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Regional Therapy of Melanoma

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Little progress has been made in the systemic treatment of melanoma, that is for disseminated stage IV disease. However, the tumour resistance to therapy, especially chemotherapy can be overcome in melanoma by high doses of anticancer agents administered regionally. The purpose of this paper is to illustrate this concept by two modes of regional treatment namely: (1) isolation perfusion of the limbs with high doses of cytokines and chemotherapy under hyperthermia and (2) local treatment of metastatic melanoma. The third part will be devoted to the role of another regional treatment, radiotherapy, where the association with hyperthermy also looks promising.
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1. HIGH DOSE CYTOKINES AND CHEMOTHERAPY IN ISOLATION PERFUSION OF THE LIMBS

In 1975, Carl Carswell, from the group of L. Old, at the Sloan Kettering Institute, discovered a soluble substance in the serum of animals treated either with BCG (bacille Calmette-Guérin) or endotoxin [1]. This substance was able to produce, on tumour-bearing animals, haemorrhagic necrosis leading to tumour regression [2, 3]. Later it was shown to be produced by activated macrophages and to consist of a peptide of 157 amino acids. The cDNA for human tumour necrosis factor (TNFα) was finally determined, rendering possible the production of recombinant (r) TNFα in *Escherichia coli*.

rTNFα was the first cytokine identified that was able to produce tumour regression comparable to the best chemotherapeutic agents [4]. However, TNFα is considered as one of the major mediators of septic shock, TNFα induces a septic shock-like syndrome which represents the major side effect of its administration, both in animals and in humans [5, 6].

Phase I studies so far indicate that the maximal tolerated single dose (MTD) in humans is equal to or less than 350 $\mu g/m^2$ intravenously [7, 8]. Under these conditions, a negligible clinical response rate has been reported in all diseases including melanoma [9–11]. The beneficial anti-tumour effects of TNFα seem to be related to endothelial cell activation and vascular damage resulting in haemorrhagic necrosis, which starts within 1–4 h after rTNFα administration, principally in tumours connected with the derma [12]. This might be due to the neovascular supply of superficial neoplastic nodules and/or some specific property of the capillary bed of tumours in the skin. Another potential consequence of local administration of rTNFα is the lysis of the extracellular matrix resulting from the release of elastase by activated polymorphonuclear neutrophils [13] as was observed in our patients. Neutrophil elastase is a major determinant of neutrophil-induced endothelial and tissue damage [14].

Since human tumour xenografts are sensitive to rTNFα and that its use is limited by a low MTD, we decided to try the administration of the compound under isolated limb perfusion for in transit melanoma metastases. Indeed this regional therapy using the chemotherapeutic agent melphalan alone is a well established procedure for treating in transit metastases of melanoma [15] with an overall complete response rate of 50% resulting in a high limb sparing [16, 17]. Therefore the administration of effective doses, that is, high doses of rTNFα, was decided in order to overcome not only the side effects, but also the lack of efficacy of systemic low dose administration. As will be seen, the pilot study with TNFα resolved the problem of systemic toxicity, but it was necessary to use rTNFα in combination therapy in order to achieve the very high response rate that we finally obtained.

Feasibility of administering high dose (HD) rTNFα in isolated limb perfusion

Isolated limb perfusion (ILP) allows the delivery of high dose of drug in a closed system with acceptable toxicity and minimal systemic side effects. With melphalan, the drug concentration reaches 10–30-fold concentrations at equilibrium following systemic administration. The experience with intratumoral TNFα administration, giving rise to more tumour responses, suggests that giving TNFα at high dose could be more efficient than the MTD. Therefore, the 3 patients in the pilot study received rTNFα only, at doses of 2, 3 and 4 mg, respectively, in the arterial line of the circuit. The 3 patients (2 females, 1 male) had regionally advanced melanoma (2 stage IIIa, 1 stage IIIab).

