, Aita, et al. also demonstrated that sunitinib-mediated inhibition of VEGF2 in pheochromocytoma PC-12 tumor cells, suppressed the synthesis and secretion of catecholamines, fundamental mediators of prefrontal cognition [66].

Clinical interest in XRT combination treatment with TKIs, that include those that selectively target EGFR and PDGF, have increased due to enhanced clinical efficacy and decreased association with adverse side effects in healthy tissues. Regrettably, clinical observations and preclinical data indicate that this combination treatment is not without toxic effects. The inability of preclinical testing to clearly identify TKI-associated severe side effects, namely cardiotoxicity, is suggested to result from the lack of appropriate cardiac assessments and insufficient understanding of the mechanisms of action of TKIs [25]. This literature review highlights several toxicities associated with XRT and TKI combinational treatment as well as the importance of allometric scaling and inter-species dose adjustments to effectively correlate *in vitro-in vivo* findings to clinical observations. Thus, additional rigorous preclinical investigation is necessary to elucidate the consequences of this treatment approach on normal cellular processes in anticipation of potential adverse effects.

Though the preclinical insights provide an important precedent to clinical combinational use, a recurrent frustration persists. Often, animal and preclinical in vivo investigations fail in their anticipated predictive guidance for several potential reasons including: differing radiation tolerance among species and cellular systems, the varying interactions of oxygen and nutrient supplying vascular and microenvironmental supporting protoplasm, comorbidity effects of disease, age, vascular compromise etc, and multiple other clinical vagaries. For example, in spite of a multitude of radioprotectors effective in animal species we have yet to find a reasonable radioprotector in humans [1].

Clinical Experience of Radiation Therapy and Tyrosine Kinase Inhibitors

Oligometastatic Cancer

Oligometastatic cancer refers to a cancer that has metastasized to no more than one to five sites. By treating a small number of metastatic sites, it is hoped that a survival advantage will accrue by eliminating resistant tumor clones. One of the first trials to explore concurrent radiotherapy with a TKI was a Phase I study of sunitinib in combination with image-guided radiation therapy (IGRT) for oligometastatic disease. The study enrolled 21 patients with 36 lesions of various malignancies (head and neck, prostate, hepatocellular, colorectal, lung, pancreas, kidney, breast, melanoma, and sarcoma cancers) and various extracranial lesions. Thirteen (61.9%) patients received prior chemotherapy and 11 (52.4%) had prior radiotherapy. Ten patients (47.6%) continued maintenance sunitinib. The maximal tolerated dose (MTD) was the third-highest dose scheme - sunitinib 37.5 mg with 50 Gy of RT. At the highest dose scheme (sunitinib 50 mg with 50 Gy of RT), two of the five patients had three dose-limiting toxicities (DLT)-transient G5 thrombocytopenia, transient G4 lymphopenia, and G3 nausea lasting more than 7 days. At the MTD, 1 of 10 patients had 3 DLTs-G4 anemia, lymphopenia, and thrombocytopenia. All 3 patients who experienced DLT were heavily treated prior to enrollment and received large volume liver radiation. The other G3 toxicities were seen in 9 patients with G3 lymphopenia, 4 patients with G3 neutropenia, 3 patients with elevated liver function tests, 2 patients with hypophosphatemia, 1 patient with G3 thrombocytopenia, and 1 patient with G3 hemorrhoidal bleeding. The patient with hemorrhoidal bleeding had hepatitis C and received liver radiation. Another patient with 2 prior courses of head and neck RT (100 Gy total) received RT to the 4th lumbar vertebrae, but developed G5 tracheal necrosis; it was not attributed to the therapy. Median follow-up was 10 months and the 1-year local control, PFS, and OS rates were 95%, 44%, and 75%, respectively. Fifteen lesions (42.9%) achieved CR, 6 lesions (16.7%) achieved PR, 10 lesions (27.8%) achieved SD, and 5 lesions (38.9%) had PD. There were unexpected complete responses in patients with pancreatic adenocarcinoma and head and neck squamous cell carcinoma. The authors felt that the combination therapy showed benefit with acceptable toxicity. For a future Phase II trial carried out at the MTD, they recommended avoiding patients with liver radiotherapy volumes with a tumor diameter measuring > 6 cm [1].

The Phase II trial to the above study was published in 2012, enrolling 25 patients with 49 lesions. In addition to the above malignancies, several other types were present in the study: sarcoma, skin squamous cell carcinoma, parotid carcinoma, thyroid carcinoma, and small cell lung carcinoma. Thirteen patients (52%) received prior chemotherapy and 10 (40%) had prior radiotherapy. RT was administered to a goal 50 Gy to extracranial lesions concurrently with sunitinib 37.5 mg; 22 patients (88%) completed the protocol treatment and 8 patients (32%) continued maintenance sunitinib. At 18 months, the local control, distant control, PFS, and OS were 75%, 52%, 56% and 71%. Median follow-up was 17.5 months with median PFS at 9.5 months and median survival was not yet reached. Seven patients (28%) had at least a G3 toxicity and all G3-G5 toxicities were attributed to sunitinib rather than radiotherapy. The G3 toxicities included 2 counts of anemia, 2 counts of neutropenia, 1 liver function test abnormality, 4 counts of thrombocytopenia, 1 hemorrhage, 1 count of hypophosphatemia. There was one case of G5 gastrointestinal hemorrhage. There were 4 deaths attributed to comorbid illness, occurring in patients who stopped sunitinib at least 30 days prior to death-including 2 cardiopulmonary arrests, 1 of uncertain cause, and 1 who had a bronchobiliary fistula without evidence of residual tumor at autopsy. That patient had small cell lung cancer and underwent 6 prior lung and liver surgeries. Overall, the authors felt that there was benefit to combination therapy but also noted that the combination is associated with a higher rate of G3 or worst toxicity. Therefore, a lower dose of sunitinib (37.5 mg) was recommended with concurrent RT along with caution in patients with coagulopathy [2].

Another paper was published combining the previous 2 studies and following up the cohorts for a median 3.6 years. The 4-year local control, distant control, PFS, and OS were 75%, 40%, 34%, and 29%, respectively. Median PFS was 12.2 months and OS was 14.1 months. On multivariate analysis, prostate or kidney cancer significantly predicted improved survival compared to other cancer types (hazard ratio = 0.25, p = 0.04). In terms of efficacy, the authors felt that there is evidence that durable complete remissions and higher long-term PFS and OS were possible with combined therapy. However, there is a higher risk of serious toxicity with sunitinib with RT [3].

