Journal of
Nuclear Medicine & Radiation Therapy

Liu et al., J Nucl Med Radiat Ther 2011, 2:1
DOI: 10.4172/2155-9619.1000106

Research Article Open Access

Interventional Oncology – Avoiding Common Pitfalls to Reduce Toxicity in Hepatic Radioembolization

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Abstract

Within the setting of hepatic neoplasia [primary and secondary], selective internal radiation therapy [SIRT], also known as radioembolization has become an accepted procedure, incorporated into the armamentarium of multidisciplinary oncologic care. The procedure itself requires an understanding of mesenteric vascular anatomy, tumor vascular patterns, liver metabolism, and chemotherapy. Given the complex nature of the treatment, unique toxicities, and complications may develop from multiple etiologies.

Strategies to reduce toxicities and complications as they relate to SIRT can be stratified into two broad categories: factors involving vascularity/vascularization, and factors involving the underlying liver parenchyma. The purpose of this manuscript is to provide the reader with a systematic review of the most commonly presenting toxicities, their etiologies, prevention strategies, and suggested therapeutic options in a practical, and concise manner. A brief discussion on the common misconceptions regarding toxicities will be included.

Introduction

The principles of radioembolization involve the intended deposition of radioactivity into the microvascular bed of a biologically active tumor utilizing a carrier-based delivery mechanism in a technique that has been described as far back as 1965 [1]. Although simple in concept, multiple considerations must be made in respect of the desired radiation dose delivered to the tumor, the required total radio activity, to achieve that radiation dose, the specific radioactivity, of each microparticle, and the physical characteristics of the microparticle, in addition to the physiologic and anatomic environment within the targeted microvascular bed.

In spite of the over 15,000 human administrations of selective internal radiation therapy (SIRT) in routine clinical practice [using both ceramic, and resin microsphere platforms], many common misconceptions persist regarding the presentation, incidence, and etiologies of toxicities leading to suboptimal dose administration, and suboptimal treatment. For instance, a common misconception that sterile water results in significant complications, toxicities, and vascular spasm has never been substantiated. Comments regarding the superiority of the administration of a larger dose [either through increased specific activity per microsphere, or through the application of partition modeling] go without merit or evidence, and in fact are contrary to published literature and do not take into account the microdosimetric response, or provide supportive objective outcome measures that justify this position. Optimization strategies in the context of chemotherapy, and cirrhosis have never been addressed by consensus, or evidence based outcomes. These incorrect assumptions translate into inconsistency in therapy and ultimately clinical outcome.

Optimized treatment strategies include standard considerations such as performance status, prior chemotherapeutic, and tumor biology/site origin. In addition, given the novel strategy in the application of SIRT, further consideration to tumor morphology, hepatic vasculature, and tumor micro vasculature also warrant consideration. Failure to incorporate all of these aspects into an appropriate treatment strategy, not only in terms of quantity of radioactivity, but also the point of administration of the radioactivity may result in toxicities that can be divided into two major categories, those that which are related to vasculature considerations [macrovascular considerations such as anatomical variation, and point of administration, as well as the micro vasculature characteristics of the tumor], and the underlying liver parenchyma. The intent of this manuscript is to provide a summarized overview of the potential toxicities relating to SIRT, and to offer potential strategies in the mitigation of these toxicities.

Hepatic vasculature as relating to toxicities: macrovascular anatomy/nontargeted embolization

The safety profile of SIRT ultimately depends on the ability to understand, and optimize both the macrovascular aspects of delivery [point of catheter administration, vascular anatomy, vascular optimization], in addition to the micro vascular aspects of delivery [arterio-venous shunting, tumor to normal parenchymal microparticle uptake ratio, and abnormal perfusion]. Balancing the appropriateness of the point of implantation with the potential of delivering particles into non-targeted areas remains the profound challenge of radioembolization. Current guidelines, and prescribed activity determination are based primarily on safety profile as opposed to intended tumor radiation dose due to the multiple factors that exist in both a microvascular, and macrovascular domain.

