Systemic Therapy, Radiotherapy, and Cardiotoxicity

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Introduction

Malignant cardiac tumors are usually sarcomas or Non-Hodgkin Lymphomas (NHL). The treatment of NHL is based on chemotherapy (CT), and surgery is commonly used as a rescue therapy to treat severe hemodynamic impairment by a large mass. CT is often effective over a short period of time in NHL (Figs. 12.1 and 12.2) and is the first choice treatment approach. The cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen has been the mainstay of therapy for several decades, and the addition, in recent years, of Rituximab (R, a monoclonal antibody) has increased its efficacy without affecting toxicity; therefore, R-CHOP is the most commonly used first-line therapy even in elderly patients, usually as many as 6–8 cycles are given [1, 2]. In non-responders or relapsing patients, high-dose therapy followed by autologous stem cell transplantation may be considered. Several standard high-dose regimens may be used: ifosphamide, carboplatin, etoposide (ICE), the same plus Taxol (TICE), etoposide, methyl prednisolone, high-dose cytarabine, cisplatin (ESHAP), dexamethasone, cisplatin, cytarabine (DHAP), and dexamethasone, cisplatin, gemcitabine (GDP) [1].

Although more frequent than primary lymphomas, cardiac sarcomas are very rare and most of the published experiences consist of case reports or small patient series. Also large institutions usually see roughly one patient/year or less (a few major referral centers may see up to 3–5 patients/year), which makes it impossible to plan randomized studies to assess the best treatment approach [3–7]. Cardiac sarcomas are a small subgroup of the more frequent (albeit rather rare) sarcomas of other sites (they represent roughly 1/100 of all sarcomas), and in most cases they pertain to the soft tissue sarcomas (STS) group. Therefore, the basic therapeutic approach should be based on extrapolation of data from the most frequent tumor sites, including STS of the extremities and trunk [4, 7–9].

Nevertheless, this approach may also be affected by some of the peculiar characteristics of cardiac compared to noncardiac sarcomas. Cardiac sarcomas tend to be high grade, angio- or leiomyosarcoma in histological subtype, and they usually have a propensity to occur at a younger age [8–10]. In addition, cardiac sarcomas are often metastatic at presentation and complete

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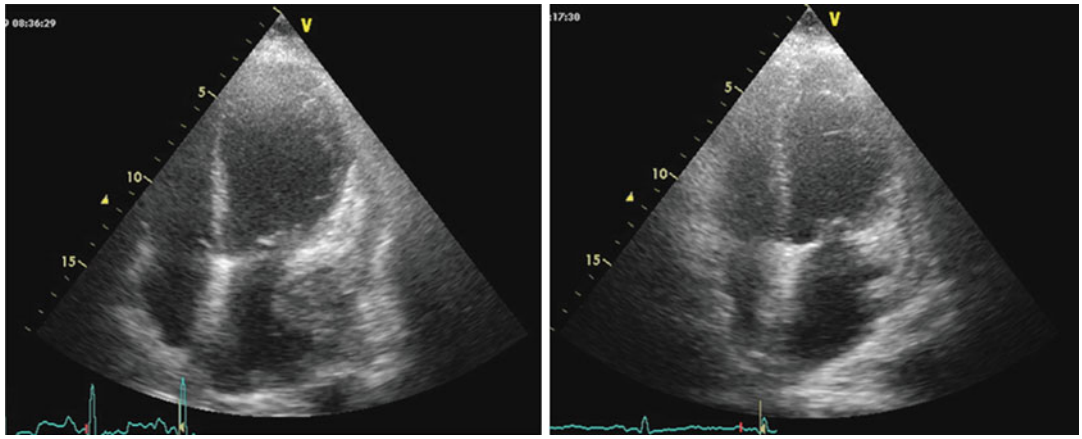

Fig. 12.1 Two-dimensional echocardiograms (apical four-chamber view) in a primary Non-Hodgkin lymphoma of the left atrium. (**a**) At diagnosis; (**b**) after two courses of R-CHOP chemotherapy (see text for acronym)

resection with negative margins is achieved in 20–45% of cases only [5, 7, 8, 11, 12]. For all these reasons, cardiac sarcomas are at higher risk of local or distant recurrence and they have a worse prognosis compared to STS of other more frequent anatomical sites, including extremities, superficial trunk, retroperitoneum, and head and neck [9].

The standard treatment for localized STS consists of adequate surgery with "wide" resection (i.e., with at least 1 cm of normal tissue around the tumor) followed by postoperative radiation therapy (RT) in most cases. Preoperative RT may be an option for large tumors or more critical tumor sites when adequate surgery with negative margins cannot be achieved [13, 14]. The role of adjuvant CT has not been yet defined so far, but clinical practice guidelines encompass it as an option in high-risk patients [14, 15].

The particular location of cardiac sarcomas makes both surgery with curative intent and the use of RT particularly challenging. While CT is mandatory in metastatic and/or locally advanced, unresectable disease, its use has been proposed for some critical locations, such as right heart/pulmonary artery sarcomas, in an attempt to increase the number of resections with negative margins [11, 16]. Therefore, a multimodality approach, including CT and/or RT before or after surgery, has been used by several authors even for localized, non-metastatic tumors, and it seems to be effective in prolonging both time to relapse and survival in some selected studies (Table 12.1). The outcome data reported in different papers are conflicting mainly for three reasons. There is a wide variety of tumor presentations (metastatic vs. non-metastatic, high-grade vs. low or intermediate grade, right vs. left heart, surgery limited to the heart or including the lung), there is no standardized surgical approach, and finally, in most studies, the multimodality therapy is limited to patients with incomplete resection or metastatic disease [11, 17–29]. Overall, when comparing studies with a multimodality approach, regardless of the surgical outcome, and historical studies with CT used in some subgroups of patients only, there seems to be a favorable trend for the multimodality approach (Fig. 12.3) [25, 29].

Systemic Therapy: Chemotherapy and Target Therapy (Table 12.2)

The "classic" and most commonly used CT regimens for soft tissue sarcomas are based on a combination of anthracyclines (ANTHRA) and ifosfamide (IFO). However, more than 50 distinct histological subtypes of sarcoma have been identified to date. Data are now available on the activity of some specific chemotherapeutic agents for some selected histological subtypes.