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs) arise from the interstitial cells of Cajal and are the most common mesenchymal tumor of the gastrointestinal tract [4-6]. Surgery is the mainstay of treatment for localized tumors, but tyrosine kinase inhibitors (TKIs) are used when the tumors are unresectable, recurrent, or metastatic [7]. Radiotherapy has not been recommended for GISTs, because the tumors were considered to be radioresistant and the fields in proximity to bowel required for therapy would cause toxicity to the intestines and other organs [4,8]. Therefor it was hoped that CMT would be particularly beneficial

to compensate for low radiosensitivity. About 85-90% of GISTs have a c-kit mutation, 5-8% have a PDGFRα mutation, and < 10 % are considered wild-type [5]. Imatinib, which inhibits c-kit and PDGFRα, demonstrated prolonged clinical response and improved overall survival, becoming the first-line TKI for management of GIST [6]. However, because of acquired resistance to imatinib, dose escalation of imatinib or use of other TKIs (Sunitinib, Regorafenib, Ripretinib, and Avapritinib) is recommended [4,7,9]. Each TKI may have unique resistance patterns, making prognosis poor for patients who start developing imatinib resistance [4,9].

Several case reports and small studies have evaluated the combination of TKI with radiotherapy. A 2007 case report presented a 55-year old male with pelvic GIST (with c-kit mutation) and multiple liver metastases. After an incomplete resection, he underwent radiotherapy (54 Gy in 2 Gy fractions to the pelvic residual tumor) with concomitant imatinib 400mg. After 27 months, the pelvic lesions completely disappeared and the liver lesions regressed after 33 months. At 37 months, the liver lesions progressed, so imatinib was increased to 600mg. After further liver progression, he was switched to sunitinib. The authors did not report any toxicity to the concomitant therapy but noted that there may have been synergy between the TKI and radiotherapy that resulted in long-term local control [10].

In 2009, a case report described a 54-year old man with locally advanced rectal GIST. He was treated with imatinib 400mg starting 1 week prior to, and during, 3D conformal radiotherapy (50.4 Gy in 1.8 Gy fractions), in clinical partial response (PR) 3 weeks later. He later underwent sphincter-saving surgical resection without perioperative morbidity and achieved pathological complete response (CR) [11].

Another case report from 2011 reported a 48-year old female with ileal GIST (with c-kit mutation) with peritoneal metastasis. The primary ileal GIST was discovered, and resected, during uterine fibromectomy. She was treated with imatinib 400mg with good radiological response. Six months later, she underwent resection of all peritoneal metastases. She then developed a new retroperitoneal mass, which was resected and her imatinib was increased to 800mg. After development of another peritoneal lesion, she was switched to several TKIs -each without response (sunitinib, nilotinib, and sorafenib). After developing a rapidly growing, symptomatic supraclavicular recurrence, she underwent external beam radiotherapy (EBRT, 50 Gy in 2 Gy fractions to the supraclavicular mass) with sorafenib. The treatment was well tolerated and resulted in the decrease and stabilization in size of the supraclavicular mass [12].

A case series published in 2017 reported 2 cases of metastatic gastric GIST treated with concurrent TKI and radiotherapy with clinical benefit and low toxicity. The first case was a 62-year old male with c-kit positive-GIST (with c-kit mutation) with liver metastases, treated initially with imatinib 400mg. The dose was increased to 800mg after an increase in size of the liver lesions. He was switched to sunitinib after developing a new paracaval lesion, then to regorafenib after progression of that lesion. Due to the lesion being unresectable, he underwent external radiotherapy (35 Gy in 14 fractions) with regorafenib. He tolerated therapy without complication and had significant improvement of his symptoms and decrease in size of the paracaval mass. Though he required a dose reduction of regorafenib, he has been stable for 3 years at time of the report. The second case was a 44-year old male with gastric GIST metastasized to liver and previously treated with imatinib and sunitinib (the mutational status was not reported). He was referred for surgical treatment after developing compressive symptoms from the gastric tumor and underwent partial gastrectomy and right hepatectomy. After surgery, he was treated with imatinib 400mg and then 800mg when the liver lesions increased in size. After a new pararenal lesion was detected, he underwent highly focalized cyberknife stereotactic radiosurgery (45 Gy in 5 fractions to the lesion) with concomitant imatinib. He had nausea, requiring discontinuation of imatinib during radiosurgery. The therapy provided symptomatic relief and stabilization of the lesion. He then developed a new supraclavicular mass, treated with sunitinib with cyberknife (32Gy in 5 sessions to the lesion). That treatment resulted in symptomatic improvement and stabilization. Unfortunately, after 5 months, the disease progressed rapidly. Toxicity was not mentioned regarding that second concomitant therapy [5].

A retrospective, single-institution study was published in 2013 addressing locally advanced and metastatic GIST treated with radiotherapy. The analysis, which studied 15 consecutive with 22 GISTs over a median 5.1 months of follow-up, included 11 patients who had concomitant TKI during radiotherapy. No mutational status was reported of the tumors. Nine of those 11 patients had radiological outcomes, however the authors did not compare outcomes of the individuals with concurrent therapy compared to those receiving just radiotherapy. Radiologic partial response (PR) was seen in 35.3%, stable disease (SD) in 52.9%, and progressive disease (PD) in 11.8% of the tumors. In the patients with concurrent therapy, there were no toxicities above Grade 2. The toxicities listed for concurrent therapy were G2 esophagitis, G2 fatigue, G1 dysgeusia, and G1/G1/G2 diarrhea, urinary frequency/urgency, and fatigue. However, due to the retrospective nature, heterogeneous follow-up, and small sample size, it is difficult to draw firm conclusions about safety and efficacy of concurrent TKI with radiotherapy for GIST [4].

In a multicenter, open-label, prospective study published in 2015, 25 patients with locally advanced or oligo-metastatic GIST were enrolled for palliative radiotherapy over a median follow-up of 19 months. Thirteen had prior surgery. All 25 patients had received imatinib prior to radiotherapy, 15 also received sunitinib, and 10 were treated with 3 or more TKIs. Nineteen continued taking TKI during radiotherapy-11 took imatinib, 4 took sunitinib, 2 took nilotinib, 1 took regorafenib, and 1 took sorafenib with everolimus. Of note, the study population had an unusually high number of wild-type GISTs at 6 (24%). Eighteen patient underwent conformal 3-D while 7 patients underwent volume reduced Intensity-modulated radiotherapy (IMRT), for a cumulative planning target volume (PTV) of 30 – 40 Gy in 1.8-2.0 Gy fractions. Progression was seen in 80% and 72% died, with a median overall survival of 19 months. The best radiologic response at 3 months was 8% PR, 80% SD, and 12% PD. The median time to first GIST progression (any site) was 4 months; the median time to targeted GIST progression was 16 months. The patients with wild-type GIST had median time to targeted GIST progression of 11 months. Interestingly, those who were not on TKI had longer median time to targeted GIST progression of 23 months (compared to 11 months). The occurrence of diarrhea (52%), nausea (36%), and fatigue (32%) increased during or after radiotherapy, but it is not reported which of those patients were on concurrent TKI. One G4 biliary tract necrosis occurred in a patient who received sorafenib with radiotherapy. Anemia was present in 84% of the patients, but was attributed to either advanced disease state or TKI therapy instead of radiotherapy. Overall, radiotherapy was well tolerated and the authors felt that GISTs demonstrated radiosensitivity. The finding that patients not on concurrent TKI having better outcomes may have been due to small patient numbers [13]. The role of CMT has not been defined for GIST tumors.