As well described in the literature, anatomical variations within the hepatic arterial anatomy can result in nontargeted embolization

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Received April 26, 2011; **Accepted** May 26, 2011; **Published** June 15, 2011

Citation: Liu DM, Cade D, Klass D, Loh C, McWilliams JP, et al. (2011) Interventional Oncology – Avoiding Common Pitfalls to Reduce Toxicity in Hepatic Radioembolization. J Nucl Med Radiat Ther 2:106. doi:10.4172/2155-9619.1000106

leading to deposition of microspheres [and consequently radiation] in a quantity that results in clinical sequelae/complication/toxicity. Simply put, the majority of toxicities from selective internal radiation therapy involving the gastrointestinal tract occur as a result of nontarget embolization [due either to failure to identify vessels that have their origin from the hepatic arterial tree that then depart the liver, or reflux of microparticles resulting in implantation in nontargeted/intended regions]. A discussion regarding the identification and optimization of vasculature is beyond the scope of this manuscript, however readers are directed towards the extensive published review articles, and angiographic approaches for further elaboration [2-5], however for the purposes of illustration, readers are provided with a brief discussion of the most common vascular considerations and their clinical presentation.

The hepatic arterial system may demonstrate anatomical variation in over 30% of presentations in a far greater percentage of patients may present with conventional anatomy which may complicate the location or method of microsphere delivery [4] requiring an exquisite understanding of the range of anatomical variations. As a result of the high variability, microsphere deposition may occur potentially anywhere from the distal esophagus to the jejunum including gallbladder and pancreas. Currently, there is no predictive method of estimating cytocidal radiation or embolic dose to terminal vascular beds, therefore it must be assumed that any nontargeted embolization [regardless of the number microspheres, or amount of radioactivity] may be toxic. Furthermore, the potential of non-targeted embolization as a result of neovascularization, and collateral flow developing from previously optimized vascular beds during the interval between mesenteric angiography/vascular optimization and implantation has been reported [5,6] further emphasizing the need for detailed re-examination of vascular supply immediately prior to the implantation of the microspheres.

The most common complication as result of nontargeted embolization is the inadvertent deposition of microspheres within the stomach. The right gastric artery [with its high variability of origin, and appearance] remains the most likely culprit, resulting in irradiation of the lesser curvature of the stomach, and radiation ulcers that may range from self-limiting [with steroids, acid suppression, controlled diet, motility agents, and sodium bismuth], to severe gastritis or perforation resulting in emergent bypass surgery [7,8]. Following coil embolization and hepatic vascular optimization, the development of collateral variant pathways to the stomach and duodenum are common, and may result in gastroduodenal radiation-induced disease [9]. Adequate identification and coil embolization of all identified right gastric arteries [as per the recommendations of the REBOC consensus panel] remains a mandatory step prior to selective internal radiation therapy [3]. Gastroduodenal ulceration rates in excess of 10% have been reported in several series; incidence decreases significantly with improved recognition of the right gastric artery, identification of the endpoint of microsphere infusion, and catheter skills that develop with increasing operator experience [10], and is a complication that amongst experienced operators should fall well below 2%.

The cystic artery remains a vessel of controversy, and must be considered in all forms of embolic therapy. Fortunately, involvement of this vessel leads to relatively few sequelae, with the vast majority of severe presentations published as case reports [11,12]. Collectively, the incidence of radiation induced cholecystitis is rare, with less than 1% requiring surgical intervention however described within the literature [13-15]. Controversy remains as to whether prophylactic coil embolization of the cystic artery is required prior to administration of microsphere therapy. Recently, McWilliams et al. [16] confirmed the safety of prophylactic gel foam and coil embolization of the cystic artery prior to implantation. The results have demonstrated a trend towards decreased complications when utilizing gel foam pledget immediately prior to radioembolization procedures, which according to the authors conclusions may be the optimal method of dealing with potential implantation of microspheres at the time of administration [16]. Whether or not the cystic artery requires prophylactic embolization still remains controversial however if the need is identified for protection of the cystic artery, this technique can be performed safely and without complication.