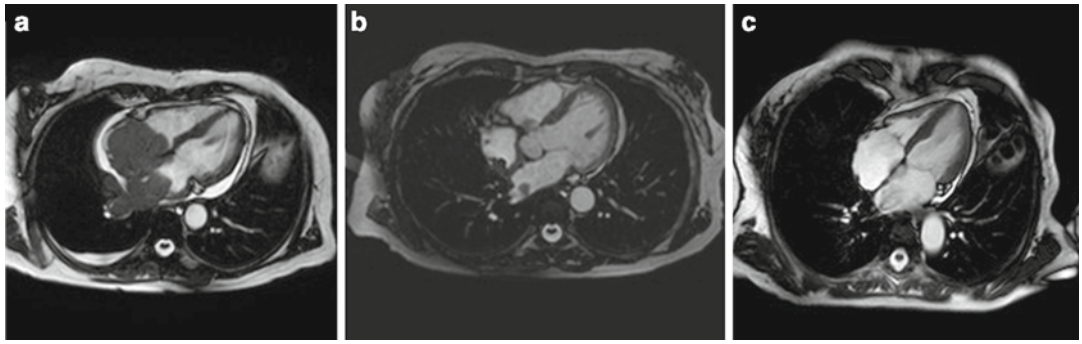

Fig. 12.2 Magnetic resonance imaging in a case of Non-Hodgkin lymphoma. (**a**) At diagnosis the mass occupies both atria, extending to pulmonary veins. (**b**) After three courses of R-CHOP chemotherapy there is a small residual mass within the left atrium. (**c**) At last follow-up after 2 years there is complete remission (see text for acronym). Courtesy of Dr. Sara Calamelli, General Hospital of Mirano (VE), Italy

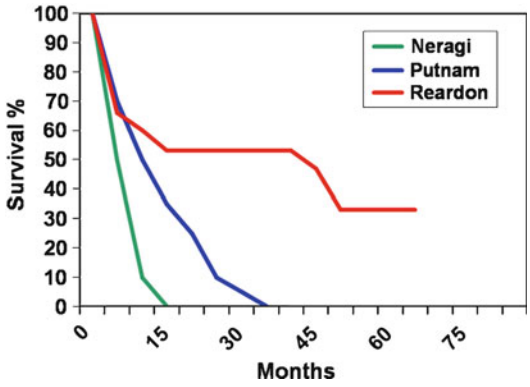

Fig. 12.3 Overall survival of patients treated with different approaches: literature cases of non-resected cases (Neragi), resected cases with or without chemotherapy (Putnam), multimodality treatment of left heart tumors with cardiac autotransplantation, and adjuvant chemotherapy (Reardon). Courtesy of Prof. Michael J. Reardon, Methodist DeBakey Heart and Vascular Center, Houston, TX, USA

This should allow, in the near future, a histology-driven CT approach for a better tailored treatment, including also cardiac sarcomas [30–33]. In addition, in the past 10 years, the increased understanding of surface receptors expression and activity as well as of the molecular pathogenesis of various tumors has led to the development of the so-called target therapy. Target therapy has significantly changed the treatment of some of these tumors such as gastrointestinal stromal tumors (GIST), dermatofibrosarcoma protuberans, and aggressive fibromatosis.

Angiogenesis, i.e., the formation of new blood vessels, is integral to the growth and metastasis of many malignancies, including STS, and it has been suggested that the balance between factors promoting the endothelial proliferation and vasal formation and factors inhibiting these processes are responsible for tumor progression [34]. Thus, a therapy affecting the creation, growth, and survival of new vessels (anti-angiogenic and/or angiotoxic) has the rationale to be effective in some tumors. The anti-angiogenic drugs showed different mechanisms of action; some may inhibit selectively a single angiogenic protein, whereas others may inhibit two, three, or a wide range of angiogenic proteins involved in endothelial proliferation and in microvascular sprouts. The drugs currently used or under evaluation in clinical trials for STS (and considered as possible options for cardiac sarcomas) are Bevacizumab, Sunitinib, Sorafenib, Dasatinib, Pazopanib, Thalidomide, and Paclitaxel [34, 35]. The successful administration of anti-angiogenic factors observed in small trials enrolling a variety of sarcomas may indicate a potential role in the treatment of highly vascular-nature cancers as heart angiosarcoma, which is the most frequent cardiac sarcoma. Anti-angiogenic therapy has some peculiar aspects compared to "classic" therapies. First, cytotoxic CT is often administered at the maximum tolerated dose with a long off-therapy interval; anti-angiogenic therapy requires endothelial cell exposure to steady blood levels of the inhibitor and anti-angiogenic

Table 12.1 Mean and median survival of patients with primary malignant tumors of the heart; literature data

Author (reference)	Years of recruitment	Year of publication	Institution	No. of patients	Treatment	Median survival (months)	Mean survival (months)	Notes
Putnam [17]	1964–1989	1991	MD Anderson	21	All treatments	11	15	
				5	Surgery	12	17	One alive
				6	Surgery + CT	17	18	One alive
				8	CT only +/– debulking	10		
Burke [18]	ND	1992	Armed Force Institute of Pathology	40	All treatments	6	11	30 complete, 10 incomplete resection; 7 perioperative deaths
				12	Surgery	3	7	
				21	Surgery + CT/RT	12	19	
Llombart-Cussac [3]	1978–1995	1998	Gustave Roussy	19	All treatments	11		
				6	Complete resection + CT	23		
				9	Incomplete resection + CT	7		
				4	CT only	5		
Centofanti [20]	1980–1997	1999	University of Turin	5	Wide resection	9	13	
Donsbeck [19]	1968–1996	1999	Multicenter	24	All treatments		16	
				8	Complete resection + CT/RT		NS	
				15	Incomplete resection/ biopsy + CT/RT	NS		
				1	No therapy			
Huo [22]	1990–2004	2006		12	All treatments	19		All pulmonary artery
				4	Surgery	9		2 alive, 1 lost to follow-up
				8	Surgery + CT/RT	21		4 alive, 2 lost to follow-up
Mayer [8]	1993–2006	2007	South West German Cancer Center	14	All treatments	15		
				6	Complete resection ± CT	15		
				4	Palliative resection + CT	15		
				4	CT only	15		
Thomas-de-Mont-preville [24]	1986–2005	2007	Marie Lannelongue, Paris	8	All treatments	26	17	
				2	Complete resection	34	34	Both intermediate grade
				4	Resection + CT	18	17	All high grade
				2	Biopsy only	ND		

