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Anti-Tumour Treatment

Isolated limb perfusion of soft tissue sarcomas: A comprehensive review of literature

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ABSTRACT

Patients with primary irresectable, locally advanced soft tissue sarcomas of the limbs form a challenging group for the treating physician. Multimodality treatment is necessary to guarantee optimal limb salvage and survival rates. Since the introduction of isolated limb perfusion in the late fifties, several treatment regimens have been proposed. Isolated perfusion with melphalan and TNF-α, as part of a multimodality treatment, is regarded as the current best treatment option today. Ongoing studies are investigating potential benefit of other doses, new chemotherapeutic agents and new techniques in perfusion and radiotherapy. This article provides a historical overview of published literature and insight in upcoming treatment techniques.

Introduction

Soft tissue sarcoma (STS) comprise a heterogeneous group of malignancies, accounting for about 1% of all cancers. They may arise in any part of the body, but develop most commonly in the extremities (45%).[1] Because STS typically present as a painless lump without loss of function or influence on the patients general health, there is usually a substantial delay before initial presentation, allowing the tumor to grow to considerable size. In case the tumor is too large for local resection or in close adherence to important structures with resection causing severe impaired limb function, neo-adjuvant therapy could be attempted in order to achieve pre-operative downsizing of the tumor. An induction treatment approach with intra-arterial chemotherapy in combination with radiation has been investigated, with good results in terms of high limb salvage and low local recurrence rates, however, morbidity rates were too high, and the treatment protocol was eventually abandoned.[2,3] Another, well documented, neo-adjuvant treatment possibility is regional limb perfusion (ILP). During the last two decades, several institutions in Europe have utilized the perfusion technique as a safe alternative for amputation.[4] A continuous search for developing and improving the perfusion technique and chemotherapeutic agents has led to numerous publications. This review provides an historical overview of literature, and describes the current status and new applications of isolated perfusion.

Landmarks in the treatment of primary irresectable soft tissue sarcoma

Klopp and colleagues were the pioneers in the field of intra-arterial chemotherapy. In 1950, they explored the benefit of intra-arterial administration of nitrogen mustard for the treatment of various malignancies in the United States.[5] Although a better tumor response in comparison with venous administration was demonstrated, complete eradication was not possible because systemic toxicity precluded maximal effective drug doses. In the late fifties, Chreech, Krementz and Ryan attempted to reduce the systemic toxicity from intra-arterial chemotherapy by introducing a new technique based on the heart–lung machine, utilizing an oxygenated extracorporeal circuit: isolated limb perfusion (ILP).[6] They started using melphalan, which is less neurotoxic, and reported good tumor response in various cancers, mainly in melanomas.[7] The first perfusion in Europe was carried out by Lebrun in Belgium in 1960, and eventually adopted in some 30 cancer centers throughout Europe.

Originally, perfusions were performed under normothermia (37–38 °C). Cavaliere was the first who experimented with hyperthermic ILP and reported enhanced tumor kill with less serious local toxicity.[8] In addition, Wieberdink et al. recommended to calculate melphalan dosage based on limb volume, instead of body weight, to reduce regional toxicity.[9] Further advancements came

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Table 1
Overview results in extremity perfusion for sarcoma.

