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Enhancing Therapeutic Radiation Responses in Multiple Myeloma

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1. Introduction

Multiple myeloma (MM) is hematologic malignancy characterized by the accumulation of malignant plasma cells in the bone marrow. The annual incidence of newly diagnosed MM cases in the United States is 3 to 4 per 100,000 people and accounts for approximately 1% of all malignant diseases (Jemal et al., 2011). MM is diagnosed at an advanced stage in 95% of patients and the median age at diagnosis is 65 years. It is a progressive malignancy that begins with monoclonal gammopathy of undetermined significance (MGUS), progresses to asymptomatic or smoldering myeloma and then symptomatic MM. MGUS is a disorder that exhibits clonal proliferation of plasma cells and can eventually evolve into MM or other B-cell disorders (Landgren et al., 2011). Clinically, patients with symptomatic myeloma have 10% or more malignant plasma cells in bone marrow, abnormal levels of serum free light chain, osteolytic bone disease, and show damage to other tissues or organs. Smoldering myeloma has the same plasma cell and M-protein characteristics of symptomatic but lacks evidence of organ damage. A rare type of MM, nonsecretory myeloma, has no detectable M-protein and accounts for only 1-5% of MM cases. Solitary plasmacytoma is a plasma cell neoplasm that has a single bone or extramedullary lesion (Mendenhall et al., 2003). MM is characterized by significant heterogeneity at the molecular level (Herve et al., 2011) and the bone marrow microenvironment plays an active role in supporting tumor growth, angiogenesis, bone disease, and drug resistance (Anderson and Carrasco, 2011). The disease initially responds to alkylating agents, corticosteroids, and thalidomide but eventually becomes refractory (Sirohi and Powles, 2004). High dose melphalan combined with peripheral blood stem cell transplant has improved the response rate in myeloma patients, but is not curative (Fassas and Tricot, 2001). To date, MM remains uniformly fatal with a median survival of approximately 50 months after diagnosis.

MM is extremely susceptible to radiation treatment and targeted radiotherapy including bone-seeking radiopharmaceuticals, monoclonal antibodies conjugated to radionuclides (radioimmunotherapy), and radiotargeted gene therapy using recombinant oncolytic viruses (radiovirotherapy) now offers a new paradigm to target this systemic malignancy. Combining targeted radiotherapy with radiation-sensitizing chemotherapeutic drugs provides additional benefit by improving treatment efficacy and extends the clinical use of radiotherapy in MM beyond palliative care or myeloablative preconditioning regimens. In this chapter, we will discuss recent advances in the field of targeted radiotherapy and chemotherapeutic drugs that have been utilized to increase radiation responses in MM patients.

2. Conventional radiotherapy in MM

Radiation therapy is a powerful treatment modality for MM (Bosch and Frias, 1988; Mill, 1975) where ionizing radiation generates free radicals that cause DNA damage, leading to the death of tumor cells. Approximately 80% of myeloma patients present with skeletal-related problems such as diffuse osteopenia, focal lytic lesions, pathological fractures, and bone pain; all these clinical manifestations are associated with myeloma bone disease that compromises quality of life and contributes towards morbidity and mortality (Kyle, 1975). Conventional external beam radiation therapy (EBRT), based on an outside-in approach, is used in MM for ablation of bony lesions and utilizes nuclear medicine methods that deliver radiation as either a local or a wide-field beam (Cole, 1989; Friedland, 1999; Price et al., 1986). EBRT has been combined with vertebroplasty and kyphoplasty for palliation of bone pain caused by vertebral compression fractures in MM patients (Hirsch et al., 2011). Radiotherapy is effective in the treatment of solitary plasmacytomas that manifest either as soft tissue disease (extramedullary tumors) or have bone involvement (osseous tumors) (Bolek et al., 1996; Kilciksiz et al., 2008; Krause et al., 2011; Lewanski et al., 1999; Tsang et al., 2001). The availability of new intensity-modulated radiation treatment (IMRT) techniques such as helical tomotherapy (HT) (Chargari et al., 2009), 3D conformal radiotherapy (3D-CRT) (Chargari et al., 2011) has enabled specific delivery of radiation to plasmacytomas with minimum normal tissue toxicity. The combination of localized fractionated radiotherapy with novel chemotherapeutic agents such as thalidomide (Marchand et al., 2008) and bortezomib (Berges et al., 2008) has provided good clinical outcomes with reduced radiotoxicity to normal tissues.