(continued)

Table 12.1 (continued)

Author (reference)	Years of recruitment	Year of publication	Institution	No. of patients	Treatment	Median survival (months)	Mean survival (months)	Notes
Simpson [5]	1975–2007	2008	Mayo Clinic	34	All treatments	12		
				15	Complete resection±CT/RT	15		
				8	Incomplete resection + CT	6		
				11	CT only or nothing	5		
Kim CH [6]	1994–2006	2008	Cornell University	24	All treatments	18		
				5	Complete resection	10		1 alive
				19	Incomplete resection + CT	25		4 alive
Kim HK [25]	1999–2007	2008	Samsung Medical Center	9	All treatments	19	19	All pulmonary artery, pneumonectomy
				4	Radical surgery	13	13	2 alive
				5	Radical surgery + CT/RT	22	25	1 alive
Zhang [10]	1975–2006	2008	Multicenter	27				4 postoperative deaths, 10 lost to follow-up
				3	Surgery	54	54	2 alive, NED
				3	Heart transplantation	27	39	All alive, NED
				7	Surgery + CT/RT	29	39	5 alive, 3 NED
Blackmon [29]	1998–2008	2008	Methodist DeBakey Heart Center	18	All treatments	29	28	All left heart; autotransplantation
				2	Surgery	3	3	
				16	Surgery + CT/RT	29	28	
Blackmon [26]	1999–2006	2009	Methodist DeBakey Heart Center	8	Complete resection + CT/RT	24		All pulmonary artery; 5 alive
Truong [7]	1990–2006	2009	British Columbia Cancer Agency	16	All treatments	8	14	
				10	Complete resection ± CT/RT		25	
				6	Incomplete resection/distant disease + CT/RT		6	
Hamidi [9]	1998–2005	2010	Multicenter	210	All treatments	6		Missing subgroup data
				125	With surgery	12		
				81	Without surgery	1		
				50	RT	11		
				159	No RT	4		

CT chemotherapy, *RT* radiotherapy, *ND* not determined, *NED* no evidence of disease

Table 12.2 Systemic schedules most frequently administered in cardiac sarcomas

	Epirubicin	*Ifosfamide*	
Dosage	60 mg/m²/die	1,8 g/m²/die	
Frequency	Days 1–2	Days 1–5	q3 weeks
Dosage	60 mg/m²/die	3 g/m²/die	
Frequency	Days 1–2	Days 1–3	q3 weeks
	Doxorubicin	*Ifosfamide*	
Dosage	50 mg/m²	5 g/m²	
Frequency	Day 1	Day 1	q3 weeks
Dosage	25 mg/m²/die continuous infusion	2 g/m²/die	
Frequency	Days 1–3	Days 1–5	q3 weeks
Dosage	30 mg/m²	3 g/m²	
Frequency	Day 1	Days 1–3	q3 weeks
	Dose intensive chemotherapy		
Dosage	75 mg/m² 72 h infusion	2 g/m²/day	
Frequency	Days 1–3	Day 1–5	q3 weeks
Dosage	90 mg/m² 72 h infusion	2.5 g/m²/day	
Frequency	Days 1–3	Days 1–4	q3 weeks
	Pegylated liposomal doxorubicin		
Dosage	20 mg/m²		
Frequency	Days 1, 15		q4 weeks
Dosage	30 mg/m²		
Frequency	Day 1		q3 weeks
	Paclitaxel		
Dosage	80 mg/m²		
Frequency	Days 1, 8, 15		q4 weeks
	Gemcitabine		
Dosage	1,000 mg/m²/die		
Frequency	Days 1, 8, 15		q4 weeks
	Gemcitabine	*Docetaxel*	
Dosage	900 mg/m²	100 mg/m²	
Frequency	Days 1, 8	Day 8	q3 weeks
Dosage	675 mg/m²	75 mg/m²	
Frequency	Days 1, 8	Day 8	q3 weeks
	Experimental drugs		
	Sorafenib		
Dosage	400 mg oral twice per day		
Frequency	Continuously		
	Imatinib		
Dosage	600 mg/die per os		
Frequency	Continuously		
	Bevacizumab		
Dosage	15 mg/kg		
Frequency	Day 1		q3 weeks

agents with a short half-life might need to be dosed daily and without any breaks [35]. Secondly, anti-angiogenic agents tend to have a biphasic, U-shaped dose–efficacy curve where blood levels that are too low or too high may be ineffective in the inhibition of angiogenesis; therefore, more is not necessarily better when it comes to anti-angiogenesis [33].

Anthracyclines and Ifosfamide

With the commonly employed first-line CT of STS, an objective response rate of 45%, including 10% of complete response and a median survival of 15 months, has been obtained [36, 37]. Accordingly, the standard systemic approach to patients with advanced/unresectable sarcomas of the heart and great vessels or to those who have progressed from earlier stages remains to be the chemotherapeutic ANTHRA-based regimen [33, 38].

Doxorubicin (DOX)-based CTs (DOX 50 mg/m^2/die on day 1 and IFO g/m^2/die on day 1 or DOX 25 mg/m^2/die on days 1, 2, and 3 and IFO 2 g/m^2/die per day on days 1–5) or epidoxorubicin (epiDOX)-based regimens (epiDOX 60 mg/m^2/die on days 1 and 2 and IFO 3 g/m^2/die on days 1–3) are now the conventional first-line treatments [39–41]. A Cochrane review showed that combination regimens, compared with single-agent DOX, achieved only marginal increases in response rates at the expense of increased toxic effects and with no improvements in overall survival [42]. Moreover, it should be emphasized that most of the CT agents used in cancer management have demonstrated a dose–response relationship. For DOX, in a randomized dose–response study the response rate was twice as high at the dose of 75 mg/m^2 as compared with 45 mg/m^2 [43]. Since response rate increases at higher doses, the increase of dose intensity may be an important strategy to favor the response rate and reduce the relapse rate. For IFO, the data are weaker, even if an higher response rate at higher doses has been reported [44]. In young patients with optimal performance status may be more useful to administer high doses of DOX (90 mg/m^2) and IFO (10 g/m^2) preceded by granulocytic growth factors and cardioprotective agents [45]. The pegylated liposomal form of DOX accumulates preferentially in tissues with increased microvascular permeability, such as the case of most tumors with active neoangiogenesis [46]. The first clinical studies with pegylated liposomal DOX in the treatment of extracardiac sarcomas have shown variable results in response rates with improved toxicity profile and at least equivalent activity in comparison to DOX [47–49]. Furthermore, pegylated liposomal ANTHRA have also produced satisfactory results in the treatment of angiosarcoma and lymphangiosarcoma [50, 51].