The technique of ILP has been described elsewhere. Priming consisted of 19 ml bicarbonate, 0.4 ml heparin and 1 l haemacel (Behringwerke, Marburg, Germany) supplemented with 1 U of either bank blood or autologous fresh blood. Perfusate flow was set as high as possible and was typically 700 ml/min for lower limb ILP. Potenial leakage of the drugs was measured with radioiodinated human serum albumin (RIHSA; Institut des Radio-Elements IRE, Fleurus, Belgium) injected into the circuit, and the radioactivity was assessed in the peripheral plasma at 5, 30 and 60 min. The arterial blood temperature of the perfused limb was maintained at 40°C during the whole ILP. Four thermistor probes were implanted in the subcutaneous tissues and into the muscles to monitor the tissue temperature, which ranged between 38 and 40°C.

Side effects

The first patient had been perfused twice for extensive in transit metastases of the lower limb, the first with melphalan alone, and the second with α-MSH melphalan, with partial remission for the first, and no change in the second. The route

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had been the iliac vessel for the first treatments, and the femoral for the third with TNFα. There were more than 40 tumour nodules and the overall leakage at 60 min was 34.4% due to the neovascularisation of the previous operating site. The second patient had more than 100 nodules over the whole lower limb and was perfused by the iliac region. Leakage was minimal.

In those 2 patients, the first during perfusion because of leakage, and the second after releasing the tourniquet—preceded by extensive wash-out by 2 l with the pump—a profound circulatory shock developed. In both cases, it responded well to fluid loading and dopamine. The third patient had 20 in transit metastases on the leg and knee. She received 4 mg of TNFα. She entered the prophylactic dopamine infusion protocol with fluid loading and had no systemic toxicity (see later). Prophylaxis of shock was given according to the protocol described. No septic shock-like syndrome was observed.

In addition to the hypotension problems, the first 2 patients—who did not receive prophylactic dopamine infusion nor indomethacin—experienced tachycardia and transient oliguria with renal toxicity (WHO grade 3) for 29 days, respectively.

All 3 patients developed chills and fever a few hours after the perfusion.

Tumour response in the pilot study

The first patient experienced a complete response although a pigmentation remained on his leg. The complete softening of the nódules remained for 7 months, and then a relapse appeared which was treated with combination therapy. The second patient presented a typical haemorrhagic necrosis of the in transit amelanotic metastases 2 days after perfusion but relapsed after 21 days. In the third patient however, only a minor response was observed.

Rationale for using a combination of HD rTNFα, rIFNγ and melphalan

It has been demonstrated that the number of the TNFα receptors on malignant cells increases when they are incubated with IFNγ [18, 19]. In addition, a synergistic antiproliferative activity of rTNFα and IFNγ has been demonstrated *in vitro* and *in vivo* using human melanoma xenografts in nude mice [20].

An enhancement of the cytolytic activity of rTNFα by hyperthermia (40°C) has been demonstrated in experimental tumours both *in vitro* and *in vivo* [21, 22]. Cytotoxic activity of rTNFα is enhanced when chemotherapeutic drugs, especially alkylating agents, are added *in vitro* and *in vivo* [23, 24]. Since melphalan is the first line ILP chemotherapy for the treatment of melanoma, we decided to combine rTNFα at high dose, rIFNγ at low dose and melphalan at the usual concentration for isolation perfusion of the limbs.

In our protocol IFNγ at the dosage of 0.2 mg is given subcutaneously on days 2 and 1. This dosage of IFNγ was chosen as it had previously received an NCI clearance for biological response modifiers (BRM) protocols. The high dose of TNFα, of 4 mg for lower limb, was chosen because it was found to be tolerable in the pilot study and since it represents a 10-fold increase of the systemic dosage for MTD. For upper limb, the dosage was initially of 2 mg and was later increased to 3 mg.