For systemic diffused myeloma disease, hemibody irradiation has been utilized, however, this method is associated with significant toxicity (Biswal, 2004; Hu and Yahalom, 2000). In MM patients, double hemibody irradiation has been combined with granulocyte-macrophage and granulocyte colony-stimulating factors (GM-CSF, G-CSF) to reduce toxic side effects of radiation on hematopoiesis (Troussard et al., 1995). Total body irradiation (TBI) has provided improved long-term survival rates for certain MM patient cohorts (Rostom, 1988). To alleviate TBI induced pulmonary complications, fractionation regimens of radiotherapy have also been evaluated in MM (Soejima et al., 2007) with improved *in vitro* clonogenic cell death of MM cell lines (Gluck et al., 1994). For hematological malignancies such as B-cell lymphoma and MM, curative radiation doses are estimated in the 20-30 Gy range, but without stem cell transplantation, a 2 Gy of radiation dose can result in hematologic toxicity (Brahme and Agren, 1987; Fletcher, 1976). Hence, clinical utilization of radiotherapy as a definitive therapeutic approach in MM has been mainly limited to a conditioning regimen prior to autologous or allogeneic stem-cell transplantation (Moehler and Goldschmidt, 2011; Snowden et al., 2011). However, in a study comparing melphalan plus TBI with melphalan alone for conditioning regimens before autologous stem cell transplantation (ASCT), melphalan alone showed less toxicity and was found to be as effective as melphalan plus TBI (Moreau et al., 2002). Technological advances such as IMRT, HT and linear accelerator-based intensity-modulated total marrow irradiation now enable the delivery of systemic radiotherapy to myeloma cells with higher and more tumoricidal doses of radiation with potential curative benefit (Wong et al., 2006; Wong et al., 2009; Yeginer et al., 2011).

3. Novel targeted radiotherapeutic agents in MM

A new generation of targeted radiotherapeutic methods such as radioimmunotherapy (Chatterjee et al., 2006; Goel, 2006), radiovirotherapy (Dingli et al., 2004; Goel et al., 2007), and bone-seeking radiopharmaceuticals have been tested for systemic radiotherapy of MM. Since these agents deliver radiation to myeloma cells either by directly targeting the cancer cells (radioimmunotherapy and radiovirotherapy) or bone (skeletal-targeted radiotherapy), they deliver radiation from the inside-out thereby minimizing normal tissue toxicity with increased tumor cell death, resulting in an overall increase in therapeutic efficacy.

3.1 Radioimmunotherapy (RIT)

Radioimmunotherapy (RIT) combines the advantages of antibody specificity, by binding to a tumor-associated antigen, with the cytotoxicity of radionuclides, resulting in targeted radiation therapy. RIT is a systemic treatment that has shown promising clinical remission rates in metastatic cancers such as non-Hodgkin lymphoma (NHL) and MM (Chatterjee et al., 2006; Mayes et al., 2011). Several monoclonal antibodies (MAbs) targeting the myeloma cell or the bone marrow microenvironment have been tested in preclinical and clinical studies (van de Donk et al., 2011); these MAbs are potentially amenable to RIT. RIT with MAb targeting the CD20 marker such as Zevalin (^{90}Y-iritumomab Tiuxetan) or Bexxar (^{131}I-tositumomab) has provided clinical benefit in B-cell lymphomas (Ahmed et al., 2010). Another CD20- targeting monoclonal antibody, rituximab, is being studied in patients with lymphocytic leukemia and other hematological diseases (NCT00669318) (Barcellini and Zanella, 2011). The monoclonal antibody, daratumumab, targets CD38^{+} MM *in vitro* and has shown promising results in selectively killing MM cells *in vivo* (de Weers et al., 2011). van der Veer et al. demonstrated a synergistic effect when tumor cells were pretreated with lenalidomide prior to treatment with daratumumab (van der Veer et al., 2011).

Most RIT developed and tested in clinical trials utilizes beta-particle emitting radionuclides in which short-range beta emitters such as iodine-131 and copper-67 are used to target small tumor cell clusters (Wun et al., 2001). Long-range beta emitters such as yttrium-90 are used to target larger tumor masses, tumor areas that remain inaccessible to RIT agents due to poor vascularity, and tumor cells that lack antigen expression by utilizing bystander radiation toxicity (Bethge and Sandmaier, 2005). RIT with alpha-emitters, such as bismuth-212, bismuth-213, astatine-211, actinium-225, lead-212 offer the advantage of a short path length with a high linear energy transfer of radiation, resulting in more specific tumor cell killing with less damage to the surrounding healthy tissues (Brechbiel, 2007). However, RIT with α-particles is fraught with challenges such as limited availability, radiolysis, suboptimal specificity of radiolabeled conjugates, and heterogeneous dose deposition in tumors (Cherel et al., 2006). In MM cell lines, Supiot et al demonstrated superior tumor cell killing by anti-CD138 (syndecan-1) B-B4 MAb labeled with bismuth-213 as compared to iodine-131-labeled antibody suggesting that alpha-RIT might be more suitable for treating single cell tumors such as MM (Supiot et al., 2002). Besides B-B4, the MAb MA5, which recognizes mucin-1 expressed by both normal and malignant plasma cells, has been coupled to bismuth-213 to target myeloma cells (Couturier et al., 1999; Supiot et al., 2005). In ASCT conditioning regimens, RIT is a good alternative to TBI as it results in less radiotoxicity for normal organ systems and delivers more radiation to tumors as reflected in improved cure rates (Gustavsson et al., 2003). MM patients have higher microvessel density than control subjects at bone marrow biopsy (Bhatti et al., 2006; Rajkumar et al., 2000). A preclinical study using bevacizumab, a humanized anti-VEGF MAb radiolabeled with Bi-213, showed promising results for prostate cancer treatment (Abbas Rizvi et al., 2008). As bevacizumab is now undergoing phase I/II clinical trials (Somlo et al., 2011), an alpha-RIT with this antibody may hold some clinical benefit for myeloma patients. It can be speculated that myeloablative conditioning protocols involving RIT with or without chemotherapy followed by ASCT may hold clinical benefit in MM. Also, approaches like pre-targeted RIT that separates delivery of the targeting molecule from radionuclide delivery can offer dose escalation (DeNardo et al., 2006) and radiolabeled high affinity antibody fragments (Goel and Batra, 2001; Goel et al., 2000) remain yet to be developed and tested in MM. The physical properties of few radionuclides tested in preclinical and clinical trials for cancer therapy are listed in Table 1.