Pancreatitis secondary to non-targeted embolization is likely to have a multifactorial etiology, including the possibility of associated toxicity from antineoplastic drugs, non-targeted embolization resulting in ischemia/obstruction, and of course the direct radiation effects from yttrium-90. Although described anecdotally, no specific case report relating to radiation-induced pancreatitis has been published in contemporary literature. However, pancreatitis associated with liver embolization has been described, utilizing both terminal embolic agents, as well as chemoembolization techniques, further emphasizing to the operator the importance of vascular optimization, and intense scrutiny during implantation to minimize the potential for reflux [17,18].

Non-targeted embolization resulting in other sequelae within the gastrointestinal, and hepatobiliary tract have been described on a case report basis. Biliary sclerosis, small bowel radiation-induced injury, and radiation-induced enterocolitis have been described, with the majority of reports having occurred following single session whole liver SIRT administration [4,13,19-21].

Techniques for optimization from a vascular perspective require an understanding of normal anatomy, anatomical variations, and intrahepatic flow patterns in the context of embolic therapy. Advanced maneuvers such as super-selective catheterization, and multiple segmental implantation minimize the potential for lower order vessel reflux, and subsequent non-targeted embolization. Along this spectrum, the concept of segmental administration and radiation segmentectomy, enables highly accurate implantation within specific segmentsand potentially extraordinarily high radiation doses [in the order of 1200Gy to the tumor, and 300Gy to the surrounding liver parenchyma] in very limited liver volumes thus resulting in complete destruction of both tumor and normal parenchyma. Barring any arterio-venous shunting and acceptable liver function, this becomes an effective strategy when dealing with oligo-metastatic disease that has well-defined vascular pedicles, potentially minimizing of the potential for non-target embolization by minimizing the amount of exposed tissue, and performing the implantation deep within the tumor vascular plexus [22].

Portal vein thrombosis

Traditionally, the presence of portal vein thrombus [most commonly in the context of hepatocellular carcinoma (HCC)] has been an absolute contraindication for chemoembolization and bland embolization due to the concerns regarding the possibility of tumor embolus. The poor prognosis of this presentation is emphasized by the abysmal median survival of 5.4 months in the setting of symptomatic or vascular invasion or extra-hepatic spread [23,24]. However, with the carrier-based delivery mechanism applied in SIRT, current literature suggests that selective internal radiation therapy is acceptably safe

and remains effective in the context of portal vein thrombosis.In the setting of hepatocellular carcinoma, median survival has been reported to range from 7.9 to 17.2 with the application of resin microspheres [25,26]. These encouraging results suggest that the carrier-based mechanism of delivery of radiotherapeutic in the setting of portal vein tumor thrombus may result in improved outcomes as compared to historical survival in the presence of macrovascular invasion, and also provide a potential setting in which the synergistic actions of multi-targeted kinase inhibitors [such as sorafenib] may complement the theoretical mechanism of action of the radioembolic by counteracting angiogenesis, and up regulation of compensatory mechanisms [27,28]. Results are pending based on a number of phase III trials examining the utility of radioembolization with adjuvant multi-kinase inhibitors, however for the purposes of discussion regarding toxicities, the application of radioembolization in the setting of portal vein tumor thrombus result in an acceptable safety profile, and tolerability, with a trend [retrospective, and single arm prospected] towards improved survival. Due to the primary therapeutic mechanism of Y90 microspheres being local irradiation as opposed to ischemia, it has been demonstrated that radioembolization may be better tolerated than traditional embolization or chemoembolization in patients with PVT. Lack of an embolic effect of Y90 microspheres has been further demonstrated by reports showing a decreased incidence of postembolization, compared with chemoembolization or transarterial embolization, resulting in an increased quality of life as compared to older trans arterial techniques [29].