Melphalan dosage was calculated according to the litre-volume method [25], 10 mg/l of perfused limb for lower and 13 mg/l for upper limb. Exchangeable limb blood volume (ELBV) was assessed with the haematocrit method and additional priming with haemacell solution was done in order to achieve a final concentration of 40 μg of melphalan per ml at the equilibrium for lower limb and of 20 μg for upper limb [26].

rIFNγ and rTNFα were injected successively as a bolus in the arterial line. Melphalan was administered 30 min later. The whole perfusion lasted 90 min. At the end of the ILP the limb was washed twice with 1 l of haemacell and 1 l of macrodex (Travenol). Recently we have replaced haemacell by plasmasteril.

Prophylaxis of septic shock like syndrome

Since the pilot study had shown a profound circulatory shock in 2 patients which responded well to fluid loading and dopamine, the patients included in the phase II study received a prophylactic treatment. It consisted in the use of continuous intravenous infusion of 2 μg/kg/min of dopamine, starting before the injection of rTNFα in the circuit and systematically during at least 48 h postoperatively. Hyperhydratation was applied before releasing the tourniquet after completion of the washout. For achieving an optimal prophylaxis of shock, electrocardiogram, urine output, blood pressure, venous and pulmonary pressures and arterial wedge pressure were recorded and monitored continuously by an arterial and a Swan-Ganz catheter from the beginning of the ILP until the second postoperative day.

Recently we added indomethacin in order to reinforce the protection of the patient against side effects, as it had been shown in animals that indomethacin can protect mice from a lethal shock from rTNFα. We used indomethacin at a fixed dosage of 50 mg for the first 4 h with a pump intravenously, starting at the beginning of the ILP before injecting rTNFα. The last 20 h to complete a full day, patients received 200 mg of indomethacin. Indomethacin was not prolonged any longer and to avoid the risk of gastric ulceration.

Efficacy of ILP with HD rTNFα, IFNγ, melphalan on unexcised in transit melanoma metastases

44 consecutive melanoma patients entered the study. Their characteristics are listed in Table 1. Patients entered the phase II study from December 1988 in Brussels to March 1992 in Lausanne, after extended work-up and informed consent.

Table 1. TNF perfusion: melanoma

No of patients (F/M)		44 (36/8)
Age (range)		60 years (22–84)
ILP (n = 46)		
Axial		1
Femoral		6
Iliac		39
Stage		
IIIa		29
IIIab		13
IV		2
Previous ILP treatment (n = 28/44)		
Melphalan		20
TNF		2
TNF-Melphalan		1
IA Cis DDP		3
IV IFα$_2$ + IL$_2$		2
Number of nodules	1–10	26
	> 10–50	11
	> 50–100	3
	> 100	4

F, Female; M, male.

Table 2.

Response	CR 39/44 (90.5%)
	PR 5/44
Follow-up time	13 months (range 1–35)
Recurrence	7/44 (16%) (2–13 months)
Distant metastases	17/44
Limb salvage	40/44*

Limb salvage not possible in 4 cases: two arterial thrombosis, one recurrence, one toxicity < hyperthermia.

The 44 patients received 46 ILP, the majority being through the iliac vessels. There were 36 female and 8 male patients. The age ranged between 22 and 84, with a median of 60. It should be stressed that we decided to treat older patients because of the well-known tolerance of elderly patients to TNF. All patients had in transit metastases (stage IIIa). In 13 cases this was associated with regional lymph node metastases and 2 patients had a stage IV, that is advanced disease, because of liver metastases which were not diagnosed at the time of the work-up.

The majority of the patients, (28/44), had been previously treated, 28 had been perfused, 3 had received intra-arterial chemotherapy and 2 had received the association of IFNα-2 and interleukin-2 (see Table 2). The tumour burden was considerable in 18 patients, that is between more than 10 and more than 100 nodules. The patients with few nodules had undergone surgery several times for local excision of in transit metastases with subsequent recurrences.