Isotope	Radiation	Physical half-life	Mean particle energy (Mev)	Maximum energy (Mev)	Tisssue range (mm)
Iodine-131	β^-, γ	8 days	0.19	0.6	2.3
Yttrium-90	β^-	2.7 days	0.9	2.3	11.3
Rhenium-188	β^-	17 h	0.8	2.1	10.4
Rhenium-186	β^-, γ	88.8 h	0.35	1.1	2.4
Lutetium-177	β^-, γ	6.7 days	0.15	0.5	1.6
Copper-67	β^-, γ	61.8 h	0.14	0.58	2.1
Samarium-153	β^-, γ	1.9 d	0.23	0.81	0.6
Bismuth-213	α	46 min	8.3	8.4	0.09
Astatine-211	α	7.2 h	6.8	7.4	0.08
Actinium-225	α	10 days	8.4	5.8	0.08

Table 1. Physical characteristics of few isotopes studied in nuclear medicine for cancer therapy.

3.2 Radiovirotherapy

Oncolytic viruses have natural or engineered tropism for tumor cells which permits specific targeting and destruction of cancer cells (virotherapy) (Parato et al., 2005; Stief and McCart, 2008). In MM, studies with measles virus (MV) (Peng et al., 2001), vaccinia virus (Deng et al., 2008; Kawa and Arakawa, 1987), vesicular stomatitis virus (VSV) (Goel et al., 2007), and coxsackievirus A21 (Au et al., 2007; Hadac et al., 2011), have demonstrated *in vitro* and *in vivo* killing of tumor cells. Attenuated MV, which is an Edmonston vaccine lineage derivative (MV-Edm), has entered clinic trials for recurrent ovarian cancer, recurrent glioblastoma multiforme, and MM (Msaouel et al., 2009; Myers et al., 2007). However, intravenous administration of MV may be less effective in patients who have been previously vaccinated with the measles vaccine as these patients' antiviral antibodies may neutralize the oncolytic MV (Liu et al., 2010; Ong et al., 2007). Liu et al. performed a study demonstrating the feasibility and efficacy of using irradiated, MV-infected myeloma cells as carriers in mice (Liu et al., 2010). Using cells as viral carriers prevents neutralization by the humoral immune response; using myeloma cells ensures that the carriers are shuttled to the bone marrow and virus is delivered to the tumor site.

Oncolytic viruses have been used for radiotargeted gene therapy whereby radionuclides can be localized at tumor sites by inducing tumor cells to express sodium-iodide symporter (hNIS) gene (radiovirotherapy) (Chung, 2002). Such "designer oncolytic viruses" that express the human NIS gene have been engineered and tested in MM (Dingli et al., 2004; Goel et al., 2007). By using radionuclides, such as iodine-123, iodine-124, or technicium-99m, combined with detection with either a γ camera, positron emission tomography (PET), or single photon emission computed tomography (SPECT)/computed tomography (CT), NIS can be used as a reporter gene to non-invasively monitor viral localization and spread. Furthermore, NIS can be used as a therapeutic transgene by allowing intracellular uptake of isotopes such as iodine-131 which can cause direct radiation damage to tumor cells, thereby enhancing the therapeutic efficacy of radiovirotherapy. Currently, a phase I clinical trial of MV-NIS given with or without cyclophosphamide for treatment of patients with recurrent or refractory MM (NCT00450814) is ongoing at Mayo Clinic (Msaouel et al., 2009). Combining MV-NIS with other therapeutic radioisotopes such as rhenium-186, rhenium-188, or astatine-211 may be worth exploring in MM. Ongoing preclinical studies have shown that using cellular virus-delivery vehicles (i.e. mesenchymal progenitor cells, monocytes, T cells) can facilitate viral delivery to tumor cells (Munguia et al., 2008; Russell and Peng, 2008; Willmon et al., 2009). Irradiated 5TGM1 myeloma cells transfected with VSV-GFP have been shown to deliver VSV to sites of myeloma tumor growth in an orthotopic human myeloma model (Munguia et al., 2008). Since intravenous delivery of radiotargeted gene therapy is prerequisite for targeting systemic myeloma tumor sites, selection of the optimal cell carrier for radiovirotherapy is expected to improve the tumor remission rate in MM.