In the setting of SIRT as a monotherapy , time to progression in those patients diagnosed with PVT was 8.0 months, with a median survival of 10 months as reported in a retrospective series of 108 patients, with similar findings reported by Tsai et. al., in a retrospective analysis of 22 patients with PVT, demonstrating a median survival of 7.7 months, significantly higher than previously reported survival in the setting of macrovascular invasion and PVT [25,26]. Similar results have been found in retrospective analysis, with median survival time reported in the order of 10 months [30]. In the setting of portal vein thrombus, toxicities in relation to elevated liver enzymes, and incidence of fulminant hepatic failure has been acceptable, thus demonstrating utility of radioembolization in the setting of portal vein thrombosis [31]. The improved outcomes of SIRT as compared to best supportive care, and previous attempts at embolic therapies suggest that toxicities associated with this procedure in the setting of portal vein thrombosis are clinically acceptable. Results are pending from three phase III trials (SORAMIC, SIRveNIB and STOP) examining the utility of radio-embolization with adjuvant multi-targeted kinase inhibitors however, for the purposes of discussion regarding toxicities, the application of radioembolization in the setting of portal vein tumor thrombus results in an acceptable safety profile and tolerability, and minimal toxicity, with a trend [retrospective, and single arm prospective] towards improved survival. Due to the primary therapeutic mechanism of yttrium-90 microspheres being local irradiation as opposed to ischemia, it has been demonstrated that radioembolization may be better tolerated than traditional embolization or chemoembolization in patients with PVT. Lack of an enduring embolic effect of yttrium-90 microspheres has been further demonstrated by reports showing a decreased incidence of post-embolization syndrome, compared with trans-arterial chemoembolization or trans-arterial embolization, resulting in an increased quality of life compared to older trans-arterial techniques [29].

Tumor and parenchyma shunting: radiation pneumonitis

Microvascular and macrovascular arterioveous shunting may occur within the histologic architectureof a tumor as a result of mechanisms related to angiogenesis, vascular erosion, and autonecrosis resulting from tumor parenchyma outstripping its own vascular supply. Furthermore, in situations of compromised hepatic reserve such as cirrhosis, arteriovenous and arterioportal shunting may also occur in non-neoplastic liver parenchyma due to degenerative transformation (e.g. cirrhosis, edema), vascular obstruction (venocclusive disease), and trauma (percutaneous tracts, biopsy etc) [32-34]. Regardless of the cause, arteriovenous shunting or sumping results in a bypass conduit for therapeutic payload from the target capillary bed, into the systemic circulation. Under normal circumstances, if the therapeutic payload bypasses the hepatic vasculature and liver, particles may have the potential to collect within the next capillary bed within the circulatory system, which exists within the pulmonary parenchyma [32].

Although there is a high statistical probability some microspheres will pass to the lung parenchyma, clinical manifestations are rare and have been reported as result of excessive liver-to-lung shunting from large arteriovenous in the liver, exclusively in patient with HCC. The clinical manifestation of excessive radiation dose to the lungs, termed radiation pneumonitis include dry non-productive cough, progressive exertional dyspnea 1-6 months after therapy, chest radiography and CT demonstrating excessive patchy consolidation with sparing of the lateral edges of the lungs and fissures [35,36].

The reported incidence of fatal radiation pneumonitis in contemporary literature is rare and essentially comprises case reports. The largest population was described in 1995, and constitutes the largest study population to date. Fatal radiation induced pneumonitis was only reported in two cases (n=80), with both cases receiving greater than 30 Gy to the lungs based on a uniform distribution model, which has resulted in the general consensus that overall lung exposure must be less than 30 Gy to mitigate this potential fatal complication [35]. Pursuant to these data, the REBOC expert consensus panel on radio-embolization has reinforced the recommendation that based on current information, single session exposure to the lung should be calculated at less than 30 Gy based on partition model, and for all intents and purposes, this is become the standard radiation dose limit for the lung [3].

The actual deposition of microspheres [in clusters, or concentrated in specific vascular beds] may have a significant impact on micro-dosimetry and consequently on the local radiation dose however, cannot be modeled in a predictive fashion given current dosimetric methodologies [37]. To further support this position [and introduce further controversy], a recent publication directly addressing the incidence of radiation pneumonitis following radio-embolization determined that assuming uniform lung distribution, in a population of 58 patients receiving greater than 30 Gy exposure based on partition modeling, none of these patients developed clinically significant radiation pneumonitis, or imaging findings associated with radiation pneumonitis. 10 patients presented with pleural effusions, atelectasis, and ground glass attenuation as incidental findings without clinical manifestations. In this series the liver-to-lung shunt fraction ranged from 4.2% to 45% [mean lung shunt fraction 20%] [38].