Taxanes

Paclitaxel and Docetaxel are natural alkaloids active for several tumor types from ovarian to breast and lung cancers. They act as cytotoxic drugs by inhibiting microtubular assembly. Paclitaxel has also anti-angiogenesis effects by inhibiting endothelial motility and proliferation as well as invasiveness [34, 52]. Many different anticancer drug combinations, including gemcitabine and docetaxel, have been demonstrated to have greater activity than gemcitabine alone [30, 53, 54]. Gemcitabine is given on days 1 and 8 at 900 mg/m^2 over 90 min and docetaxel at 100 mg/m^2 over 60 min. Typically the most sensitive histological type to the combination of gemcitabine and docetaxel in the salvage setting is fibrohistiocytic sarcoma (or malignant fibrous histiocytoma) [33]. Weekly paclitaxel has been shown to carry out an important role in the treatment of patients with heart angiosarcoma [55]. In a retrospective study enrolling 32 patients with pretreated angiosarcomas, 3 out of 5 patients with heart angiosarcoma showed stable disease or response to paclitaxel [56]. Not surprisingly, the weekly paclitaxel schedule (80 mg/m^2/die) is linked to diverse activities, from anti-angiogenesis to pro-apoptotic effects. In a series of in vitro and in vivo experiments it has been observed that low-dose schedules of paclitaxel were significantly capable of causing an inhibition in endothelial cell proliferation, motility, and invasiveness [52, 57, 58]. There is abundant evidence, therefore, that the weekly paclitaxel possesses different mechanisms of action compared with triweekly paclitaxel. However, the activity of taxanes is higher in scalp angiosarcoma than in primary angiosarcomas of other sites and ineffective for other histological subtypes of STS [59].

Target Therapy (Bevacizumab, Tyrosine Kinase Inhibitors)

Bevacizumab (Avastin®) is a humanized monoclonal antibody which neutralizes all isoforms of vascular endothelial growth factor (VEGF) and it is approved for the treatment of metastatic colorectal cancer, metastatic non-squamous non-small-cell lung cancer, metastatic breast cancer, recurrent glioblastoma multiforme, and metastatic renal cell carcinoma. Though the inhibition of tumor angiogenesis was originally thought to simply aggravate hypoxia, VEGF inhibition has also been shown to induce so-called *vascular normalization*, a restoration of normal structure, function, and flow to the disorganized vessels characteristic of malignant tumors, allowing an improvement of the delivery of oxygen, nutrients, and cytotoxic CT to the tumor. Bevacizumab has been shown to have a limited antitumoral activity as monotherapy; therefore it has been combined with cytotoxic or cytokine therapy. Data about the use of bevacizumab combined with DOX in STS are limited, and this approach deserves further investigation [34]. Some patients with cancer are or become refractory to VEGF-inhibitor treatment; a mechanism of acquired resistance is the increased reliance on alternative pro-angiogenetic factors that do not use the VEGF pathway. VEGF blockade inhibits sprouting angiogenesis, but may not be as efficient in suppressing other modes of tumor vascularization. Therefore, inhibitors of several pathways implicated in tumor growth angiogenesis and metastasis may offer advantages over inhibition of a single pathway. Sunitinib inhibits the tyrosine kinase receptors (RTKs) VEGFR1-3, platelet-derived growth factor receptor alpha (PDGFR-α), platelet-derived growth factor receptor beta (PDGFR-β), FMS-like tyrosine kinase 3 (FLT-3), c-KIT receptor, RET, and colony-stimulating factor receptor type 1, some of which have been implicated in tumor growth angiogenesis and metastasis. There is no clear evidence on utility and efficacy of this agent in the treatment of heart sarcomas since the available data come from anecdotal case reports and no prospective randomized trials have been conducted. On the other hand, it is also possible that sunitinib efficacy may be underestimated when local evaluation of anatomic response is performed using changes in tumor size according to RECIST criteria [60]. Sorafenib inhibits the RTKs VEGFR1-3, FLT-3, c-KIT, PDGFR-β, and p38 tyrosine kinases, which block the VEGF- and PDGF-dependent angiogenesis. In a phase II trial that evaluated the activity of sorafenib in patients with metastatic sarcoma, five of 37 patients with angiosarcoma had a partial response (response rate 14%); in this subgroup median progression-free survival was 3.8 months whereas median overall survival was 14.9 months. Therefore this study provides important information on the relative activity and safety profile of this drug used in this setting of patients [61], demonstrating that sorafenib has activity against angiosarcoma and minimal activity against other sarcomas. In a nother study imatinib (600 mg/die) used in patients with advanced or metastatic angiosarcoma attained a response rate about 12% whereas the non-progression rate was only 20% at 3 months [62]. Other angiogenic regulators as endostatin and caplostatin could carry out, in the future, an important role in the treatment of heart sarcomas [33, 63]. In conclusion, at the present, the recommended first-line regimen in cardiac sarcomas remains to be the ANTHRA/IFO; taxanes and/or gemcitabine have demonstrated a good activity, are used in the metastatic setting, and may be considered as first line for angiosarcomas (Figs. 12.4 and 12.5). New targeted drugs are under evaluation and may be used in relapsing or refractory tumors. An interesting new field of research in target therapy is focused on cancer stem cell characterization and on the proteomics approach, but it is still far from clinical application [64].