3.3 Skeletal-Targeted Radiotherapy (STR)

Bone-seeking radionuclide therapy enables the delivery of precisely focused radiation to the major bone marrow sites where myeloma cells reside and reduces the radiation exposure of healthy organs. Samarium-153-ethylene diamine tetramethylene phosphonate (153-Sm-EDTMP or ^{153}Samarium lexidronam) is an US Food and Drug Administration (FDA)-approved radiopharmaceutical that demonstrates good therapeutic ratio for a dose of 1 mCi/kg for palliation of pain in cancer patients with osseous metastases (Lamb and Faulds, 1997; Lewington, 2005). Reversible myelosuppression is the only significant toxic effect of 153-Sm-EDTMP; retreatment with 153-Sm-EDTMP is considered a safe, feasible, and efficacious for palliative treatment of bone metastasis (Serafini, 2000). 153-Sm-EDTMP is taken up by portions of the skeleton undergoing active remodeling resulting in rapid clearance from the blood (Bayouth et al., 1994). 153-Sm-EDTMP has also been used for total marrow irradiation in myeloablative clinical protocols for MM (Abruzzese et al., 2008; Anderson et al., 2002; Dispenzieri et al., 2003; Dispenzieri et al., 2010; Dispenzieri et al., 2005; Macfarlane et al., 2002). In non-transplant situations, 153-Sm-EDTMP treatment reduced pain in more than 70% of patients with osteoblastic metastases (Serafini, 2001).

Several other investigational radiopharmaceuticals such as rhenium-186-hydroxyethylidenediphosphonic acid (^{186}Re-HEDP) (Lam et al., 2004) and 166-Holmium-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonate (^{166}Ho-DOTMP) (Breitz et al., 2006) have been developed for targeted radiotherapy of bone malignancies (Jansen et al., 2010). In one preclinical study, EDTMP labeled with 166-dysprosium/166-Ho was used to establish an *in vivo* generator system for myeloablative radiotherapy/chemotherapy protocols in MM (Pedraza-Lopez et al., 2004).

4. Chemo-radiotherapy for MM

Chemotherapy alone has been proven to be insufficient treatment for patients with MM; however, when combined with radiation or stem cell transplantation, chemotherapy can improve the rate of remission (Galli et al., 2005). High-dose chemotherapy combined with ASCT is considered a standard part of initial therapy for patients with MM. Over 75% of myeloma patients are over 50 years old at diagnosis; the majority of these patients do not qualify to receive aggressive therapeutic protocols involving ASCT due to their advanced age (Gautier and Cohen, 1994; Palumbo and Gay, 2009; Turesson et al., 2010). Chemotherapy can be combined with radiotherapy (chemo-radiotherapy) permitting chemotherapy and/or radiation to be offered at reduced dosages; such regimens may also inhibit the emergence of therapy resistant disease frequently seen with prolonged usage of high dosing regimens (Greenstein et al., 2002). In MM, tumor microenvironment has been shown to induce myeloma-cell drug resistance (Shain and Dalton, 2009).

Chemotherapy has been combined with STR in MM in a study in which sequential therapy with 153-Sm-EDTMP, melphalan, and bone marrow transplant resulted in less radiotoxicity in non-hematopoietic organs as compared to TBI in preclinical studies (Turner et al., 1993). Recently, STR using 153-Sm-EDTMP has been combined with high-dose melphalan and ASCT was used as a myeloma-conditioning regimen and found to be safe and well tolerated (Dispenzieri et al., 2010). Similarly, in primary refractory myeloma patients, conditioning with 166-Ho-DOTMP plus melphalan was found to be both safe and efficacious as compared to melphalan alone (Clapp, 2004; Giralt et al., 2003).

Radiation therapy has been shown to induce apoptotic cell death of endothelial cells (Garcia-Barros et al., 2003) and recently treatment of MM with regimens combining a designer anti-angiogenic drug and radiotherapy showed promising preclinical results for the treatment of focal MM (Jia et al., 2010). Bisphosphonates have also been studied in combination with other treatments, like thalidomide, to target myeloma cells in patients with osteolytic lesions (Ciepluch et al., 2002). Zoledronic acid and pamidronate are anti-catabolic nitrogen-containing bisphosphonates used in MM therapy (Pozzi and Raje, 2011). Combining bisphosphonates with radiotherapy for treatment of myeloma bone disease has been suggested as a method for improved myeloma control (Ural and Avcu, 2007; Yeh and Berenson, 2006).