Tumour response

In all cases, an early and spectacular softening of the tumours was seen within the first 3 days after high dose of TNFα ILP, as the first sign of tumour response, an observation which was never made after chemotherapy alone. Objective regression rapidly appeared. Table 3 gives the account of the responses. They were 39 out of 44 complete responses (90.5%) and 5 partial remissions. There has been no failure after the triple drug regimen. Mean time to objective response was 9 days for complete response (CR) and 16 days for partial response (PR). A striking observation is that most CR occurred with bulky tumours with numerous nodules and that the 5 PR were at least with 75% tumour shrinkage.

Table 3. Systemic toxicity (n = 60)

	Symptom	No. of patients	Severity
Chills, fever	mean 39.1°C (38–40.9)	53	
Blood pressure	Hypotension	7	mild
		3	MOF
Lungs	Hypoxia–ARDS	18	mod → severe
		3	MOF-
Kidneys	ARF	3	2 grade 4
			1 grade 3
Liver	Bilirubin	18	
	ENZ + bilirubin	15	4 grade 3
			2 grade 4

ARDS = adult respiratory distress syndrome.

Median follow-up time has been 13 months and only 7 out of the 44 patients (16%) developed recurrence in the perfused limb. However, 17 out of the 44 developed distant metastases. This observation strongly suggests that a state of regional resistance to the tumour developed; it was dependent on the high dose of treatment received. In an illustrative case all the nodules disappeared, including those very close to the tourniquet; CR duration was 8 months and at that time generalisation together with recurrence in the perfused limb appeared but only at the root of the limb, where perfusion had not been optimal. Figure 1 shows the isolation perfusion survival and disease-free interval.

Since the first aim of such a therapy is limb salvage from unnecessary amputation for such a poor prognosis population, it is of interest to know that 40 out of the 44 patients kept a functional limb. There have been four amputations: two for arterial thrombosis, not related to TNF itself as it was associated to troncular atheromatosis, one for heavy recurrence and one for accidental burn caused by excessive hyperthermia.

Toxicity of ILP with rTNFα, rIFNγ and melphalan

We analysed systemic toxicity from a whole population of 60 patients because the same protocol was applied to soft tissue sarcoma and carcinoma patients. In Table 4 it can be seen that chills and fever occurred in most patients with a lag period of 5 h. It is of interest to note that this peak does not correspond to TNFα levels, but to that of interleukin-6. Hypotension in the postoperative period was only severe in 3 patients who developed a multi-organ failure (MOF). It should be stressed that 2 out of 3 patients were reperfused with TNFα because of partial remission or recurrence and had a significant systemic leakage. The third patients had an ulcerated and infected invasive carcinoma of the leg and subsequently developed a true

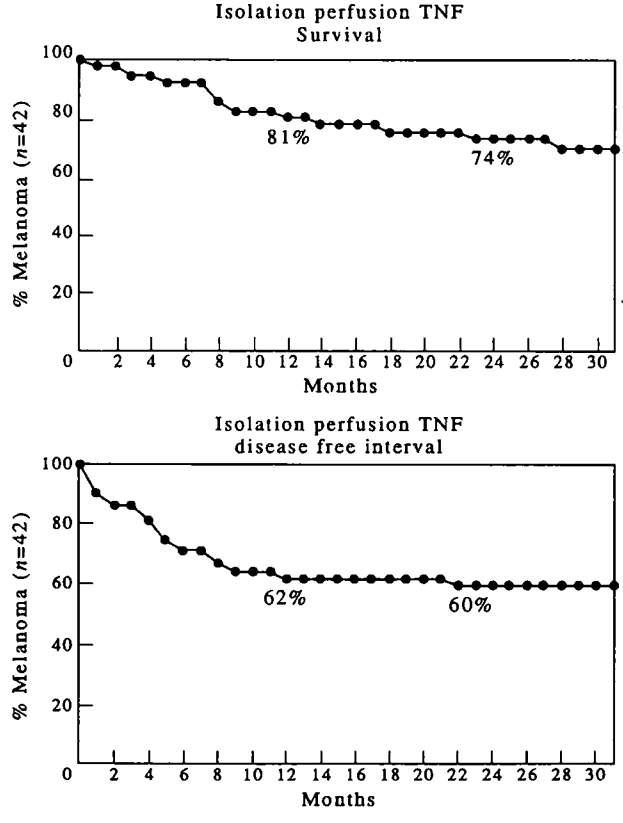

Fig. 1.