Renal Cell Carcinoma

Renal cell carcinoma (RCC) is among the top ten most common malignancies in the world and 20% have metastasis at diagnosis [14,15]. Brain metastasis occurs in about 4-17% of RCC [16]. For localized RCC, surgery is the standard treatment, but recurrences occur in over 30% and metastasis develop in another 30%.(14) Systemic therapies, including TKIs, immune checkpoint inhibitors, mTOR inhibitors, and bevacizumab, are the standard of care in metastatic RCC, but few achieve complete or durable response [11,14,15,18]. Even when TKIs are combined with immunotherapy, complete response is achieved in about only 3% [11]. RCC is considered one of the most radio-resistant malignancies, but evidence shows that RCC may respond better to high-dose, hypofractionated radiation therapy [14,15]. Stereotactic body radiotherapy (SBRT) may be noninferior to metastatectomy of oligometastatic lesions [11]. There is evidence of synergy between RCC systemic therapies and radiotherapy, as both TKI and immune checkpoint inhibitors provoke an immunostimulatory response [14]. An abscopal effect can occur in metastatic RCC – when non-irradiated lesions regress after radiotherapy of the targeted lesion [14]. It is postulated that the abscopal effect is due to alterations in the immune response against the tumor [14].

One of the first prospective studies was open-label and published in 2012. It enrolled 22 patients with progressive metastatic RCC, all treated with prior nephrectomy and on sunitinib concurrently during radiotherapy. Median follow up was 14.3 months and 72.7% of the tumors were clear-cell RCC. Their metastatic lesions were both intracranial and extracranial and were treated with a median 12 fractions of 3.5 Gy (2.5 Gy for brain) for a total dose of 40 Gy. At 3 months, 2 patients had CR, 9 had PR, 2 had MR, 8 had SD, and only 1 had PD-tumor control rate was 95.5%. One G4 hypertension led to heart failure and 3 G3/G4 nausea. Regarding skin toxicity, only 2 G2 cases were reported and controlled with topical cortisone. The authors stressed that due to the short follow-up, PFS and OS were not calculable. However, they felt the efficacy was promising with low short-term toxicities attributed to combination therapy [13].

In a prospective, multicenter study published in 2019, 17 patients with metastatic clear-cell RCC on systemic therapy were treated with stereotactic body radiotherapy (SBRT). The patients had to have 2 metastatic lesions in the same extracranial organ – one that would be irradiated and the other would be the control. Six of the patients were on sunitinib, 1 was on sorafenib, 1 was on lenvatinib with everolimus, 5 were on nivolumab, 3 were on everolimus, and 1 was on temsirolimus. The primary end-point was safety-only 2 patients suffered G1 toxicities (esophagitis and skin erythema); none had a G2 or higher toxicity. The response rate for targeted lesions was 76.5% (29.4% CR, 47.1% PR)-including 1 patient who had an abscopal effect (regression of multiple lung and mediastinal lymph node metastases). For control lesions, 1 lesion progressed while the others were stable. Fraction amounts ≥ 10 Gy was associated with complete response [14].

A retrospective study published in 2020 evaluated 56 patients with metastatic RCC with 103 unresectable lesions over a median 21.7 months of follow-up. Most of the tumors were clear-cell (60.7%). All the patients continued their TKI therapy throughout SBRT-44.6% on sunitinib, 23.2% on axitinib, 23.2% on sorafenib, and 9.0% on a different TKI. Nephrectomy was performed in 83.9% and metastatectomy was performed on 37.5%. The most common SBRT dosing was 35 to 45 Gy in 5 fractions either for curative intent (32.1%; all metastatic sites irradiated), for major tumor burden (35.7%; largest tumor accounts for ≥ 50% of the total

tumor burden), or for symptomatic relief (32.1%; relief of pain, spinal cord compression, or bleeding). During follow-up, 68% switched to second-line TKI after systemic disease progression; 2 switched because of drug-intolerance, and 2 discontinued systemic therapy because of toxicity. Thirty patients (54%) experienced toxicity and 5 patients had G3 as the worst toxicity (1 perforation of skin lesion requiring skin flap surgery, 1 neuropathy after neural invasion, 3 anemia). Half of the G3 toxicity cases were on axitinib and the others were on sunitinib. Objective response rate was 84.5% - 19.4% CR, 65.0% PR, 12.6% SD, 2.9% PD. Patients who underwent SBRT before TKI failure had a CR rate of 34% compared to 7% in patients who had SBRT after TKI failure. The 2-year local control (LC) rate was 94%. The median overall survival was 61.2 months with 2-year survival at 71% and 5-year survival at 58%. The 2-year survival of patient treated for curative intent was 93%, for major tumor burden was 68%, and for symptom, relief was 58%. The 5-year survival for patients who achieved CR was 86% compared to 48%. Overall, the authors felt that combination therapy was well tolerated and demonstrated an improvement in survival, which seems to be better when SBRT was started before TKI failure [11].

A retrospective, multicenter study published in 2020 evaluated the role of SBRT in extracranial RCC lesions. It enrolled 48 patients with 57 extracranial lesions with the majority being clear-cell RCC (93.7%). Before starting SBRT, 95.8% were on systemic therapy (including TKIs) and 58.3% continued their systemic therapy during treatment. There was no significant difference in outcomes of patients on concurrent systemic therapy with SBRT compared to those who held systemic therapy. Eighteen patients (37.5%) did not restart systemic therapy, but their lesion progression-free survival was not significantly different to those who restarted systemic therapy. Overall, 72.4% of lesions were progression-free at 40 months with local control rates of 83.6% and 72.4% at 1 and 2 years, respectively. The SBR dose per fraction did not significantly correlate with lesion progression-free survival (< 6 Gy versus ≥ 6Gy). Median progression free survival was 28.9 months and median survival was 49.2 months with 93.7% and 84.9% alive at 12 and 24 months, respectively. Over time, the mean size of the lesions continued to decrease after SBRT. There were no toxicities of G3 or higher; only 6% had toxicities (1 case with G1 toxicity was on concurrent systemic therapy). In conclusion, the authors felt that SBRT to extracranial RCC lesions was safe and had clinical benefit [15]. Over half of the patients were on concurrent systemic therapy, but there was no additional benefit. Lack of detail about the type of systemic therapy used and the potential small numbers limit that information.