Our increased understanding of the role of endogenous and therapy-induced oxidative stress, which results from an imbalance in the production of reactive oxygen species (ROS) and cellular antioxidant defenses, offers a biochemical rationale for designing novel ways to induce oxidative stress-mediated killing of cancer cells while sparing healthy tissues (Gius and Spitz, 2006; Goel et al., 2011; Spitz et al., 2004). Below are few cytotoxic agents that have been shown to induce ROS-mediated anti-myeloma activity. It is reasonable to hypothesize that combining radiation with such chemotherapeutic agents, that partially act by altering the redox parameters, may lead to increased anti-myeloma cellular activity.

Dexamethasone (Dex), a synthetic glucocorticoid, is an agent commonly used to treat MM. Although most newly diagnosed patients are sensitive, prolonged Dex therapy results in the development of Dex resistance and treatment failure (Alexanian et al., 1992; Greenstein et al., 2002). We have recently proposed a novel combination of Dex plus radiation for treatment of MM in which the combination of 153-Sm-EDTMP radiotherapy and Dex should selectively enhance killing of myeloma cells (Bera et al., 2010). Normal BM hematopoiesis would be protected via a mechanism that involves the selective increase of certain types of oxidative stress in myeloma cells (Bera et al., 2010).

Proteasome inhibitors - Bortezomib (BTZ, also known as Velcade/PS-341) is boronic acid inhibitor of the catalytic site of the 20S proteasome and is first in the class to be approved by the FDA for clinical use (Terpos et al., 2008). BTZ induces myeloma cell apoptosis in its supportive bone marrow microenvironment by disrupting multiple signaling pathways affecting cell cycle and survival related proteins like NF-κB, p53, and Bax among others (Mitsiades et al., 2002). BTZ inhibits NF-κB activation by stopping IκB degradation (Goel et al., 2005; Hussein, 2002). BTZ was approved for the treatment of relapsed/refractory MM patients in 2003 and data suggest that the initial combination of BTZ with immunomodulatory drugs (IMiD) can increase the response rate in MM patients (Blade and Rosinol, 2008). Studies have shown that cellular upregulation of target enzymes is a common mode of resistance to several types of chemotherapeutic drugs (Schimke et al., 1984). In one study, high levels of acquired BTZ resistance were seen after *in vitro* selection using stepwise increases in BTZ concentrations which were achieved by selective overexpression of a structurally altered β5 proteasome subunit (Oerlemans et al., 2008). In an effort to overcome BTZ resistance, novel proteasome inhibitors are being developed that act through mechanisms distinct from BTZ (Ruschak et al., 2011). Our group has shown that BTZ/PS-341 can sensitize myeloma cells to conventional radiotherapy by both intrinsic and extrinsic apoptotic pathways (Goel et al., 2005). BTZ acts as a "radiation modifier" in MM predominantly by attenuating endogenous and IR-induced NF-κB activity; indeed, several relevant molecularly targeted drugs are being tested and developed in combination with ionizing radiation to specifically target and eliminates the tumor cells while simultaneously decreasing radiotoxicity toward normal tissues (Begg et al., 2011). Using the orthotopic, syngeneic 5TGM1 myeloma model, we demonstrated that the combination of BTZ with 153-Sm-EDTMP resulted in increased survival time without a corresponding increase in the myelosuppressive effects of 153-Sm-EDTMP (Goel et al., 2006). In a phase I trial, combining 153-Sm-EDTMP with BTZ was well-tolerated and showed clinical activity in patients with relapsed or refractory MM (Berenson et al., 2009).

Studies have shown that BTZ induces apoptosis in cancer cells by increasing ROS generation in mitochondria (Ling et al., 2003; Yu et al., 2004) and endoplasmic reticulum (Fribley et al., 2004). Besides radiation, proteasome inhibitors have been combined with ROS-generating chemotherapeutic drugs like histone deacetylase (HDAC) inhibitors (Feng et al., 2008; Feng et al., 2007b; Heider et al., 2008; Miller et al., 2007; Pei et al., 2004), non-steroidal anti-inflammatory drugs (Minami et al., 2005) and rituximab (Bellosillo et al., 2001; Wang et al.,

2008) with improved elimination of cancer cells. In MM, combined treatment of BTZ with the Bcl-2 inhibitor (Pei et al., 2003) or HDAC inhibitors (sodium butyrate, suberoylanilide hydroxamic acid, PXD101) (Feng et al., 2007b; Pei et al., 2004) have shown synergistic myeloma cell killing by oxidative injury. Recently, BTZ was shown to induce Nrf-2-mediated antioxidant responses by upregulating glutamate cysteine ligase and heme-oxygenase I HMOX1 (Nerini-Molteni et al., 2008). Clinically, BTZ has been combined with 153-Sm-EDTMP with good clinical outcomes in MM with reduced radiotoxicity to normal tissues (Berenson et al., 2009; Berges et al., 2008).