Table 4. Indomethacin

9 patients	1 Squamous cell carcinoma 1 Sarcoma 7 Melanoma	
4/9 Leakage > 10%	⇒	No hemodynamic toxicity No lung toxicity No kidney toxicity
Temperature		37.3–38.2°C

septic shock from bacterial mobilisation induced by the isolation perfusion. Since this case, we decided to exclude patients with ulcerated tumours unless they have been successfully treated to eliminate pathogens. The last patient died of septic shock, and 1 of the 2 other cases also died, not from septic shock but from a suffocating iatrogenic pneumothorax. Therefore there has been only one lethal toxicity out of 60 perfusions.

Lung toxicity deserves some comments as it represents hypoxia and adult respiratory distress syndrome incipiens. 3 patients had a MOF and 18 moderate to severe hypoxia which required intubation for a few days. It should be stressed that in some patients the X-rays of the thorax showed diffused hyperdensity of both lungs accompanied with a drop of pO_2 and of saturation without any dyspnoea which resolved spontaneously after 1 or 2 days.

Acute renal failure was found in 3 cases: there were two grade IV and one grade III. Dialysis was required for the 2 cases with grade IV and was reversible in each case except for 1 who died from a true septic shock.

Bilirubin increase as seen in septicaemia was encountered in 18 patients, but the association of increase of enzymes and hyperbilirubinaemia was found in 18 patients, with 4 grade III and 2 grade IV liver failure. The 2 grade IV were associated with the MOF (see below).

Haematological toxicity was encountered in most patients with a drop of leucocytes and of platelets in the 3 first days with recovery after 30 days, but there has been one case of WHO grade IV for leucocytes and platelets. In that case the cumulative systemic leakage during perfusion reached 31%, indicating that this toxicity can be attributed to melphalan.

Regional toxicity to rTNFα was minimal, as the majority of patients had only a grade II skin toxicity as we reported before. Levels of TNFα and interleukin-6 were recorded in about 20 patients. No correlation was found between the level of TNFα released from the perfused tissues after the perfusion and intense washout, indicating and individual sensitivity to the toxicity of cytokines.

Although we felt that dopamine perfusion and fluid loading were the major components of shock prophylaxis, we decided to add indomethacin in 9 patients. 4 of them experienced a cumulative leakage of more than 10%. In those patients there has been no haemodynamic lung or renal toxicity. In addition, no chills were observed, and the temperature ranged between 37.3 and 38.2°C. Of interest is the fact that the peripheral levels of TNFα and interleukin-6 did not change as compared to those patients who did not receive indomethacin. Out of the 9 patients, 8 experienced a complete and 1 a partial response, confirming observations in mice, that indomethacin protects from lethal shock without interference with the anti-tumour effect in the human.

Discussion and conclusion

Our work indicates that it is possible, by isolated limb perfusion to apply an effective high dosage of cytokine, achieving a never reported response rate in human melanoma with acceptable toxicity. It is indeed the first evidence that the high efficacy of TNFα in animals can be confirmed in humans, provided a selection of the diseases is made, that is regional disease, and that a high dosage of TNFα is administered together with IFNγ and melphalan. We feel that the association of chemotherapy with rTNFα is useful, since we had an indication of the reversibility of the cytokine when used alone in a pilot study, and from the many data in the literature. However, the necessity of using IFNγ, although supported by experimental data, has not been proven in patients. Therefore we have decided to activate a phase II randomised trial, when in one arm IFNγ will be omitted.