Another retrospective study evaluated the role of Stereotactic Radiosurgery (SRS) for brain metastasis of RCC. The majority of tumors were clear-cell RCC (91.7%). It enrolled 120 patients with 362 brain lesions, of whom 30.8% were on systemic therapy at the time of first radiosurgery. TKIs was the most common type of systemic therapy (65%)-69% of TKI users were on sunitinib, 14% on axitinib, 12% on sorafenib, and 5% were on pazopanib. SRS was administered in a single fraction by linear accelerator for 63 patients and later by Gamma-Knife in 61 patients. For local control outcomes, control rate was 94% and 92% for at 12 and 36 months for a median brain PFS of 11 months. By the end of follow-up, 51% of intracranial lesions progressed. In multivariate analysis, PTV minimal dose ≥ 17 Gy and concomitant TKI were significantly associated with local tumor control. Survival at 12 and 36 months was 62% and 29%, respectively. By the end of follow-up, 83% had died for a median survival of 13.5 months. Seventeen patients (14.2%) had G3 or G4 adverse events -8 had radionecrosis (3 symptomatic, 2 required salvage neurosurgeries), 4 developed worsened epilepsy, 4 developed intracranial hemorrhage, 6 had symptomatic severe intracranial hypertension from peritumoral edema, and 1 went into coma and died a few weeks after radiation (unknown etiology). The authors found that their rate of radionecrosis was similar to a retrospective study published in 2017 of 1650 patients with 2843 intracranial metastasis of various malignancies. That study found 8% of lesions developed radionecrosis at 12-months. There was a significant difference among patients concurrently receiving targeted therapy (including TKIs)-8.8% versus 5.3%. Those on concurrent VEGFR TKIs had a 14.3% chance versus 6.6% and those on concurrent EGFR TKIs had a 15.6% chance versus 6.0% [20]. Overall, Klausner, et al. felt that SRS in the era of TKI was safe and effective in this population [16].

A retrospective study of 106 patients with 55 spinal and 51 cerebral metastasis from RCC was published in 2011. All of the patients were on concurrent TKI (45 on sunitinib and 61 on sorafenib) and received CyberKnife SRS administered in a single fraction. Median follow up was 14.7 months with local tumor control of 98% at 15 months, overall survival of 15.2 months. For spinal metastases, local control rate at 24 months was 94.1% and survival at 24 months at 49% (median overall survival of 17.4 months). Patients with cerebral metastases had local control rate at 24 months of 96.6% and survival at 24 months was 25% (median overall survival of 11.1 months). Additionally, pain significantly improved after SRS. Within 6 weeks of SRS, 6 G1-G2 episodes of toxicity were documented-2 tumor hemorrhages (G2), 2 convulsions (G2), and 1 abdominal pain (G1). The 2 hemorrhages were intracranial but were asymptomatic and no treatment was necessary. One patient on sunitinib had fatal cerebral bleeding 3 months after SRS-but it occurred in tumors that were not targeted by SRS and considered to be due to disease progression. The convulsions occurred within

3 weeks of SRS and were controlled by cortisone treatment. The authors felt that SRS with concomitant TKI was safe and effective for spinal and cerebral metastasis of RCC [21].

A retrospective study of explored safety and efficacy of concomitant TKI with spinal SRS for metastatic RCC. The study evaluated 100 patients who underwent 151 spinal SRS treatments divided into 4 cohorts. Cohort A was on concurrent first-line TKI; Cohort B was systemic therapy-naïve; Cohort C was on second-line TKI after first-line failure; and Cohort D was no longer on TKI after failure. An additional negative-control Cohort E was established who did not undergo SRS, but continued TKI. SRS was given as either a single-fraction (10-18 Gy) or hypofractionated (21-24 Gy in 3 fractions) regimen. At 12 months, local failure rate was lowest in Cohort A (4%) and highest in Cohort E (57%). Cohorts B, C, and D had 24-month local failure rates of 20%, 27%, and 19%, respectively. A similar incidence of pain flare (17%) and post-SRS vertebral fracture (21%) were seen across Cohorts A to D. There were no G3 toxicities in the cohorts taking TKI with SRS (Cohorts A or C). The study suggested that SRS while on concurrent first-line TKI was safe and effective for treatment of spinal metastasis from RCC.(22)

Gastrointestinal perforation is a rare complication for both TKI therapy (0.2%) and high-dose radiotherapy (0.6%) [23]. The intestines can tolerate approximately 50 Gy of radiation [23,24]. Three cases were published of patients with gastrointestinal perforation in the setting of sorafenib and radiotherapy for metastatic RCC. The first case was a 61-year old female with clear-cell RCC and cutaneous metastasis who was started on sorafenib after diagnosis. She experienced rapid regression of the cutaneous lesions but no change in her primary tumor. Five weeks later, she developed severe pain from lytic lesions of L4 vertebra. She received 1 fraction of 6 Gy to L3-L4-holding sorafenib 2 days prior to therapy and restarting it 3 days later. One week after radiotherapy, she was admitted for bowel perforation and expired the next day. Biopsy of the colon revealed multiple perforations of the transverse and sigmoid colon, ischemic enteritis with radiation effects, and vascular changes with thrombus formation. There was no evidence of tumor in the biopsy [24].

Two other cases of gastrointestinal perforation were described in a 2012 report. The first was a 61-year old female with clear-cell RCC treated initially with radical nephrectomy. After developing multiple lung metastases, she started interferon alpha. One the lung lesions progressed and she developed new lesions of the left femur and left acetabulum; she received palliative radiotherapy (30 Gy in 10 fractions) and started sorafenib with interferon alpha a week later. Four weeks after radiotherapy, she experienced sudden abdominal pain and was found to have a sigmoid colon perforation on emergent laparotomy. She had sigmoidectomy with colostomy but died of severe sepsis and multiple organ dysfunction 29 days later. Surgical pathology revealed 2 ulcers near the solitary perforation, with full-thickness invasion of eosinophils around the ulcer along with some neutrophilic invasion. The blood vessels were narrow with some thrombus formation. The second case was in a 48-year old male with clear-cell RCC who initially underwent radical nephrectomy. After developing lung metastasis, he started interferon alpha until developing new lesions in the right iliac bone, T3 vertebra, and mediastinal lymph nodes. He was switched to sorafenib and palliative radiotherapy to the right iliac and T3 (30 Gy in 10 fractions). He then developed 3 new brain lesions, treated with Cyberknife. After developing lytic lesions of L2-L4 vertebrae, he had palliative radiotherapy (30 Gy in 10 fractions). Two months later, he developed sudden abdominal pain and was found to have a solitary sigmoid colon perforation without evidence of tumor on emergent laparotomy. He had a sigmoidectomy with colostomy and was eventually discharged from the hospital, but died 3 months later due to disease progression [23].