Non-steroidal anti-inflammatory drugs (NSAIDs) are non-selective cyclooxygenase inhibitors (for Cox-1 and Cox-2) that were developed as anti-inflammatory agents (Rigas and Sun, 2008). Nitric oxide-donating sulfosalycylic acid was used mainly for chemo-preventive effects (Rigas and Kashfi, 2004). Recent studies have shown that NSAIDs induce apoptosis in a variety of tumor cell lines including hematological malignancies (Bernard et al., 2008; Robak et al., 2008). Drugs like SC-58125 and SDX-101 without Cox-2 inhibitory activity induces cytotoxicity, overcomes drug resistance and enhances the activity of dexamethasone in MM (Feng et al., 2007a). SDX-308 (an indole-pyran analog of SDX-101) also shows anti-myeloma effect (Feng and Lentzsch, 2007; Lentzsch et al., 2007), inhibits RANKL-stimulated NF-κB activation and osteoclast formation (Feng et al., 2007a), and β-catenin/T-cell factor pathway (Feng and Lentzsch, 2007; Yasui et al., 2007). Sulindac also shows anti-myeloma effects by accumulation of p53, Bax, and Bak in mitochondria mediated by p38 MAPK activation downstream of ROS production (Seo et al., 2007).

Arsenic trioxide (ATO)- Preclinical data shows ATO activity in B-cell lymphoma and MM (Bahlis et al., 2002; Gartenhaus et al., 2002; Grad et al., 2001). In myeloma cell lines ATO-mediated oxidative stress has been shown to upregulate proapoptotic Bcl-2 family proteins with release of cytochrome c and apoptosis (Karp and Lancet, 2005; Santucci et al., 2003). However, gene expression studies in myeloma cell lines have suggested ATO may result in a protective antioxidant response by upregulating genes such as HMOX1 and metallothionein-2A (Zhou et al., 2005). Studies have shown that the sulfhydryl oxidizing action of ATO exerts cytotoxic effects by elevating oxidative stress and by inhibiting the proper function of the glutathione/ glutathione peroxidase system (Dalton, 2002; Hussein, 2003). In support of this mechanism, myeloma cell lines with lower antioxidant capacity were found to be sensitive to ATO-induced apoptosis (Zhu et al., 2000). Agents that deplete cellular glutathione, such as green tea, ascorbic acid, PI3K/Akt inhibitor, and buthionine sulfoximine have been shown to enhance ATO-induced apoptosis (Bachleitner-Hofmann et al., 2001; Gartenhaus et al., 2002; Grad et al., 2001; Nakazato et al., 2005a; Ramos et al., 2005). ATO has been combined with trolox (an analogue of α-tocopherol) with increased apoptosis in acute promyelocytic leukemia and myeloma cell lines (Diaz et al., 2005; Diaz et al., 2007). In acute myeloid leukemia cell lines ATO has been combined with polyunsaturated fatty acid docosahexaenoic acid (forming toxic lipid peroxidation products) with increased oxidative cell death (Bachleitner-Hofmann et al., 2001; Gartenhaus et al., 2002; Grad et al., 2001; Nakazato et al., 2005a; Ramos et al., 2005; Sturlan et al., 2003). Recently, ATO and 2-methoxyestradiol have been combined with BTZ to enhance BTZ-induced toxicity in myeloma cell lines via inhibition of β-catenin protein accumulation (Zhou et al., 2008). The use of ATO in B-cell lymphoma and MM clinical trials has however resulted in modest success. In MM patients that are refractory to conventional salvage therapy, ATO produced responses in 3/14 patients and prolonged stable disease in a fourth patient (Munshi et al., 2002). ATO has also been combined with BTZ is patients with relapsed/refractory MM and objective responses were observed in 6/22 patients (Hofmeister et al., 2008). However, ATO when combined with DVd (Doxil, vincristine, and dexamethasone) in 11 newly diagnosed myeloma patients failed to improve the response rate compared to DVd alone (Hofmeister et al., 2008). Overall, ATO has shown promising preclinical and clinical responses in malignant B-cells.