Author	Year	Study	Cytostatics	*N*	CR %	PR %	NC %	LS %	LR %	5-year survival %	Remarks
Krementz et al.[79]	1977	Single	M/Act-D/HN2	17	0	35	65	NS	NS	NS	Historical
Muchmore et al.[80]	1985	Single	M/Act-D/NH2/various	51	6	12	82	NS	NS	NS	Historical
Stehlin et al.[81]	1984	Single	M/Act-D	65	NS	NS	NS	94	NS	73	Historical
Lehti et al.[82]	1986	Single	M/Act-D	64	NS	NS	NS	100	11	67	Feasibility EBRT
Krementz[83]	1986	Single	M/Act-D	56	NS	NS	NS	100	21	65	Historical
Hoekstra et al.[13]	1987	Single	M	14	NS	NS	NS	100	7	69	Historical
Pommier et al.[18]	1988	Single	Cisplatin	17	0	18	82	NS	NS	NS	Cisplatin
Di Filippo et al.[84]	1988	Single	M/Act-D	55	NS	NS	NS	78	24	48	Historical
Klaase et al.[17]	1989	Single	Dox/M	13	7	0	93	61	0–24	44–77	Doxorubicin
Kettelhack et al.[85]	1990	Single	M/Act-D	9	NS	NS	NS	78	33	66	Historical
Eggermont[86]	1993	Single	TNF/M_IFN	20	55	40	5	90	NS	NS	TNFα
Hill et al.[45]	1993	Single	TNF/M	8	100	0	0	64	NS	NS	Low-dose TNFα
Fletcher et al.[90]	1994	Single	Cisplatin	75	NS	NS	NS	NS	7	100–48	Largest cisplatin study
Rossi et al.[14]	1994	Single	Dox	23	NS	74	26	91	27	48	Doxorubicin
van Ginkel et al.[16]	1996	Single	Cisplatin	4	NS	NS	NS	NS	NS	NS	Cisplatin
Eggermont et al.[21]	1996	Multi	TNF/M_IFN	55	18	64	18	84	13	NS	First multicenter
Eggermont et al.[4]	1996	Multi	TNF/M_IFN	186	18	57	25	82	11	NS	Beromun_registration
Santinami et al.[48]	1996	Single	TNF/M	10	70	20	10	89	NS	NS	None
Rossi et al.[91]	1996	Single	TNF þ Dox	18	NS	NS	NS	81	10	NS	None
Gutman et al.[51]	1997	Single	TNF/M_IFN	35	37	54	9	85	0/31	NS	None
Olieman et al.[88]	1997	Single	TNF/M	25	40	52	8	NS	NS	NS	Angiographic response
Olieman et al.[68]	1998	Single	TNF/M (IFN)	34	35	59	6	85	14	60	Feasibility EBRT
Olieman et al.[24]	1998	Single	TNF/M (IFN)	9	44	33	23	89	22	0	Palliative treatment
Lev-Chelouche et al.[30]	1999	Single	TNF/M (IFN)	5	20	80	0	80	NS	NS	Kaposi sarcoma
Lev-Chelouche et al.[27]	1999	Single	TNF/M (IFN)	6	33	50	17	100	33	NS	Desmoid
Lev-Chelouche et al.[87]	1999	Single	TNF/M (IFN)	13	38	54	8	85	38	NS	Multifocal
Eggermont et al.[92]	1999	Multi	TNF/M_IFN	246	28	47	25	76	NS	NS	Definition irresectability
Rossi et al.[42]	1999	Single	TNF þ Dox	20	26	64	10	84	10	64	None
Lejeune et al.[56]	2000	Single	TNF/M_IFN	22	18	64	18	77	14	86	None
Daryanani et al.[15]	2000	Single	Carboplatin	4	NS	NS	NS	100	NS	NS	Carboplatin
Lans et al.[29]	2002	Single	TNF/M_IFN	16	56	31	13	80	NS	NS	Lymphangiosarcoma
Noorda et al.[58]	2003	Single	TNF/M_IFN	49	8	55	37	57	13	48	None
van Etten et al.[93]	2003	Single	TNF/M_IFN	29	38	38	24	76	NS	NS	Elderly patients >75 years of age
Di Filippo et al.[41]	2003	Single	Dox_TNF	NS	22	55	23	77	7	69	Phase I and II study Dox and Dox þ TNF
Feig et al.[38]	2004	Single	Dox	31	NS	NS	NS	NS	NS	NS	Doxorubicin
Rossi et al.[39]	2005	Single	TNF/Dox	21	5	57	38	71	19	57	TNFa þ doxorubicin
Grunhagen et al.[53]	2005	Single	TNF/M_IFN	240	24	50	26	82	NS	±45	Largest single center
Grunhagen et al.[53]	2005	Single	TNF/M_IFN	48	38	31	29	85	NS	36	Dose reduction
Bonvalot et al.[46]	2005	Single	TNF/M	100	36	29	35	77	24	NS	Dose reduction
Grunhagen et al.[28]	2005	Single	TNF/M_IFN	12	17	58	25	100	17	NS	Desmoid
Lans et al.[22]	2005	Single	TNF/M_IFN	26	20	50	30	65	27/45	40	Previous irradiated recurrences
Grunhagen et al.[94]	2005	Single	TNF/M_IFN	64	42	45	13	82	45	39	Multifocal/recurrent sarcoma
Grunhagen et al.[95]	2006	Single	TNF/M_IFN	217	18	51	31	75	26	49	Prognostic factor
Grunhagen et al.[25]	2006	Single	TNF/M_IFN	37	16	68	16	92	NS	NS	Palliative treatment
Schlag and Tunn[96]	2006	Single	TNF/M_IFN	125	19	53	28	81	18	NS	None
Thijssens et al.[64]	2006	Single	TNF/M	39	NS	NS	NS	NS	NS	NS	Quality of life
Thijssens et al.[47]	2006	Single	TNF/M	64	NS	NS	NS	89	NS	61	Value adjuvant RT
Hayes et al.[44]	2007	Single	TNF/M	18	NS	NS	NS	NS	NS	NS	None
van Ginkel et al.[57]	2007	Single	TNF/M_IFN	73	25	69	6	60	NS	70%	70% Long-term LS outcome
Hoven-Gondrie et al.[60]	2007	Single	TNF/M_IFN	32	NS	NS	NS	NS	NS	NS	Vascular morbidity
Pennacchioli et al.[97]	2007	Single	M or Dox with or without TNFa	88	32	59	8	83	27	NS	Melphalan or Doxo with or without TNFa
Cherix et al.[50]	2008	Single	TNF/M	51	25	41	28	76	35	44	Long term results
Hoven-Gondrie et al.[61]	2008	Single	TNF/M	73	NS	NS	NS	NS	NS	NS	Long term effects according to LENT–SOMA
Bonvalot et al.[26]	2009	Single	TNF/M	100	19	39	42	87	14	NS	None
Di Fillippo et al.[98]	2009	Single	TNF_Dox	75	34	48	18	85	21	62	TNF and Doxorubucin
Nachmany et al.[55]	2009	Single	TNF/M	42	17	36	47	???	42	NS	High vs Low dose TNFa
Lasithiotakis et al.[23]	2010	Multi	TNF/M	6	17	50	33	100	NS	NS	Recurrent disease
Wray et al.[40]	2011	Multi	TNF/M Doxo	17	6	64	30	41	NS	NS	Phase II trial: comparison of two regimens
				12	NS	NS	NS	NS	NS	NS	
Grabellus et al.[43]	2011	Single	TNF/M	53	NS	NS	NS	NS	11	NS	Histologic response
Deroose et al.[49]	2011	Single	TNF/M	208	18	53	29	81	30	42	Long term results largest single center
Hoven-Gondrie[54]	2011	Single	TNF/M	102	22	55	23	77	15	NS	TNF dose reduction
Deroose et al.[69]	2011	Single	TNF/M	122	4	66	29	89	21	NS	Role of adjuvant RT