The mechanism whereby this treatment produces such a fast and effective tumour collapse has been addressed, using morphology, immunohistology, angiography and cytokine measurements. We found that the *primum movens* of tumour destruction is due to a direct effect of TNFα in addition to IFNγ on the tumour endothelium. Within a few hours after the isolation perfusion with TNFα, there was an induction and an amplification of the expression of adhesion molecules, which was the cause of a high recruitment of polymorphonuclear leucocytes (PMN) which invaded the metastatic nodules, a phenomenon accompanied with endothelial destruction. The latter effect was dramatically demonstrated by the angiographic disappearance of the tumour hypervascularisation within 1 week of perfusion. Thus melanoma metastasis early softening and subsequent destruction in more than 90% of the cases seems to be related to a *primum movens* which is the destruction of the tumour microvascularisation.

It is of importance to note that in most cases, whether the tumour burden was high or not, and even when the patients had a recurrence after previous therapy, a complete response was obtained readily after a single application of this combination therapy including high dose TNFα. This observation leads to the impression that this regional therapy produces a systemic effect leading to a state of resistance of the patient to a tumour with long lasting remission, as witnessed by the disease-free interval and the survival curves. Indeed there is a systemic effect if one considers the systemic side effects and the cytokine levels which have been recorded in the peripheral blood. The concentration of TNFα in the perfusate amounts to 2 μg/ml, which is a lethal dose eliminated by intense washout. It should be stressed that we found a plateau level since there is no breakdown of TNFα outside the general circulation, especially without liver passage. However, our results indicate that TNFα is subsequently released into the general circulation because it was retained within the intercellular space and the lymph vessels.

We reported a mean concentration of 30 ng of TNFα in the circulation [27], which is far in excess of that previously reported as a TNF concentration accompanying death from multi-organ failure and septic shock. Eventually patients dying from septic shock present a TNFα concentration which does not reach the ng levels! Therefore we question the concept of considering TNFα as the main and/or the sole effector of septic shock toxicities. Indeed it has been shown that endotoxin associated to TNFα dramatically increases toxicity in animals. Therefore our proposal is that TNFα being given at a high amount to patients suffering from cancer, but not from septic disease, do not have a significant levels of endotoxin and therefore do

not experience the high toxicity which has been reported in septicaemia. At this point we should stress the fact that we experienced one case of lethal shock because the patient had an infected tumour on the perfused limb, associated presumably to endotoxaemia.

Since our first report on the successful use of rTNFα, IFNγ and melphalan in isolation perfusion [28], Eggermont in Rotterdam and Schraffordt Koops in Groningen have tested the present protocol. The addition of their melanoma cases at the time of writing permits addition of 8 more cases. The overall response rate from a total of 51 evaluable cases with in transit metatases is 46 complete responses (90.5%) and 5 partial responses (9.5%) and 5 recurrences, 43% have been recorded in Rotterdam but it is too early to conclude, the overall local recurrence rate being 19%. At this time metastases rate has been 18 out of 52, that is 36.5%.

The role of IFNγ is still questioned, as it may be that the upregulation of TNFα receptor may lead to more circulating soluble receptors. Therefore we decided to design a randomised phase II study, where we compare the triple association to the association of TNFα with melphalan. This restricted trial is conducted by Lausanne, Rotterdam and Groningen. The aim is to test whether the addition of IFNγ increases a response rate obtained with the association of high dose rTNFα with melphalan.

In conclusion, these results demonstrate, for the first time, a rapid, impressive and sustained response of in transit melanoma metastases to high dose rTNFα when administered regionally in combination with IFNγ and chemotherapy. This triple drug regimen appears to be an attractive therapeutic approach in the treatment of regionally advanced melanoma, especially in the case of melphalan failure. The rate of limb sparing has been 48 out of a total of 52 cases treated in Brussels, Lausanne, Rotterdam and Groningen, that is 92% of patients with a very severe tumour burden.

Because of the unacceptable systemic toxicity of such a regimen, it should be limited to isolated perfusion of limbs. Moreover, great care must be taken to avoid septic shock-like syndrome using fluid loading, dopamine and indomethacin administration.