Motexafin gadolinium (MGd) is a metallotexaphyrin that acts by generating ROS and depletion of reducing metabolites such as protein thiols, thioredoxin, NADPH, ascorbate, and glutathione besides other mechanisms of action (Evens, 2004). It is a broad-spectrum anti-cancer agent that in under clinical trials as a single agent and in conjunction with radiotherapy and chemotherapy (Evens, 2004). MGd induces ROS-mediated toxicity in chemotherapy-sensitive and -resistant myeloma cell lines and in primary myeloma cells (Evens et al., 2005b). In B-cell lymphoma cell lines, MGd has been shown to sensitize cells to IR (Magda et al., 2001), disrupt intracellular zinc homeostasis by inducing metal response element-binding transcription factor-1 (MTF-1)-regulated and HIF-1-regulated genes (Lecane et al., 2005), and inhibit HMOX1 activity (Evans et al., 2007). MGd has shown single agent activity in very heavily pretreated B-chronic lymphocytic leukemia /small lymphocytic lymphoma patients, and showed complete remissions in combination with zevalin for relapsed B-cell NHL (Evens et al., 2005a). MGd is yet to be combined with radiotherapy and chemotherapy in clinical treatment of MM.

Myeloma and lymphoma cells harbor Ras mutations and respond to cell death by the **farnesyltransferase inhibitor (FTI)** (Karp and Lancet, 2005; Santucci et al., 2003). Manumycin (Man)-A induces apoptosis in B-cell tumors by inhibiting prenylation (Frassanito et al., 2002) and also by generating ROS that inhibits Ras/MEK/ERK and Ras/PI3K/Akt pathways by cleaving MEK and Akt (Sears et al., 2008). R115777 (zarnestra/tipifarnib) is a FTI that has shown promising clinical results in acute myeloid leukemia, myelodysplastic syndromes, chronic myelogenous leukemia, and MM and with anti-tumor effects noted independent of Ras mutations (Martinelli et al., 2008). In breast and thyroid cancer cells, similar to Man-A, R115777 was shown to perturb the redox balance and induce caspase independent DNA damage and apoptosis (Pan et al., 2005). With the recent understanding of the role ROS in FTI-induced tumor cytotoxicity, further studies may show a more promising role of these agents in Ras harboring B-cell malignancies.

Imexon, a cyanoaziridine, directly impairs mitochondria function via decreasing levels of cellular thiols, and by inducing oxidative damage of mitochondrial DNA (Dvorakova et al., 2000; Dvorakova et al., 2001; Salmon and Hersh, 1994). Imexon has shown activity in MM (Dvorakova et al., 2000; Salmon and Hersh, 1994; Samulitis et al., 2006) and promyelocytic leukemia (Dvorakova et al., 2001), and large cell lymphoma cell lines (Hersh et al., 1993). In myeloma cell lines, imexon treatment is associated with decreased levels of cellular thiols (cysteine and glutathione) with partial rescue of cytotoxicity by N-acetylcysteine and theonyltrifluoroacetone (inhibitor of mitochondrial complex II) (Dvorakova et al., 2000; Dvorakova et al., 2001). Also, resistance to imexon has been correlated with increased Cu/Zn superoxide dismutase 1 expression in myeloma cell lines (Samulitis et al., 2006). In an imexon-resistant myeloma cell line and peripheral blood mononuclear cells from normal volunteers and advanced cancer patients, imexon treatment resulted in adaptive response by up-regulation of thioredoxin reductase-1, glutaredoxin-2, and peroxiredoxin-3 that is thought to be mediated by increased AP-1 binding and nuclear levels of NF-E2-related factor 2, Nrf2 (Baker et al., 2007). In a myeloma cell line, imexon showed synergistic cytotoxicity with chemotherapeutic drugs such as cisplatin, dacarbazine, and melphalan (DNA-alkylating agents), cytarabine, fluorouracil, and gemcitabine (pyrimidine-based anti-metabolites), docetaxel (taxane), dexamethasone (glucocorticoid), and BTZ (Baker et al., 2007; Scott et al., 2007). In advanced cancer patients imexon showed clinical activity with decrease in plasma thiols and resulted in partial response in a heavily pretreated patient with B-cell NHL (Dragovich et al., 2007). The preclinical and clinical findings suggest that combining imexon with alkylating agents and pyrimidine-based anti-metabolites could result in a ROS-mediated increase in therapeutic responses in MM patients.