Radiation Therapy

Historically, RT has played a minor role in the management of patients with cardiac sarcomas primarily because of the low tolerance of the whole heart to RT and the challenge associated

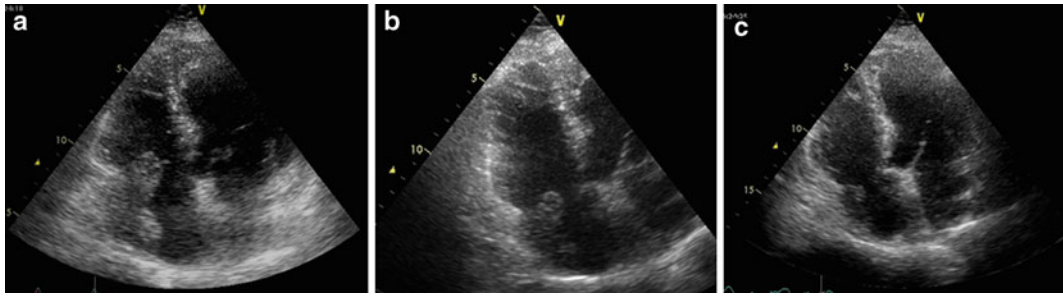

Fig. 12.4 Transthoracic two-dimensional echocardiogram (apical four-chamber view) in a case of angiosarcoma. (**a**) At diagnosis a large mass infiltrates the right atrial and right ventricular walls and prolapses through the tricuspid orifice. (**b**) After three courses of Taxol chemotherapy the mass is reduced in size. (**c**) After IMRT-Tomotherapy the mass is further reduced in size. At this time the patient underwent complete resection (see text for acronym)

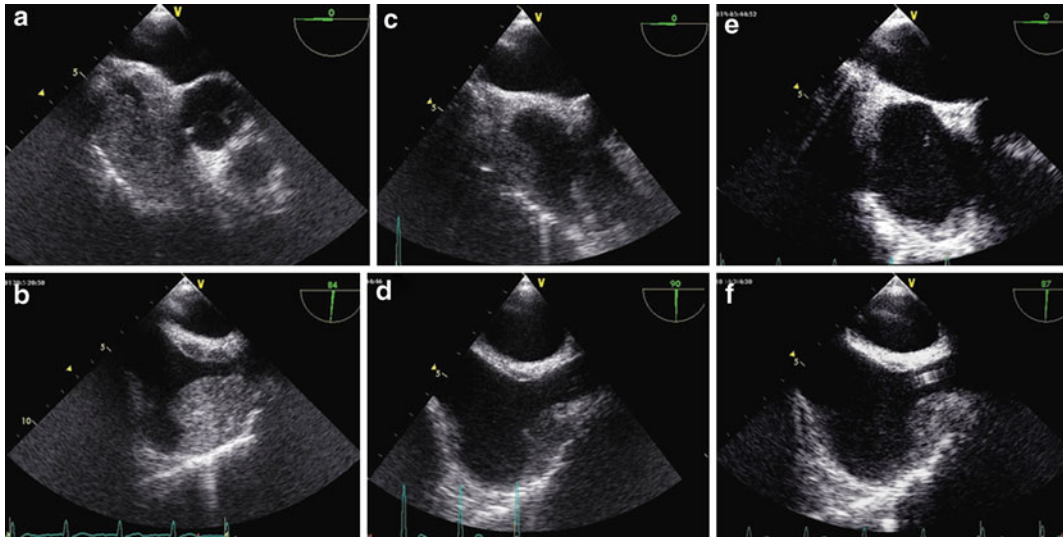

Fig. 12.5 Transesophageal echocardiogram in a case of right atrium angiosarcoma. Top horizontal plane, bottom sagittal plane. (**a**) At diagnosis a mass infiltrates extensively the right atrial walls, roof, and interatrial septum and is judged unresectable. (**b**) After chemotherapy with IFO plus liposomal DOX the mass is markedly reduced in size. (**c**) After tomotherapy the mass is further reduced in size; the interatrial septum is no more infiltrated. The patient underwent then successful removal of the whole residual mass (see text for acronyms)

with delivering highly conformal RT to the cardiac tumor, or tumor bed after resection, while sparing the non-tumor-bearing surrounding heart tissue. Although a clear correlation of dose-volume predictors for acute and late radiation-induced heart disease (RIHD) has not yet been defined, a risk >5% of RIHD after whole-heart RT of 30–35 Gy given over 4 weeks is reported [65]. Such dose of 30–35 Gy is lower than the dose required to eradicate the tumor.

Advancements that allow the safe delivery of higher dose RT to cardiac tumors include advanced imaging to improve tumor definition, 3-dimensional radiation (3D-CRT) planning techniques to deliver high dose which conform tightly to the tumor, image-guided RT (IGRT) to localize the tumor at the time of treatment, organ motion evaluation for appropriated planned target-volume definition, and improved knowledge of the partial volume tolerance of the heart

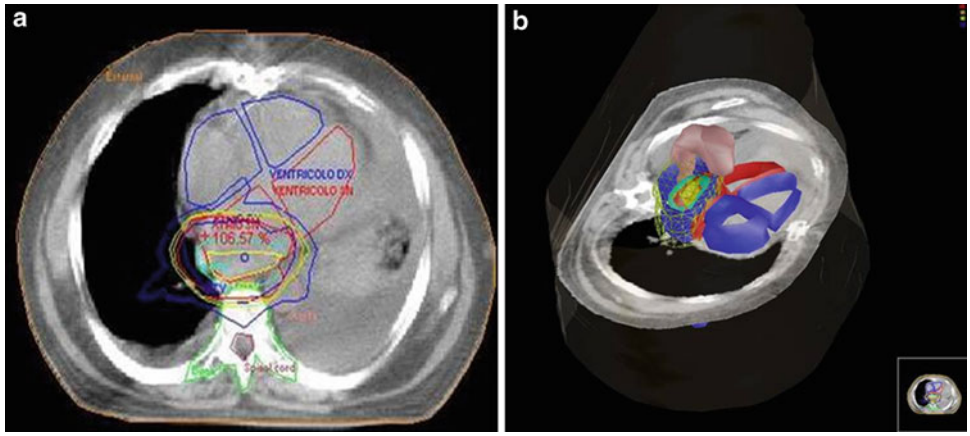

Fig. 12.6 Radiotherapy plan of 3D conformal radiotherapy for a left atrial sarcoma infiltrating the interatrial septum, atrial roof, lateral and posterior free wall, and posterior mitral annulus. (**a**) 2D plan, aiming to give 45 Gy in 25 fractions to include all the left atrium and the involved structures with organ motion margins (sparing uninvolved heart), and higher dose up to 59.4 Gy limited to the residual tumor mass. (**b**) 3D reconstruction

to radiation [66–69]. With such technological advances, it has been possible to deliver a higher dose to cardiac tumors than was previously possible with a low risk of complications. An example of a 3D-CRT plan for a patient with left atrial sarcoma is reported in Fig. 12.6.