Several case reports describe pulmonary fistula formation in patients with metastatic RCC treated with sunitinib and radiotherapy. One case was a 40-year old male initially treated with nephrectomy for RCC. He developed metastasis in the brain, mediastinum, and lung-including a subcarinal tumor obstructing the bronchus intermedius. He was treated with cerebral and thoracic radiotherapy and then started sunitinib. Two months later, there was significant reduction with necrosis of the subcarinal tumor and a large perforation of the bronchus intermedius. Sunitinib was discontinued followed by rapid progression of the tumor. Eventually he was treated with an endobronchial stent, but passed away after developing a new bronchial obstruction under the stent [25]. Another case occurred in a 51-year old male who had RCC initially treated with radical nephrectomy and sorafenib for lung metastasis. Three years later, he had SRS to the left inferior lobe for a lung lesion (36 Gy) and then started sunitinib. He presented 2 years later with sudden epigastric pain and was found to have a perforated paracardial ulcer of the stomach. He was conservatively treated with proton-pump inhibitors and was discharged. He was readmitted for acute respiratory distress and found to have a fistula from the gastric fundus to the left pleura and pericardium. He underwent surgical treatment and was eventually discharged on postoperative day 20. The authors believe that the gastro-pleuro-pericardial fistula was due to the combination of sunitinib and prior radiotherapy that intensified radiation-induced endothelial damage leading to tumor vessel destruction and necrosis [26].

Non-Small Cell Lung Cancer

The largest amount of studies looking at concurrent TKI and RT are for non-small cell lung cancer (NSCLC). NSCLC is the leading cause of cancer-related deaths and make up 80% of lung cancers [28,29]. At diagnosis, most patients are at an incurable stage [28]. During the course of disease, 40% will develop brain metastasis, including 10- 25% found at diagnosis [27]. Epidermal growth factor receptor (EGFR) is overexpressed in lung cancer and those with mutations in EGFR are predicted to have advanced disease [28]. Further, radiation of tumor cells activates EGFR, which may lead to acceleration of tumor growth and radioresistance [30]. EGFR-TKIs, such as gefitinib, erlotinib, and icotinib are first-line systemic agents for advanced NSCLC [28].

One meta-analysis was published in 2019 by Liu, et al. [67] summarizing prospective trials of locally advanced or metastatic NSCLC (stage III or IV), without prior local treatment, and on concurrent EGFR-TKI with Thoracic RT (TRT) [68-75]. Twelve studies of 446 patients were analyzed. The pooled CR was 6%, PR was 44%, SD was 29%, and PD was 15%. The pooled 1-year and 2-year OS rates were 52% and 26%, respectively. The median PFS was 8.1 months and median OS was 15.2 months. Rates of rash, diarrhea, esophagitis, anemia, interstitial pneumonia, nausea and vomiting, granulocytopenia, and oral ulcers were 42%, 27%, 32%, 12%, 12%, 21%, 21%, and 11%, respectively. While the data only evaluates uncontrolled Phase 2 studies, the authors noted that the combination provided better survival benefits compared to radiotherapy alone. The toxicity information is limited, but the pooled incidence of G1 to G3 esophagitis was 32% and G1 to G2 interstitial pneumonitis was 12% [28].

One of the earliest studies included in the Liu, et al. [67] meta-analysis was a prospective feasibility trial of stage III NSCLC that was terminated early. Okamoto, et al. [76] reported on 9 patients recruited to undergo protocol treatment of gefitinib started 2 weeks prior to thoracic RT (60 Gy in 2 Gy fractions). The primary endpoint was a 90% completion rate of a planned 28 patients [76-85]. Five patients could not complete the protocol treatment- 2 had progression before TRT was started, 1 developed G3 radiation pneumonitis, 1 developed G1 gefitinib-associated pneumonitis, and 1 had progression of the primary tumor after 46 Gy of TRT. The most common toxicities were G1-G2 esophagitis and skin rash. Four patients had G3 toxicity-3 had elevated hepatic transaminases and 1 had pneumonitis. All 4 patients who completed protocol treatment had PR with a PFS of 4.5, 14.6, 19.6, and > 73.6 months. 3 of the four patients were alive > 60 months without local recurrence. During the trial, EGFR mutation testing became available, so 8 were able to have post-hoc mutation analysis; 2 had EGFR mutations. Those 2 patients completed therapy, had PFS of 14.6 and 19.6 months, and had OS of 63.7+ and 67.5 months. The authors recommended planning combination therapy for those with EGFR mutations.

Another early study included in the Liu, et al. [67] meta-analysis was reported by Zhuang, et al. [86] It was a prospective, feasibility study of erlotinib with concurrent thoracic RT for inoperable Stage III/IV NSCLC; the primary endpoint was development of radiation pneumonitis of the 24 enrolled patients, 46% were stage IIIA, 29% were stage IIIB, and 25% were stage IV; 42% were treated with palliative RT; the median RT dosing was 57 Gy total in 2 Gy fractions; and the median time on erlotinib was 41.5 days. About half of the patients received neoadjuvant chemotherapy (54%) and adjuvant chemotherapy (50%) [87-90]. Median follow-up was 31.5 months and 9 patients (37.5%) developed G2 or worst radiation pneumonitis. Four cases (16.7%) had G2, 2 (8.3%) had G3, and 3 (12.5%) had G5. PTV was found to have a statistically significant effect on the incidence of radiation pneumonitis (relative risk = 1.007, 95% Confidence interval 1.001-1.013). The 3 patients who died from radiation pneumonitis had 56-60 Gy administered; one case developed during RT, another 2 days after completion of RT, and the last 3 weeks after RT completion. Despite treatment with methylprednisolone, the patients died between 1 and 6 weeks after onset of symptoms. The authors recommended careful monitoring for patients treated with concurrent erlotinib and thoracic RT [31,32].