As a result of these findings, it may be concluded that the commonly practiced reduction in prescribed activity due to the presence of nominally excessive liver-to-lung shunting (defined as >10%) should not be performed. Instead, a prescribed activity reduction should only be performed in those cases where the lung radiation exposure [assuming a uniform distribution] is greater than 30 Gy. Utilizing both body surface area [BSA] and partition models, situations may

arise where arbitrary prescribed activity reduction may still result in excessive radiation dose to lungs as a result of high body surface area [BSA], large liver as a result of tumor infiltration [partition], borderline pulmonary shunt perfusion, and possible pulmonary compromise [surgery, COPD, emphysema]. As a result, a more refined and safer methodology is a determination of exposure to the lungs based on standard partition methodology with an understanding of the inherent limitations of this method, with the assumption of uniform lung distribution. Utilizing this model as opposed to arbitrary prescribed activity reduction in cases of excessive liver-to-lung shunting, provides the additional safeguard of ensuring that [assuming uniform lung distribution] the pulmonary parenchyma does not receive an excessive radiation dose that is likely to result in lung pathology and clinical sequelae [3].

Liver parenchymal considerations

Underlying liver parenchyma as it relates to toxicities: Historically, utilizing conformal beam external beam radiation, the phenomena of radiation-induced liver disease (RILD) has been recognized in whole liver doses as low as 35Gy [39]. Given the well-defined phenomena of angiogenesis arising from hepatic arteries and directed towards tumors [40], selective hepatic arterial administration results in preferential deposition of radioactive microspheres into the dense microvascular plexus of the tumor, while minimizing the radioactivity deposited into normal liver parenchyma. Although technetium-99 macro-aggregated albumin [MAA] scans have been commonly accepted as surrogates for radioactive microsphere deposition, much controversy still exists regarding the correlation in biodistribution of the two types of particles [41,42]. Despite the limitations in determination of the true microdosimetry within the tumor due to the variations in vascularity, cumulative dose from ceramic microspheres have been reported as high as 482Gy administered over several sessions without significant toxicity as reported by Young et al. [43]. The long-term implications of such large radiation doses and their association with radiation-induced fibrosis and/or radiation-induced liver disease was not described in the analysis [43]. Recent studies investigating the use of ceramic microspheres in the setting of hepatocellular carcinoma have noted that increased risk of liver toxicities are observed during single administration of doses of greater than 150 Gy [44].

The long-term clinical sequelae of excessive parenchymal exposure to yttrium-90 microspheres is still unknown. Liver damage associated with radioembolization has been a poorly understood phenomenon with limited clinical data. As the presentation of RILD is rare, small retrospective data sets constitute the majority of experience. The largest and most detailed prosepctive series to date, reported by Sangro et al. [20] consisted of a population of 45 patients without evidence of previous chronic liver disease. Following an exhaustive analysis of pre- and post-treatment variables, and diagnosis with both primary and secondary tumors of the liver (in both chemotherapy-naive and chemotherapy-treated settings), classic presentations of RILD, (mimicking siniosodal obstruction syndrome and presenting within 60 days of treatment) were found more commonly in patients who had received previous chemotherapy, elevated pre-treatment bilirubin levels, and large radiation dose to normal liver but independent of receiving chemotherapy after radioembolization [20].

Cirrhosis

The complex interaction between the microvascular capacitance and the hypervascularity of a metastatic or primary neoplasm within the liver parenchyma ultimately dictates the ratio of microsphere deposition within the tumor and parenchyma compartments. Typically, the hypervascularity of the tumor far outweighs the "normovascularity" of the liver parenchyma, resulting in a preferential deposition of microparticles, and thus radioactivity, within the tumor itself. Factors that may result in a compromise of hepatic function secondary to inflammatory or post-inflammatory processes such as nonalcoholic steatohepatitis [NASH], chemotherapy-associated steatohepatitis [CASH], or viral hepatitis, and conditions resulting in fibrosis or compromise of hepatic function may lower the safe/acceptable threshold of radiation dose and embolic load of the underlying liver parenchyma.