Intensity-modulated RT (IMRT) is another technological advancement that facilitates the delivery of highly conformal RT. With IMRT, radiation is delivered with multiple small fields ("segments") within each beam, producing a modulated fluence pattern for each beam angle. Computer-aided, automated optimization of segments weights (or "inverse planning") is conducted to obtain to the best target coverage and sparing of dose to normal tissues. Clinical experience with IMRT for the treatment of cardiac sarcomas is limited. However, planning study comparison between IMRT and 3D-CRT suggests that IMRT may have a potential benefit for some patients with cardiac sarcomas [70]. The Tomotherapy system, a technological facility, is a dedicated IMRT linear accelerator that integrates IMRT by means of dynamic rotational therapy (helical tomotherapy) and IGRT by means of megavolt computerized tomography (MVCT) allowing an optimal, evaluated, and optimized target-volume dose distribution, and a daily accurate patient positioning [69]. An example of a IMRT-IGRT tomotherapy plan for a patient with right atrial sarcoma is reported in Fig. 12.7. With 3D-CRT or, more recently, by IMRT-IGRT Tomotherapy, it is possible to give RT dose as high as 45–59.4 Gy/25–33 fractions, over 5–6 weeks in patients with unresectable or partially resected cardiac sarcomas, as recently reported by our group [70]. Echocardiography examination was used in the treatment planning for organ motion evaluation and margin target-volume definition. Individualized dose constraints to left and right ventricle were included (Fig. 12.7). Two patients with unresectable tumor at presentation had major response to CT-RT and underwent a successful complete surgical resection. At a median follow-up of 22 months (range 3–84 months), nine patients were alive and six of them free of disease. In our experience, RT for cardiac sarcomas demonstrated a feasible approach, also when combined with CT and surgery. These results confirm previous published experiences in selected series of patients (Table 12.1). Technological advances in RT planning and delivery and further insight into RT cardiac tolerance appeared crucial in minimizing the risk of RIHD. Further experience is needed to confirm these encouraging results and to attempt a multidisciplinary approach with curative intent also in these unfavorable sarcomas.

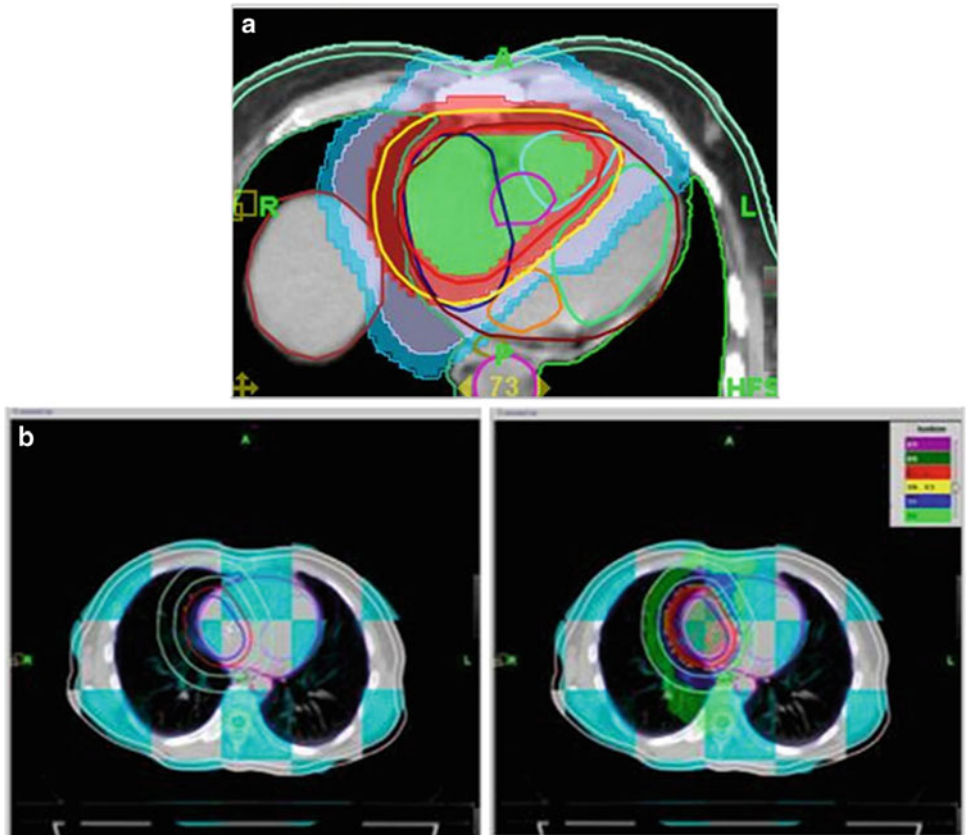

Fig. 12.7 Radiotherapy plan of preoperative IMRT-IGRT tomotherapy for a tumor involving the right atrium (roof, lateral free wall, tricuspid annulus). This patient had unresectable angiosarcoma and was treated with 45 Gy with a highly conformal plan with IMRT to include all the atrium with organ motion margins and a simultaneous dose escalation up to 54 Gy in 25 fractions limited to the tumor (equivalent to 60 Gy in 2 Gy fraction). Uninvolved heart was optimally spared (see text for acronyms). (**a**) Radiation planning before treatment. (**b**) Planning and treatment computed tomography fusion before each radiation fraction