Wang, et al. [42] published an article included in the Liu, et al. [67] meta-analysis, reporting a prospective trial of 14 advanced (stage IIIB/IV) NSCLC who had progressed after at least 1 chemotherapy regimen (93% platinum-based) [33]. Most of the patients (85.7%) and 50% had brain, lung, or pleural metastasis. Gefitinib was started 1 week before SBRT and continued for a median 7.5 months after therapy. The radiation dose was from 45 to 60 Gy in 3 to 5 fractions. One patient withdrew due to G3 diarrhea and stomatitis; 1 patient had a dose reduction for toxicity. Acutely, there were 6 counts of G3 toxicity (1 rash, 1 stomatitis, 1 esophagitis, 1 diarrhea, 1 pneumonitis, and 1 fatigue). The most common acute toxicity was G1-2 fatigue (50%) and pneumonitis (36%). Late-term toxicities were mostly radiation pneumonitis-mostly G1-G2, but 2 patients (14%) developed G3 radiation pneumonitis [91-98] with a median follow-up of 15.5 months, the 1-year local control rate was 83.9% and OS was 69.6%. Median PFS was 7.0 months and OS was 19.0 months. The authors noted that combination therapy in this population appeared to be well tolerated and effective.

Pan, et al. [99] published a study of 122 senile patients with adenocarcinoma (22.1% Stage II, 77.9% Stage III) undergoing initial therapy. There were 3, nonrandomized treatment groups-Group A was treated with gefitinib and

SBRT, Group B was treated with SBRT alone, and Group C was treated with gefitinib alone. SBRT was γ-ray, totaling 36-48 Gy in 4-6.5 Gy fractions (8-12 fractions). At 2 months, response rate (CR + PR) for Group A was 68.6% (8.6% CR), for Group B was 51.1% (2.2% CR), and for Group C was 40.5% (7.1% CR). For short-term efficacy, Group A was significantly better than Group C (p = 0.014), but approaches significant difference over Group B (p = 0.116). Group A had better PFS (7.8 months) than both Group B (5.9 months) and Group C (5.1 months). Group A also had better OS (15.5 months) than both Group B (9.6 months) and Group C (10.3 months). Group A had more G3 toxicities (7) than Group B (0) and Group C (2). The Group A G3 toxicities were 2 rashes, 3 diarrhea, 1 nausea/vomiting, and 1 dyspnea. The Group C G3 toxicities were 1 rash and 1 diarrhea. The overall most common toxicities were skin rash and diarrhea. The authors reported that combination therapy had better short- and long-term benefits when used as first-line regimen with acceptable toxicities [34].

Iyengar, et al. [100] published results of a Phase II trial of Stage IV NSCLC who had failed at least treatment of chemotherapy with limited oligometastatic disease. Twenty-four patients with 52 lesions were treated with erlotinib (starting 1-3 weeks prior to RT) and cytoreductive SBRT in 1-3 fractions to all non-brain and non-intestinal sites. Mutational status was tested in 13 patients (54.2%) but all were negative for EGFR exon 19/21 mutation. Erlotinib was continued for a median 183 days and the patients were followed for a median 16.8 months with the primary endpoint being progression of any site. At 3 months, CR was achieved in 21.3% of targeted lesions and PR was achieved in 51.1%. Median PFS was 14.7 months and OS was 20.4 months. Only 3 local failures occurred starting at 9 months after treatment. Ten patients failed at new distant sites (outside the radiation field) and 10 had no recurrence at last follow-up. Those who had intrathoracic treatment had lower chance of progression (hazard ratio = 0.080). Notable toxicities included 1 G5 acute respiratory distress syndrome/pneumonia, 4 G4 toxicities attributed to either SBRT or erlotinib (not described), and 2 G3 toxicities attributed to SBRT (pneumonitis and vertebral compression fracture). The authors concluded that the PFS and OS were superior to historical stage IV NSCLC patients who progressed through at chemotherapy [35].

Swaminath, et al. [101] published results of a Phase II trial of newly diagnosed stage III/IV or recurrent NSCLC focusing on quality of life improvement with combination erlotinib and palliative thoracic RT. Forty patients were recruited, but 55% of the group was recruited over 3 years and tended to have more advanced disease. Most of the patients had squamous cell carcinoma (63%) and distant metastatic disease (60%). Mutational status was not available to the investigators. Only 22.5% had prior surgery, 5% had prior systemic therapy, 5% had prior RT, and 2.5% had prior biologic therapy. Erlotinib was started 1 week before RT for a total of 3 weeks; 65% completed the full course of erlotinib without adjustment. Four patients were unable to tolerate Erlotinib during RT and 3 stopped the drug due to toxicities (hyperglycemia, acute renal injury, and nausea/vomiting). There were 2 serious toxicities that were attributed to protocol therapy-1 G4 rash and 1 G3 nausea. The planned thoracic RT dose was 30 Gy in 10 fractions and 87.5% received the full course. The primary endpoint was quality of life as measured by the Lung Cancer Symptom Scale. Only 62.5% completed the LCSS at week 4 due to death or poor health, but there was a significant improvement over the baseline by 12.5 points. It did not reach the prespecified goal of a 17.5 point improvement and was similar to other studies' reported improvement from RT alone. There was also a significant improvement in cough with therapy at 4 and 8 weeks. At the end of the trial, 32 patients died-27 from disease progression. Median PFS was 3.2 months and OS was 5.2 months. The authors noted that there was no pneumonitis, but it may have been underreported. Toxicities were likely difficult to discern from the advance disease state. The authors felt that combination therapy did not offer much quality of life improvement compared to RT alone in this population [29].

Verma, et al. [102] published a Phase II trial of 34 patients with previously untreated stage III lung adenocarcinoma treated with palliative TRT and concurrent gefitinib. The trial was conducted in India; with most of the patients stage IIIB (73.5%), male (58.8%), and smoker (52.9%). EGFR overexpression was found in 32.4% of the patients. Gefitinib was started with RT and continued until progression. Palliative RT was administered for a total of 30 Gy in 10 fractions. There was significant improvement in symptoms of coughing, dyspnea, chest pain, and blood in sputum. At 1 and 6 months, disease control rates (CR + PR + SD) were 100% and 56%, respectively. There were no complete responses, with 1 and 6 month partial responses at 68% and 38%, respectively. Over a median follow-up of 7 months, PFS was 6 months and OS was 7 months. Univariate analysis found that OS was positively affected by non-smoking status, EGFR overexpression, and quality of life, while female gender trended toward a positive effect. There were no G4 or higher toxicities and the most common toxicities of all grades were rash (59%) and diarrhea (38%). Only 2 patients had G3 rash and 2 patients had G3 diarrhea. Radiation pneumonitis and lung fibrosis were seen in 15% and 6% of patients, respectively, and 1 had G3 pneumonitis. The other G3 toxicities were 1 anemia, 3 leukopenia, and 1 thrombocytopenia. The authors found the combination therapy had a favorable safety profile and promising outcomes in this population [36].