2. LOCAL TREATMENT OF METASTATIC MELANOMA

The most frequent site of metastases from cutaneous melanoma are the non-visceral sites in 59%, the lung in 36%, the brain and the liver in 20%, and the bone in 17% [29]. However, in a small number of patients, metastases may be isolated or localised to one single organ, thus appropriate for a local treatment.

Surgical excision of lung metastases has been proposed when they are truly isolated. The median survival range from 16 to 24 months and long term 5 years survival rates was 12–33% [30, 31]. These encouraging results were not reported by all institutions [32].

Liver as the single site of metastases in cutaneous melanoma is even more unusual, and resectability is rarely possible because of diffuse involvement. When the resection could be performed, it produced long-term survivors [33]. But the majority of these patients could be candidate for loco-regional treatment by the hepatic intra-arterial route. Different chemotherapeutic agents have been tested in a small number of patients with disappointing efficacy. Promising results, however have been obtained with fotemustine, a new nitrosurea with pharmacokinetics are characterised by a high hepatic extraction rate. Among 17 patients, two complete and six partial responses were recorded. Due to the presence of extrahepatic metastases in half of the patients, the impact on survival could not be evaluated [34]. Immunotherapy may also have a better activity when administered through the hepatic artery [35].

Ocular melanoma has a different pattern of dissemination. In 85% of patients, the liver is the initial site of metastases, and bone or lung metastases develop in less than one third of the patients [36]. Locoregional therapy into the liver with cisplatin and polyvinyl sponge produced 1 complete and 13 partial remissions among 30 patients (46%) and a median survival time of 11 months, whch can be favourably compared with 2–6 months after conventional therapy [37]. Similar results have been obtained by hepatic intra-arterial fotemustine. Two complete and five partial responses for an overall response rate of 44% were achieved. The median survival was 10 months and the toxicity was minimal with a treatment given on an outpatient basis [38]. Other chemotherapeutic agents were not shown to have any significant activity.

3. RADIOTHERAPY OF MALIGNANT MELANOMA

For decades it was believed that melanoma was a radioresistant tumour and should in no case be treated with radiotherapy. However, for 10–15 years there has been a re-appraisal of the use of ionising radiations in this type of cancer [39]. A large body of radiobiological and clinical data was accumulated on melanoma indicating the usefulness of this therapeutic modality in well defined clinical situations [40]. Radiotherapy can provide excellent palliation in recurrent or metastatic melanoma, has a curative role in ocular melanoma and may be used as an adjuvant postoperative treatment in selected situations. In addition, the combination of hyperthermia with radiation looks to be a promising form of therapy as shown in recent studies [41].

Radiobiology

Although radiotherapy is now generally accepted by most oncologists as a useful tool in the treatment of melanoma, there is still considerable disagreement on the optimal way to deliver radiation. This is due to the controversial radiobiological aspects of this tumour.

Different melanoma cell lines were tested *in vitro* and have shown a fairly wide range of radiosensitivity patterns [42]. Cell survival curves, at increasing single doses of radiation, may vary considerably from cell line to cell line, especially with regard to the initial part of the curve called 'shoulder'. The larger the shoulder, the greater the efficiency of a cell line to repair sublethal radiation damage and the greater its resistance to low dose fractionation. The curvature can be quantified by the alpha/beta ratio, which are the coefficients of the linear and quadratic terms (respectively, the irreparable and reparable components) of the linear-quadratic model of a cell survival curve. A low α/β ratio (i.e. 1–5) indicates a high sublethal damage repair capacity and a high α/β (i.e. 15–30) the opposite. Although many common human cancers have a high α/β ratio, a proportion of lines and strains derived from melanoma were shown to have an α/β ratio below 5 [42]. To treat these tumours efficiently, fractionated radiotherapy should be given with fairly large doses per fraction. However *in vitro* data are heterogenous and some melanoma lines have high α/β ratio. Estimations by Overgaard from clinical radiation dose-response data in melanoma disclosed rather low α/β values [40]. In a review of 618 radiotherapy-treated malignant melanoma, in which many

variables were analysed, Overgaard found that the only parameter related to response was the dose per fraction. Dose per fraction > 4 Gy yielded 59% CR, versus 33% CR for dose per fraction < 4 Gy ($P = 0.001$), confirming older data by Habermalz [43]. According to Trott, these studies were flawed with a very heterogenous distribution of tumour sizes and total doses and the results cannot be taken as evidence that malignant melanoma respond better to large fractional doses than to conventional dose [44]. It should also be noted that many normal tissues have a low α/β ratio, and are thus more susceptible to developing late complications with high dose per fraction.