As defined by Young et al. [43] if patients are stratified based on Okuda score, those patients with lower stage hepatic compromise may tolerate higher radiation doses without liver toxicities suggesting that the degree of cirrhosis, or liver compromise may affect the non-tumorous liver tissue's ability to recover from radiation insult [43]. Furthermore, investigation with ceramic microspheres in the treatment of hepatocellular carcinoma demonstrated prognostic factors associated with increased toxicities to be the following: treatment total bilirubin of greater than 3.0mg/dL, and associations of toxicity with higher single session liver dose [44].

A trend towards higher radiation dose administration [which may result in increased and excessive liver parenchymal exposure] has developed in clinical practice without evidence, or support. In previous publications, tumor response for hepatocellular carcinoma has suggested an improved survival in those patients receiving >120Gy exposure based on open laparotomy, and intra-arterial infusion with liquid scintillation counting of multiple liver biopsies in a population of 18 patients [45]. This initial publication had essentially provided the standard partition model dose that is commonly used in clinical practice. However, fundamentally limitations remain as to the understanding of tumor response utilizing low linear energy transfer (LET) sustained low-dose radiation therapy. To further this point of controversy, recent publications have described significant increases in radiation exposure which have been deemed acceptable in the order of 390 Gy during multiple sessions of administration. However, it is important to note that these publications have overlooked late-phase RILD and the long-term implications of SIRT, examining only the relationship between acute liver dysfunction, and amount of prescribed activity [43]. Furthermore, and just as important is the fact that current prescribed activity models [BSA, and traditional partition models] assume uniform distribution of particles within the compartment of implantation, which is fundamentally incorrect. Currently, the microvascular capacitance, or tumor to normal uptake ratio is not accounted for, likely resulting in excessive radiation deposition within the tumor itself [when utilizing the partition model]. Theoretically, with improved understanding of dose administration, predicted dosimetry as it pertains to tumor response will likely result in decreased overall radiation exposure to normal liver parenchyma, thus decreasing toxicities associated with patients presenting with compromised hepatic function. In spite of these limitations, currently, standard acceptable methodologies remain the partition modeling technique, and body surface area determined presribed activity as outlined by the REBOC consensus panel [3].

Contemporary strategies for mitigation of complete hepatic parenchymal collapse, manifesting as radiation-induced liver disease have included prescribed activity reductionin the setting of chronic inflammatory conditions, heavy pre-treatment with chemotherapy, or prior surgical resection resulting in a decreased functional liver volume, as well super-selective techniques [which serve to concentrate

Class	Complication/Toxicity	Incidence (%)	Reference	Management
Constitutional	Fatigue	28-52	22,69,71	Self Limiting Steroid
	Abdominal Pain/discomfort	16-19	22,69,71	Self Limiting Steroid Analgesics
	Nausea	6-13	22,71	Steroid Antiemetics
Hepatic/Tumor Vasculature	Gastritis	5	10	Analgesics Antiemetics Bismuth Motility Agent H2 blocker or Proton pump inhibitor Partial gastrectomy
	Cholecystitis	3 (1% requiring surgery), case reports	13-15	Observation Cholecystectomy
	Radiation Pneumonitis	0-6	35,38	High dose steroids
Hepatic Parenchyma	Biochemical Liver Toxicity: Grade III or higher (ALP, AST, ALT, bilirubin) (transient)	6-27	22,43,44	Self Limiting
	Radiation Induced Liver Disease (RILD) or failure	0-20	20,44,45,70	Diuretics High dose steroids Defibrotide Low-dose heparin Ursodeoxicolic acid Pentoxyfylline
	Portal Hypertension; Fibrosis	Case Reports	13,19,72	Observational TIPS
	Biloma/abscess	1	14	Observational Drainage
	Ascites	11 (advanced liver disease)	69	Drainage
	Encephalopathy	3 cases (more common after second treatment)	44	Lactulose Supportive
	Hemobilia	Single reported case	44	
Systemic Toxicities	Pancytopenia	Case Report (likely due to free Yttrium-90 unbound to microsphere)	73	Supportive

Tabe 1: Summary of commonly encountered toxicities, reported incidents, and potential management options.