Cai, et al. [103] published a randomized Phase II study of 316 patients with stage III/IV NSCLC who had failed at least one first-line treatment, assigned to combination TKI with conformal RT or TKI alone. Most of the patients were male (62.3%), stage IIIB (40.8%), and had adenocarcinoma (54.7%). The EGFR mutation rate was 30.1% and KRAS mutation rate was 10.1%. Of the patients getting RT, 54.7% received it for palliative intent. Erlotinib was used in 51.6% and the remainder used gefitinib. The combination arm had significantly better response rate (RR, 45.3%) and disease control rate (DCR, 89.6%) compared to TKI alone arm (24.8% and 64.8%, respectively). Median PFS and OS for the combination arm were 6.5 months and 14.1 months, which trended toward significant difference from TKI alone arm (5.0 months and 12.6 months). In the combination arm, having EGFR mutation positively correlated with survival, while TNM stage and KRAS mutation negatively affected survival. The two groups had similar rates of hematologic, gastrointestinal, rash, and mucosal toxicity, but the combination arm had more esophagitis. The combination arm had more cases of interstitial pneumonia, but that was not significantly different. There was 1 G1 radiation pneumonitis. Overall, the combination arm demonstrated clinical benefit in RR and disease control rate in the population with previous treatment-failure with mostly similar rates of adverse events [37].

A recent meta-analysis published by Wang X, et al. [104] included 24 studies of 2810 patients to evaluate for differences in combination TKI with RT versus monotherapy in the treatment of NSCLC with brain metastases. Included studies were either 24% prospective (8 studies, 665 patients, 1 Phase III) and were divided into combination TKI with RT (1241 patients), TKI-only (470 patients), and combination RT with or without chemotherapy (1099 patients). The combination therapies were concurrent in 1027 patients and sequential in 214 patients. The objective response rate (ORR) and disease control rate (DCR) combination therapy was 64.0% and 82.7%, respectively, which were significantly better than monotherapy (40.5% and 71.9%, respectively). The relative risk for ORR was 1.32 (95%CI: 1.13-1.55) and RR for DCR was 1.12 (95%CI: 1.04-1.22). However, compared to TKI as monotherapy, combination therapy was not significantly different, with an RR for ORR of 1.25 (95%CI: 0.99-1.56) and RR for DCR of 1.10 (95%CI: 0.93-1.29). Combination therapy resulted in greater OS and intracranial-PFS (i-PFS) compared to monotherapy, with hazard ratio (HR) of for OS at 0.72 (95%CI: 0.59-0.89) and for i-PFS at 0.64 (95%CI: 0.50-0.83). Combination was not significantly different for extracranial-PFS (ex-PFS), with a HR of 0.64 (95%CI: 0.35-1.15). Combination therapy compared to TKI-only resulted in only significant difference in i-PFS, with a HR of 0.78 (95%CI: 0.45-0.98). When comparing just patients with EGFR mutations, there was no significant improvement in combination therapy over other treatments. Only concurrent combination therapy had a benefit in OS and i-PFS as sequential combination therapy was not significantly different from monotherapy. Asian patients and adenocarcinoma patients each had improved OS and i-PFS. Adverse events were more frequent in the combination group (20.2%) than monotherapy (11.8%) with a RR of 1.34 (95%CI: 1.11-1.62). Rash (42.2% versus 6.7%, RR of 6.72, dry skin (15.9% versus 1.4%, RR of 8.16), and diarrhea (19.6% versus 7.8%, RR = 2.17) were the most significant differences between combination and monotherapy. Pneumonitis was not significantly different (9.3% versus 4.9%, RR of 1.78, 95%CI: 0.32-9.92). In summary, combination therapy had significant benefit in ORR, DCR, OS, and i-PFS compared to monotherapy for NSCLC patients with brain metastasis. However, compared to TKI alone, there was significant improvement only in i-PFS. Adverse events occurred more often in combination therapy, especially rash, dry skin, and diarrhea [27].

In summary the CMT of lung cancer utilizing TKIs and RT remains experimental but hopeful. Many studies suggest improvement of local control and progression free survival but that success is associated with potentially significant toxicity. Randomized prospective studies will be required to define the role of TKI and RT combinational treatment.

Delayed Onset Radiation Reactions

There have been reports of the Vascular Endothelial Growth Factor (VEGF) receptor TKI, sunitinib, being associated with delayed-onset radiation-associated toxicities, such as Radiation Recall Pneumonitis (RRP) or hemorrhage. In one case, a 65-year old male with metastatic clear-cell renal cell carcinoma (RCC) underwent thoracic radiotherapy for spinal compression due to a metastatic lesion. He then started sunitinib 14 days after radiotherapy and developed radiation recall pneumonitis 14 days later. After a 3 day course of prednisolone, his symptoms improved over 7 days and has switched to sorafenib [38]. Another case of radiation recall pneumonitis occurred in a 49-year old female treated with metastatic clear-cell RCC. She received palliative radiation to the left shoulder and right hip (total 30 Gy) and started sunitinib 3 weeks later for new lesions in the lung and mediastinum. During her fourth course of sunitinib, she developed dry cough with a new ground glass opacity in the left upper lobe. After decreasing in her dose of sunitinib from 50mg to 37.5mg, the coughing resolved within 3 weeks. However, the radiographic findings remained in the left upper lobe [39]. In an open-label phase II study of sunitinib for progressive nasopharyngeal carcinoma with prior radiotherapy, enrollment was stopped after 2 patients died of hemorrhagic complications. Out of the planned 23 patients for stage I of the trial, 14 were enrolled. Nine (64%)

had hemorrhagic complications-6 epistaxis, 3 hemoptysis, and 2 hematemesis. Nine of the patients received concurrent chemotherapy, 9 had pulmonary metastases, and 3 had prior palliative radiotherapy to the thorax. Two patients who died from epistaxis or hematemesis within the first 4 weeks of sunitinib treatment; both had local recurrent tumors that encased the internal carotid artery. Both patients had significant reduction in the size of the tumor in response to sunitinib, but likely had fatal blow out of the carotid artery. Though there was no control group and enrollment was stopped early, the authors felt that the incidence and severity of hemorrhagic complications was worsened by addition of sunitinib [40].