Clinical data

Primary treatment of melanoma. Surgery is the preferred treatment of cutaneous or mucosal melanoma. There are some situations however where surgery is not possible due to medical reasons or anatomical locations. For example in some head and neck melanomas, the lesions can be controlled by radiotherapy alone or by radiotherapy following minor surgical excision [45].

Ocular melanoma. Enucleation has been the traditional treatment of ocular melanoma. Radiotherapy now represents an alternative with obvious advantages. Cobalt plaque therapy has been used for almost 30 years and was felt to be therapeutically equal to enucleation [46].

A wealth of experience has been accumulated with high-precision proton-beam therapy (PBT) at the Harvard Cyclotron Laboratory, at the Berkeley Laboratory and at the Paul Scherrer Institute, Villigen, Switzerland. In these centres over 2800 patients were treated with PBT for uveal melanoma with outstanding results: 96% of the tumours were locally cured [47]. The doses were in the order of 70 Gy in 7–8 days. Complications included glaucoma and vasculopathy, and were felt to be acceptable. Proton beam therapy should be now considered as the treatment of choice for ocular melanomas [48].

Adjuvant radiotherapy

Experience with adjuvant postoperative radiotherapy is limited. In stage IB and II melanoma, regional relapse following surgery may be as high as 50%, suggesting a more aggressive approach. However, randomised studies failed to show an improvement in survival when radiotherapy was added to lymphadenectomy [49]. Harwood and Cummings reported the results of postoperative RT on 22 patients with microscopic residual melanoma following lymphadenectomy [39]. Patients received 24 Gy in three large fractions of 8 Gy [39]. The local control was 82%, but 55% eventually died from distant metastases.

Palliative radiotherapy for recurrent or metastatic melanoma

Radiotherapy can provide excellent palliation in recurrent or metastatic melanoma. Radiotherapy for superficial lymph node metastasis resulted in a remarkable palliative effect, expressed by tumour regression and reduced pains [50].

Schedules including fairly large doses per fraction are generally recommended. In one randomised study, two high-dose per fraction schemes of, respectively, 9 Gy × 3 or 5 Gy × 8 twice weekly were compared, and provided an overall response rate of 97% with no difference between the two schedules [51]. In case of brain metastases, the response rate is on average around 60–70%, with a mean survival of about 4 months; in this situation however, there is no evidence that large dose per fraction is superior to conventional fractionation [52]. Other sites can be treated with a good palliative effect, including intrathoracic, visceral and bony metastases [53]. However, bone metastases do not seem to be dependent on the dose per fraction.

In summary, radiotherapy has an important role in the treatment of advanced or metastatic melanoma, but one of the major obstacles in obtaining tumour control is the tumour volume. Radiotherapy should preferably be given to small lesions, rather than waiting until they have become too extensive [54].

Combined radiation and hyperthermia

Several of the early clinical studies of combined hyperthermia and radiation were on melanoma [55]. This was due both to the accessibility of superficial melanoma to local hyperthermia and to radiobiological characteristics of these tumours implying the use of few large fractions in conjunction with heat. A review by Overgaard of approximately 800 tumours treated with radiation alone or radiation and heat disclosed a much higher response rate when combined treatment was used. The isoeffective thermal enhancement ratio [41] was 1.6, indicating a very significant improvement of the effect when heat was added to radiation. The role of hyperthermia added to radiotherapy will need to be confirmed in randomised trials.

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