Cardiotoxicity

Anthracyclines

Cardiotoxicity has been known as one of the most important and limiting side effects of DOX and other ANTHRA for decades. The exact pathophysiology has been debated for a long time, and is probably due to a complex interaction of several factors: iron-mediated formation of Reactive Oxygen Species (ROS), membrane lipid peroxidation, inhibition of nucleic acids and protein synthesis, altered calcium homeostasis, mitochondrial disruption, apoptotic response, formation of toxic alcoholic metabolites (DOXOL), and alterations of the cardiac-specific gene expression. The final myocyte damage is then both iron-dependent and iron-independent [71–73]. Ultrastructural early alteration in damaged myocytes consists of distension of sarcoplasmic reticulum to form sarcoplasmic vacuoles, followed by myofibrillar lysis and focal proliferation of sarcoplasmic reticulum, disruption of myofibrils, atrophy, and necrosis; interstitial edema and eventually fibrosis are observed in more severe forms; myocardial damage has been reported to be most severe in the left ventricle (LV) and in the ventricular septum, intermediate in the right ventricle and the left atrium, and least in the right atrium [74]. Each single dose of DOX causes an irreversible cardiac damage; for this reason the cardiotoxicity is cumulative, even for CT given many years apart. The final effect is

diastolic and systolic left ventricular dysfunction and, in the most advanced stages, congestive heart failure (CHF). In an attempt to reduce cardiotoxicity, several DOX analogues have been developed: EpiDOX, Idarubicin (orally available), Mitoxantrone, and—more recently—liposomal DOX formulations. The incidence of both asymptomatic and symptomatic cardiac dysfunction depends mostly on the cumulative dose: CHF is rather low (around 5%) up to a total dose of 400 mg/sm of DOX and then increases exponentially (raising to 26% at a dose of 550 mg/m^2 and to 40% above 700 mg/m^2), and asymptomatic LV dysfunction is observed in 9% at a cumulative dosage of 250 mg/sm, and 65% above 550 mg/m^2 [75]. Several risk factors have been indentified for ANTHRA cardiotoxicity: age <18 and >60 years, preexisting cardiac disease (ischemic, hypertensive) and/or LV dysfunction, concomitant RT involving the heart, and high concentration of the single dose [75, 76]. Of particular concern is the delayed onset of cardiotoxicity in long-term cancer survivors; recent studies have demonstrated that the alcoholic metabolites (like DOXOL and EpiDOXOL) are retained within the myocardial cell much longer than the parent drug, and may represent a lifelong toxic reservoir inducing a heart frailty when exposed to other stressors and that these toxic metabolites increase when DOX is administered together with taxanes [71, 77]. A number of strategies have been explored to prevent or reduce ANTHRA cardiotoxicity: changes in infusion schedules; association of antioxidants (vitamin E, selenium, and so on), calcium-channel blockers, iron-chelators (as Dexrazoxane), angiotensin-converting enzyme (ACE) inhibitors, and beta-blockers; and cardiac monitoring with serial LV function assessment or with biomarkers as troponins. The most effective ways to prevent cardiotoxicity are [73, 78–81]:

(a) The concomitant use of dexrazoxane, an iron-chelating agent, that has been proven to significantly reduce cardiac dysfunction without affecting the antineoplastic effect of DOX.
(b) The use of prolonged infusions (>6 h; preferably 48–72 h continuous infusions) rather than bolus administration.
(c) The use of EpiDOX that is roughly 30% less cardiotoxic compared to DOX, and less potentiated by the concomitant use of taxanes.
(d) The use of liposomal formulations that limit the cardiac uptake of the drug leaving unaltered the tumor delivery.

CHF due to ANTHRA toxicity was considered refractory to medical therapy for years; at present, the use of conventional drugs as ACE-inhibitors and beta-blockers has been proven effective both in treating overt cardiotoxicity and in preventing the progression of LV dysfunction in subjects at high risk with preclinical signs of cardiac damage [82–85]. So, besides the above-mentioned strategies to prevent cardiotoxicity, a strict monitoring during the treatment is recommended; at the first signs of LV dysfunction therapy with ACE-inhibitors should be started.

Ifosfamide

The main reported toxicities of IFO are nephrotoxicity and neurotoxicity. From the cardiac point of view it has been usually considered safe, but cardiac toxicity in high-dose (>10 g/m^2) treated patients has been reported, and is significant (>10%) when using >15 g/m^2 [83, 86–88]. Possibly, there is a link between nephrotoxicity and cardiotoxicity: the LV dysfunction follows usually an increase in blood creatinine, and—according to a recent experimental study—IFO-induced Fanconi syndrome may cause a carnitine deficiency dangerous for the heart [87, 89]. Since IFO is usually given together with ANTHRA, a strict follow-up using echocardiography and myocardial damage biomarkers (in order to early diagnosing and treating LV dysfunction) is recommended [83].

Taxanes

Taxane cardiotoxicity is mainly evident as self-limiting supraventricular arrhythmias (atrial fibrillation, sinus bradycardia), but they may also increase DOX (much less EpiDOX) toxicity, as above mentioned, altering ANHTRA pharmacokinetics and possibly promoting the formation

of toxic metabolites [71, 72, 87]. To prevent this problem, the two drugs should be administered apart, and DOX before taxanes. Cases of allergic myocarditis have also been reported, mostly with paclitaxel; some authors argued that they could be due not to the drug itself but to its solvent, the Cremophor EL [72, 87]. Moreover, anaphylactic reactions (ARs) have been frequently described with taxanes, with a mortality reported more often with docetaxel than paclitaxel; prophylactic pre-medications did not significantly impact mortality from ARs with docetaxel, but was associated with significantly lower mortality from ARs with paclitaxel [90].

Vascular Endothelial Growth Factor Blocking Agents and Tyrosine Kinase Inhibitors