the activity within visualized lesions as opposed to micro metastatic disease] such as sequential lobar administration, selective segmental administration, and high-dose segmental administration [viz. radiation segmentectomy technique]. The differences in specific toxicities and safety profiles between sequential lobar administration and whole liver adminstration have not been investigated but intuitively, preservation of liver parenchyma from exposure to radiation [based on both the stochastic, and deterministic models] should result in decreased parenchymal compromise. Current standards for the treatment of radiation-induced liver disease include diuretics for mild cases and sustained high-dose steroids and possibly defibrotide for more severe cases and associated veno-occlusive disease seen in the acute setting. Sangro et al. [45] also suggested preventive measures such as low-dose heparin, ursodeoxycolic acid, and pentoxyfylline for patients deemed to be at high risk. Nevertheless in remains that the long-term implications of post-SIRT fibrosis have not been fully investigated nor has an effective treatment strategy been instituted following profound sustained chronic radiation-induced liver injury [45].

Chemotherapy

As the energy associated with beta particle emission [electronic] is defined as low LET radiation, which is driven by free radicals [hydroxyl radicals], the biological damage results in the creation of the highly reactive molecules originates from unpaired valence electron propagation. Commonly referred to as indirect action, this type of biological damage is highly susceptible to chemotherapy sensitization, and as with any radioactive source, consideration of the synergistic effect must be made and incorporated into a prescribed activity plan and method of administration.

In the context of SIRT, the synergistic effects of free radical generation resulting in increased vulnerability to chemotehrapy, and by the same token radiosensitization, may result in injury to the normal liver parenchyma as a result of failure or compromise of repair mechanisms. It is well-established in the literature that specific classes of chemotherapeutics may act as potent radio sensitizers. Furthermore, many of these chemotherapeutics may have preferential metabolism to their active metabolites within the liver [46-53].

The phenomena of radiosensitization/chemosensitization have been used to advantage in earlier reported experience with SIRT in the treatment of liver-dominant metastatic colorectal carcinoma. SIRT in combination with concomitant hepatic arterial infusion of FUDR or systemic infusion of 5-fluorouracil has been reported, with the synergistic effects resulting in either statistically significant delay in time to progression [54] or improved overall survival [55]. In a small phase 2 randomized trial, single administration of radioembolic in addition to a regimen of systemic 5-fluorouracil/leucovorin chemotherapy resulted in increased time to disease progression as compared to 5-fluorouracil/leucovorin chemotherapy alone, and prolonged overall survival with acceptable toxicities [median survival of 29.4 months versus 12.8 months], with neutropenic sepsis developing in a single patient [n=21] [56]. Tolerances to multiple types of chemotherapies have been established for a number of different regimens. In a phase I dose escalation trial utilizing irinotecan, maximum tolerated dose was achieved without de-escalation, suggesting that full dose administration of irinotecan in patients who experienced relapse after previous chemotherapy can be well-tolerated for doses as high as 100 mg/m^2 with median survival in this population of 12.2 months and progression free survival of 6.0 months, experiencing self-limited abdominal pain and nausea, lethargy, and anorexia [57]. Similar acceptable toxicities have been demonstrated a phase III trial with first-line FUDR administration [55], as well as in a phase II trial in a heavily pretreated chemotherapy–refractory (i.e. salvage) population with concomitant protracted infusion of 5-fluoruracil [54].

The phenomenon of radiation recall [which can occur months to years after previous radiation exposure] has been an issue of concern regarding internal organ damage secondary to high-dose radiation [58-60]. Although this is been rarely observed, as per the conclusions of Sharma et al. [63] those patients undergoing first-line chemotherapeutic regimens utilizing a platinum-based therapeutic regimen may require a dose reduction in the initial cycles in order to minimize radio sensitization, which is thought to have accounted for the increased incidence of neutropenia in the study population. Like other platinum-based compounds used routinely in chemoradiation [cervix, head, neck, esophagus], the radiosensitization effects of

platinum based chemotherapies are well known in the context of external beam radiation, with toxicities presenting [primarily neutropenia] at doses of greater than 60 mg/m^2 [61,62]. Similar dose reductions have been recommended in patients receiving SIRT and platinum based therapies based on phase II first-line trials [63]. In summary, these chemotherapeutics may make the target organ [in the case of radioembolization, the liver] susceptible to radiation-induced liver failure [20].