Naturally occurring compounds – Several natural compounds have been shown to induce cytotoxicity in B-cell lymphoma and MM cells via increased oxidative stress. Studies have shown that procarbazine (a plant sesquiterpene lactone) induces myeloma cell apoptosis by mechanisms that involves ROS (Wang et al., 2006) or by inhibiting NF-κB and caspase-dependent and -independent pathways (Suvannasankha et al., 2008). Procarbazine generates H_2O_2 during oxidation to its azo derivative (Berneis et al., 1963), has been incorporated in a combination chemotherapy called MMPP (ranimustine, melphalan, procarbazine and prednisolone) however this regimen did not show superior chemotherapy over MMCP (with cyclophosphamide) in MM (Nagura et al., 1997). It has been shown that these compounds can induce Nrf2/antioxidant response element pathway and antioxidant enzymes resulting in increased resistance to oxidative damage (Umemura et al., 2008). Resveratrol, a polyphenolic compound (stilbenes) has been shown to be both chemo-preventive and possess anti-tumor effects, presumably by altering intracellular redox reactions that regulate the activity of Nrf2 (Aggarwal et al., 2004). The anti-tumor effect of resveratrol has been hypothesized to occur in a ROS-dependent pathway (Dong et al., 2008; Juan et al., 2008; Sekhar et al., 2002). Resveratrol induces apoptosis in B-cell lymphoma (Faber and Chiles, 2006; Faber et al., 2006; Shimizu et al., 2006) and MM by several mechanisms (Bhardwaj et al., 2007; Boissy et al., 2005; Sun et al., 2006) and synergizes with radiotherapy (Baatout et al., 2004) and paclitaxel chemotherapy (Jazirehi and Bonavida, 2004). Curcumin (diferuloylmethane), a phytochemical compound of turmeric induces apoptosis by inhibition of NF-κB and STAT3 activation in myeloma (Bharti et al., 2003a; Bharti et al., 2003b; Bharti et al., 2004) and B-cell lymphoma cell lines (Hussain et al., 2008; Mackenzie et al., 2008). In B-cell lymphoma, curcumin has been shown to down modulate Syk cell activity and Akt activation (Gururajan et al., 2007), and a ROS-mediated lysosomal rupture and caspase activation with ascorbic acid-mediated enhancement of curcumin's action has been reported (Skommer et al., 2006). Catechin (epigallocatechin-3-gallate), green tea polyphenol has been shown to increase ROS levels with an increase in apoptosis in MM and lymphoma cells with enhanced killing when combined with ATO (Nakazato et al., 2005b) or etoposide (Nakazato et al., 2005a). Chaetocin (a thiodioxopiperazine produced by fungi) is a competitive and selective substrate for thioredoxin reductase-1 (Tibodeau et al., 2008) and induces myeloma cell apoptosis by oxidative stress (Isham et al., 2007). Parthenolide (a sesquiterpene lactone from herb feverfew) induces ROS-mediated apoptosis in MM cells (Wang et al., 2006) targets both myeloma and bone marrow microenvironment by caspase-dependent and -independent mechanisms (Suvannasankha et al., 2008) with anti-angiogenic effects (Kong et al., 2008).

5. Conclusion

Although major advances have been made in the treatment of MM, this disease remains incurable (Jemal et al., 2011). Myeloma tumors are considered to be inherently radiosensitive; thus the importance of radiation therapy as a part of a comprehensive treatment approach is expected to provide a clinical benefit in MM protocols. Modern radiotherapy now offers new methods and techniques to deliver high doses of radiation with enhanced anatomical precision to cancerous sites. Targeted radiotherapy using monoclonal antibodies conjugated to radionuclides, radiotargeted gene therapy using recombinant oncolytic viruses (radiovirotherapy), and bone-seeking radiopharmaceuticals now offer a new paradigm to target this systemic malignancy. Furthermore, increased understanding of the dysregulation of cancer signaling pathway(s) have lead to novel preclinical and clinical chemo-radiotherapy protocols that may offer improved response rates for MM patients.

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7. List of abbreviations

MM, multiple myeloma
MGUS, monoclonal gammopathy of undetermined significance
NHL, non-Hodgkin lymphoma
TBI, total body irradiation
EBRT, external beam radiation therapy
IMRT, intensity-modulated radiation treatment
HT, helical tomotherapy
CRT, conformal radiotherapy
RIT, radioimmunotherapy
ASCT, autologous stem cell transplantation
MAbs, monoclonal antibodies
MV, measles virus
VSV, vesicular stomatitis virus
NIS, sodium-iodide symporter gene
SPECT, single photon emission computed tomography
CT, computed tomography
PET, positron emission tomography
STR, skeletal-targeted radiotherapy
BTZ, bortezomib
Dex, dexamethasone
NSAIDs, non-steroidal anti-inflammatory drugs
ATO, arsenic trioxide
MGd, motexafin gadolinium
FTI, farnesyltransferase inhibitor

EDTMP, ethylene diamine tetramethylene phosphonate
HEDP, hydroxyethylidenediphosphonic acid
NF-κB, nuclear factor- κB
Nrf2, NF-E2-related factor 2
IMiD, immunomodulatory drugs
ROS, reactive oxygen species

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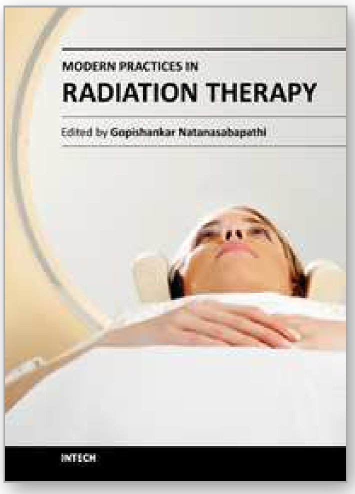

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