Sunitinib was also associated with a high incidence of hemorrhage in two Phase II trials of progressive head and neck squamous cell carcinoma (HNSCC), many of whom were previously treated with radiotherapy. Choong, et al. [105] in an open-label Phase II trial enrolled 22 patients with HNSCC of which 77.3% had prior radiotherapy and 86.4% had prior chemotherapy. Although the report does not describe the time elapsed between radiotherapy and TKI therapy, 8 patients (36.4%) had hemorrhagic events-3 had G1 epistaxis, 2 had pulmonary hemorrhage (1 had G2, 1 had G3), 2 had gastrointestinal bleed (1 had G3, 1 had G4), and 1 had G3 superficial tumor hemorrhage. One patient with a base-of-the-tongue tumor developed an upper gastrointestinal bleeding and died [41,106]. The other open-label Phase II trial enrolled 17 patients with progressive HNSCC, of whom 47% had prior chemoradiotherapy. There were 10 bleeding complications in 7 patients (41.2%), with the most severe being a G3 bleeding around the tracheostoma. Both of the studies failed to meet the primary, efficacy end-point [41,42].

In contrast to Choong, et al. and Fountzilas, et al. [107,108] an open-label Phase II study of palliative sunitinib for progressive HNSCC did met its primary, efficacy end-point as 50% of the 38 patients achieved at least SD. In this study, 76% had prior radiotherapy and 45% had prior chemotherapy. However, 13 (34.2%) had head and neck bleeding. Six of them were at least Grade 3: 1 was G3, 1 was G4, and 4 were G5. All except the G4 had prior radiation to the head and neck. Five of the 6 had locoregional relapse was within <5 mm of the carotid artery-but did not invade the artery. The sixth patient had lung metastases but did not have locoregional relapse; instead developed extensive necrosis in the previously irradiated oropharynx. Developing or worsening of tumoral skin ulceration or fistulization occurred in 15 patients (39.5%) [43].

Sorafenib was studied in an open-label, Phase II trial of progressive HNSCC published in 2007. The study enrolled 27 patients, of whom 96.3% had prior radiation therapy and 70.4% had prior systemic therapy. It did not meet its primary, efficacy end-point of objective response rate. One of the 2 deaths in the study was from nasopharyngeal hemorrhage, but the authors felt that the cause was likely related to the underlying malignancy [44]. An open-label, Phase II trial of an experimental TKI, SU5416 (semaxinib), for progressive head and neck cancer was published in 2007. Of the 35 patients enrolled, 91.4% had prior radiation and 74.3% had prior chemotherapy. It also did not meet its primary, efficacy end-point of overall median survival to 7 months. One death was due to hemorrhage of the external carotid artery, which was encased by tumor. He was admitted several days into the his first treatment with SU5416, for neck bleeding and died one week later. The authors felt that the event was likely due to local disease invasion, but could not rule out drug-related toxicity [45].

Gefitinib, an epidermal growth factor receptor (EGFR) inhibitor, was also associated with tumor-hemorrhage. In a randomized, Phase III trial comparing Gefitinib to Methotrexate for recurrence HNSCC, 486 patients were randomized into 3 arms (low-dose gefitinib, high-dose gefitinib, and methotrexate). Most of the patients received radiotherapy (98.6%) and 35.6% received prior chemoradiation. There was no significant difference in overall mortality; the primary end-point. Unexpectedly, there were more tumor-hemorrhage events in the gefitinib arms compared to methotrexate arm (8.9% low-dose gefitinib, 11.4% high-dose gefitinib, and 1.9% methotrexate). Most of the tumor-hemorrhages were G1 or G2 (82.4%) for the gefitinib arms, but there were no G3-G5 tumor-hemorrhages in the methotrexate arm. Three gefitinib patients died from tumor hemorrhage, but the authors did not attribute the cause to gefitinib [46].

Lastly, Batchelder and Lehr evaluated the efficacy and toxicity of the addition of TKIs to radiation therapy based therapy for a multitude of cancers including cancers of the head and neck, esophagus, lung, and brain. Four hundred and five studies met their inclusion criteria encompassing 5,284 patients. Four trials examined a small molecule TKIs and radiation therapy (1,192 patients) and 7 studies evaluated TKI receptor antibodies and radiation therapy (4,092 patients). The addition of TKIs to radiation therapy did not improve overall survival. Among all patients, it did not worsen toxicity rates but on subgroup analysis TKIs and radiation, therapy did increase grade 3+ toxicity. The investigators concluded that the risks of TKI-related toxicity should be weighed against any benefit that TKIs afford in progression-free survival [47].

Discusssion and Conclusion

TKIs have taken a prominent role in modern oncology therapeutics with remarkable benefits, assuming that as

targeted therapy, they are less toxic than chemotherapeutic agents. For over 100 years, radiation therapy has shown remarkable curative and palliative effects. As over 50 percent of cancer patients, will receive radiation therapy during the course of their cancer treatment, the interaction of TKIs and radiation therapy will no doubt occur with increasing frequency. Therefore, their toxic and therapeutic interactive effects must be clear to optimize the benefit of TKIs while minimizing their potential interactive toxicities. Multiple studies have attempted to demonstrate a therapeutic advantage with the combination treatment but to date no definitive benefit can yet be clearly defined, while significant enhancement of toxicity has been shown in several studies [109,110].

Though several studies have suggested a therapeutic benefit of TKI/XRT combinational treatment, the variations of sequencing, dosing, previous treatment- both chemotherapeutic and radiotherapeutic, tumor site, normal tissue variables pertaining to radiosensitivity, the tumor bed as related to the tumor microenvirement, other concomitant medication drug-drug interactions, etc. mitigate our ability to render specific recommendations [111] Additionally radiation therapy may have significant pharmacokinetic effects, depending on the organ site irradiated; radiation may perturb drug absorption, distribution, metabolism and excretion [1]. Further studies will be required to define the role of TKIs and radiation therapy in combination in clinical practice. Lastly, considering the heterogeneity of cancers, the unique exposures to TKIs may vary both within and without cancers.

Considering the above, it is important to note that the interactive effects of radiation and TKIs will remain "a work in progress" [111], New forms of radiation dosing and delivery, new TKIs [112], combinations and additions of immunotherapeutics, chemotherapeutics, sequencing strategies etc. will impact the therapeutic ratio and success of combinational TKI/ radiationtherapy. For instance Jia and An recently demonstrated enhanced pneumonitis from osimertinib when combined with pulmonary radiation therapy [112].

In summary our data demonstrates potential benefits as well as harm at a minimum the following pertain:

- Careful observation and followup is mandatory when TKIs are combined with radiation therapy.
- We would recommend that the United States Food and Drug administration issue guidance on the utilization of these combinational treatments when used with therapeutic radiation as part of their review process.
- An awareness of benefit and harm, which does not yet exist should be disseminated to both medical and radiation oncologists.
- Potential benefits and harms should be relayed to patients as part of the informed consent process.
- Premature presentation of symptomatic cough, shortness of breath, esophagitis, mucusitis, inflammations etc. should initiate prompt re-evaluation of the treatment plan.
- We must be prepared for an expansion of these aspects of radiation/drug interactions considering the blistering expansion of new molecular entities

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