However, prior chemotherapeutic exposure, external beam radiation, and other types of radiosensitization mechanisms have not been demonstrated conclusively to increase the incidence of radiation-induced liver disease [RILD]. Recently, two multi-center prospective clinical trials have reported the safety and efficacy of the use of SIRT in metastatic colorectal carcinoma patients who had been heavily pretreated with, and were refractory to, all standard chemotherapies and available contemporary biologic therapies. In both studies, the body surface area method was utilized to determine prescribed activity with resin microspheres in a single session whole liver administration, with no significant toxicities or manifestations of radiation-induced liver disease [54,64].

The use of radioembolization as monotherapy in the context of heavily pretreated patients with systemic or biologic therapies although demonstrating safety, should be performed with an understanding of potential compromise of hepatic reserve secondary to conditions such as chemotherapy associated steatohepatitis, (CASH) [65], chemotherapy associated siniosoidal obstructive syndrome (SOS) [66], prior liver resection, or potentially vascular endothelial growth factor inhibitors (anti-VEGF agents) [67]. In general, prescribed activity reductions by as much as 25% have been recomended in those patients who have been potentially compromised liver parenchyma however no currently accepted guidelines, or consensus has been reached on this issue.

Constitutional symptoms

Self-limiting clinical toxicities/constitutional symptoms are also noted, and inherent to SIRT therapy. Approximately 20 to 50% of the population has described CTC SAE v3.0 grade fatigue that is self-limiting, beginning approximately 48 hours after implantation, lasting up to one week [68,69]. Symptoms can be controlled through low-dose steroid administration [in non-diabetics], which may also treat mild nausea and anorexia [57].

Nausea and vomiting [grade 3 or greater] have been reported in as many as 20% of patients undergoing radio-embolization [55,70]. Management with a low-dose steroid or standard antiemetic therapy may control the symptoms, which typically resolve within 1 to 2 weeks treatment. Mild abdominal pain is commonly reported.

Late onset of nausea, vomiting, hematemesis, anorexia, or bloody diarrhea may indicate potential gastrointestinal ulceration secondary to non-target delivery into the gastrointestinal musoca. If symptoms present in a delayed fashion, further investigation may be warranted through endoscopy, or cross-sectional imaging [including the arterial phase] to identify mucosal bleeding, inflammation, or perforation. Table 1 provides a summary of commonly encountered toxicities.

Summary

Toxicities as related to radio-embolization can be divided into two broad categories: complications resulting from non-target embolization due to reflux/aberrant vascular anatomy [resulting in damaged organs in the mesenteric vasculature] and arteriovenous shunting [resulting in radiation induced pneumonitis], and compromise of hepatic function secondary to liver parenchymal injury [resulting in radiation-induced liver disease, or acute hepatic dysfunction].

As a result of these unique and severe complications, optimization of the intra-arterial implantation of yttrium-90 microspheres is obtained through adequate review of patient history [liver function, lung function, chemotherapy exposure, computed tomography angiography], detailed interrogation and optimization of the mesenteric anatomy [through highly detailed angiograms, super-selective catheterizations, and appropriate redistribution/embolization strategies], and adequate assessment of technetium-99 MAA intra-arterial injection to determine pulmonary shunt fraction to allow for determination of partition model-based radiation dose to the lung mass. However, inevitably post radio-embolization syndrome [presenting as fatigue, abdominal pain, and elevation in liver transaminase levels] is common and self-limiting. Differentiation between self-limiting and transient clinical toxicities and those that may require more aggressive therapy and/or intervention is an essential component of this treatment paradigm (Table 1). Anatomical variations, and unintentional reflux of microparticles still represent the majority of complications and present as an inflammatory process relating to the end organ [gastric, duodenal, pancreatic, pulmonary,cholecystic] implantation.

The underlying liver parenchyma also warrants equal consideration, as this appears to be a significant factor in the presentation of RILD. Compromised hepatic function appears to be the key factor and as a result RILD may manifest at lower radiation exposure levels as a result of pre-existing chronic inflammation or hepatic compromise. Dose reduction strategies should be implemented to minimize the potential for irreversible damage to the liver in this setting however, this realm remains an area of active research and no definitive guidance has been elucidated, thus creating further challenges in the determination of appropriate prescribed activities of yttrium-90 microspheres.

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