Two types of side effects have to be considered: on-target (due to the same mechanisms acting as antitumoral; these effects may be also a biological marker of antineoplastic efficacy) and off-target. The VEGF block (by the monoclonal antibody Bevacizumab and the tyrosine kinase inhibitors (TKI) Sunitinib and Sorafenib) causes hypertension (mainly by reducing the nitric oxide release by the endothelial cells, by interfering with renal physiology, and by increasing the vascular resistance), thromboembolism, and hemorrhages [90–92]. Moreover, the activation of VEGF is crucial in wound repair, in maintaining capillary density in the hypertrophied heart, and for the neoangiogenesis in ischemic and diabetic heart disease; its block may then have deleterious effects in patients with preexisting cardiac diseases or undergoing cardiotoxic CT. There are some differences among the pharmacokinetics of these three drugs: Sunitinib and Sorafenib have an half-life of hours, while Bevacizumab half-life varies from 10 to 50 days (mean 20) in different patients: during prolonged treatments, then, Bevacizumab may cause a progressively worsening hypertension. After introducing in the market Sunitinib and Sorafenib, an unexpectedly high rate of cardiovascular side effects, including a direct myocardial damage, has been noticed. Besides the effects due to the VEGF block, in fact, there are a number of off-target effects common to the whole class of TKI: most important are myocardial damage and prolongation of QT interval at ECG (with the risk of life-threatening ventricular arrhythmias). Different molecules have different cardiotoxicity, and besides the dozens of TKI already in use, there are hundreds still under evaluation: the topic of TKI cardiotoxicity is an everyday changing field, and the mechanisms are still to be defined [92, 94]. In fact, the role in cardiac physiopathology of the 90 human tyrosine kinases (and, then, the effect of their block) is largely unknown; some of them protect the myocardial cell from ischemic or oxidative stress, are involved in the reparative process after myocardial ischemia, or have generally an antiapoptotic action. According to the most recent studies, TKI-induced LV dysfunction is due to a direct cytotoxic effect, with mechanisms different from ANTHRA cardiotoxicity, cannot be prevented by dexrazoxane, and is not always reversible upon withdrawal of the drug or even with commonly used cardiac therapy with ACE-inhibitors and beta-blockers; the risk is inversely proportional to the selectivity of TKI [94–96]. Since LV dysfunction seems to be more frequent in patients with uncontrolled hypertension, and according to the experimental data, probably the cardiotoxic effect of anti-VEGF drugs may be due to a combination of hypertensive stimulus and of inhibition of the homeostatic mechanisms protecting the myocardium from the pressure overload stress (on-target effect); as regards Sunitinib and other multitarget TKI, there might be additionally a direct cytotoxic effect (off-target effect). For these reasons, the only strategies to prevent LV dysfunction are presently an accurate management of hypertension and a regular echocardiographic follow-up.

Radiotherapy

Data about radiation heart disease are derived by studies in two kinds of human populations (the atomic bomb survivors and the long-term survivors of tumors—mostly Hodgkin's disease and left

Table 12.3 Echocardiographic ejection fraction (EF) before chemotherapy (CT), after CT and before radiotherapy (RT), and at last follow-up after RT

Sex, age (type of RT)	CT/RT INTENT (surgical status)	Site	EF before CT (%)	EF before RT (%)	EF after RT (%)	Follow-up (months)	State at follow-up
m 57 (3D-CRT)	Curative (unresectable)	LA	58	65	58	101	Alive NED
m 61 (IMRT)*	Adjuvant (R2 resection)	PA		64	68	20	Dead of 2nd neoplasm
m 25 (3D-CRT)	Curative (unresectable)	RA, SVC	60	62	49	36	Dead of local progression
f 58 (IMRT)	Adjuvant (R1 resection)	LA, LV	64	62	58	36	Alive with metastases
m 44 (3D-RT)	Curative (unresectable)	RA, RV	69	65	66	12	Dead of metastases
f 69 (IMRT)	Curative (incomplete resection	LA	72	72	70	15	Dead of metastases
m 39 (Tomo)	Adjuvant (R2 resection)	RA, IAS	68	58	63	20	Dead of metastases
m 72 (Tomo)§	Neoadjuvant #	RA, RV	70	69	59	16	Dead of local relapse
f 57 (Tomo)	Adjuvant (R2 resection)	RA, LA	72	72	68	21	Alive with local disease
m 39 (Tomo)	Palliative after local relapse	Pericardium	70	53	63	13 after relapse, 34 overall	Dead of local progression
m 44 (Tomo)	Neoadjuvant #	RA, IAS	62	64	65	16	Dead of metastases

Patient signed with: asterisk symbol did not receive any CT, signed with section symbol taxanes only, and signed with hash symbol had radical surgery after neoadjuvant CT/RT

3D-CRT 3-dimensional conformational RT, *IMRT* intensity-modulated RT, *Tomo* tomotherapy, *f* female, *m* male, *nd* not determined, *IAS* interatrial septum, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *NED* no evidence of disease

breast cancer—undergone therapeutic irradiation), and by animal experiments. Ionizing radiation may cause acute symptomatic effects, and chronic or delayed effects. Coronary artery disease, valvular heart disease, and constrictive pericarditis are the typical chronic side effects affecting long-term survivors: they become clinically evident usually 10 years after treatment, with increasing incidence at longer follow-up [67]. Since the 5-years survival of patients with malignant cardiac tumors is still low, the main problem, in these particular patients, is the acute or medium-term cardiac toxicity. The first acute effect of irradiation is a pro-inflammatory effect, with endothelial damage of medium-large vessels and microvessels, pericarditis, and myocarditis; mast cells seem to have a protective effect [66–68]. Pericardium is the most frequently affected site: acute pericarditis is associated with edematous swelling of the pericardial layers: it may present in a painless effusive form with spontaneous recovery, or as an acute fibrinous pericarditis (with classical signs and symptoms of pericardial rubs and pain) that can be cured with Nonsteroidal Anti-inflammatory Drugs. In both cases, pericardial effusion is usually mild to moderate, and in 80% of cases there are no reliquates, while in 20% the disease evolves toward a constrictive pericarditis [97]. The microvessel damage is followed by a persistent decrease in capillary density and eventually leads to chronic myocardial ischemia and degeneration; an impairment in myocardial perfusion may be observed in the first months after RT, even if the increased risk of clinically evident RT-linked ischemic heart disease becomes statistically significant only after 10 years [68, 97–100]. In our experience, using modern radiation techniques, we did not observe any clinically relevant myocardial dysfunction on the short-medium term of observation in 11 patients with cardiac tumors treated with RT with or without previous CT, including three long-term >30 months survivors [70] (Table 12.3).

Conclusions

Malignant heart tumors are usually aggressive and have a dismal prognosis. The mainstay of therapy for sarcomas is radical surgery. Multimodality treatment including systemic therapy and/or RT seems to prolong the time to relapse and overall survival. Most of the treatments have a considerable risk of cardiac toxicity, but this risk should be balanced against the risk of tumor progression. Since the survival is usually limited to few years, the main concern is to prevent short- and medium-term toxicity. CT adverse effects may be prevented with careful dosage of drugs, cardioprotective agents, and strict monitoring of cardiac function. Short- and medium-term cardiac toxicity of RT may be limited using modern radiation techniques. A number of new targeted therapies are under evaluation and will hopefully improve the outcome of this severe pathology.

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