

## INTRAARTERIAL CHEMOTHERAPY IN LOCALLY ADVANCED AND RECURRENT EXTREMITY TUMORS

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Gazi Medical Journal 1997; 8 : 62-66

### SUMMARY

**Purpose :** Most of the soft tissue sarcomas, malign melanoma, and skin cancers which are localized on extremities are treated surgically. On the other hand, for locally advanced extremity tumors, surgical treatment can not provide an improvement in survival as the only treatment modality. In these cases, intraarterial chemotherapy has been performed since 1960's for increasing the resectability and having a chance for radiotherapy. Based on these proposed advantages, we started a prospective study with intraarterial chemotherapy in locally advanced extremity tumors. **Methods :** In Ankara Oncology Hospital, between 1992-1995, 15 patients with locally advanced extremity tumors were arterially catheterized. Eight of them were female, seven were male, and the mean age was 52.6. The tumors were localized on lower extremity in 12 cases and the upper extremity in 3. Before intraarterial chemotherapy, 12 patients were treated with different modalities. Deticine and Cisplatin were applied for melanomas, 5-Fluorouracil and Cisplatin for skin cancers, and Adriablastin for soft tissue tumors. **Results :** Complications were observed in 4 cases due to port catheter systems. In 14 cases, various toxic side effects were seen after intraarterial chemotherapy. Four patients were out of follow and one patient could not receive intraarterial chemotherapy because of catheter occlusion. Ten cases could be evaluated for response; partial remission was observed in 6 cases, progressive disease in 3, and stable disease in 1 case. Mean follow-up period for these nonresponding 4 cases was 6 months, and was 11 months for the responding 6 cases. **Conclusion :** We suggest that intraarterial chemotherapy can be used as a neoadjuvant modality for increasing the surgical resectability of locally advanced extremity tumors.

**Key Words :** Extremity, Intraarterial, Chemotherapy.

### INTRODUCTION

Soft tissue sarcomas, malignant melanoma, and skin cancers localized on extremities are generally treated with surgery. Especially for soft tissue sarcomas, radiotherapy and high dosage chemotherapy could be applied before or after surgery for increasing survival. In spite of these radical therapy modalities, it has been reported that

local recurrence rates after surgery for soft tissue sarcomas are 30-60 % (1). Similar results have also been noted for locally advanced malignant melanoma and skin cancers. It was seen that for locally advanced cases, other treatment modalities should be applied in addition to surgery. Amputation had been accepted as the best treatment for locally advanced extremity tumors in the past years (2). Recently, extremity conserving surgical

treatment modalities have become popular. As a neoadjuvant setting, surgical resectability can be increased and local recurrence rates can be decreased with intraarterial chemotherapy (3-9). Intraarterial chemotherapy for locally advanced extremity tumors can be applied before surgery as a neoadjuvant treatment, as the primary curative treatment, or as a palliative agent for irresectable cases. In this study, intraarterial chemotherapy was applied to a group of patients for increasing the surgical resectability in locally advanced extremity tumors.

### PATIENTS AND METHODS

Arterial catheters were applied to 15 patients with locally advanced extremity tumors in Ankara Oncology Hospital between 1992 and 1995. There were 8 female and 7 male patients, and the mean age was 52.6. It was noted that there were no distant metastases, and primary surgery or radiotherapy couldn't be applied. Tumors were localized on the lower extremity in 12 patients and the upper extremity in 3. Histopathologic types of the tumors were; epidermoid carcinoma in 3, malignant melanoma in 7, and malignant mesenchymal tumor in 5 patients (Table 1). Four patients had no treatments before intraarterial catheterization, but 11 patients had been treated with surgery. The

medical history included only one extensive excision in 4, two extensive excisions in 5, and extensive excision plus inguinal dissection in 2 patients. Radiotherapy and chemotherapy had been applied in 2, chemotherapy in 3, and radiotherapy in 1 patients for adjuvant setting. Other than these 11 surgically treated patients, 1 patient had been treated with primary radiotherapy before intraarterial chemotherapy (Table 2).

Arterial catheterization was performed via a.thoracica dorsalis and truncus thyrocervicalis for upper extremity tumors in 3 cases. In lower extremity tumors, 10 catheterizations were performed via a.epigastrica inferior and a.circumflexa ilium superficialis in 2 cases who had undergone inguinal dissection before.

Deticine 250 mg/m<sup>2</sup>/24h continuous intraarterial infusion was applied for 5 days in 6 malign melanoma patients. For epidermoid carcinoma patients (3 patients), 5 Fluorouracil 600 mg/m<sup>2</sup>/24h continuous infusion was applied intraarterially for 5 days. Adriablastin 20 mg/m<sup>2</sup>/24h continuous infusion was administered for 3 days for malign mesenchymal tumors in 5 patients.

Histopathologic Type	Lower Extremity	Upper Extremity	Total
Epidermoid carcinoma	2	1	3
Malign melanoma	7	-	7
Malign mesenchymal tumor	3	2	5
Total	12	3	15

Table 1 : Distribution of patients according to tumor localization and histopathologic types.

Previous Treatment modality	Number of Patients
Radiotherapy + Chemotherapy	1
Surgical treatment	11
One extensive excision	4
Twice extensive excisions	5
Extensive excision + inguinal dissection	2
After Surgical treatment	
Radiotherapy + Chemotherapy	2
Chemotherapy	3
Radiotherapy	1

Table 2 : Treatment modalities applied before intraarterial chemotherapy.



## RESULTS

Among the 15 patients who were catheterized intraarterially, 1 patient could not receive chemotherapy because of catheter occlusion. Port site skin necrosis were noted in 2 cases, port site infection in 2, catheter occlusion in 2 and arterial rupture, bleeding in 1 case (Table 3). All of these complications were seen in 4 patients. In one case (malign mesenchymal tumor in upper extremity) bleeding occurred due to arterial rupture after adriablastin chemotherapy. This bleeding was controlled immediately and the defect was repaired with otologous vein graft.

Complications	Patients
Port site skin necrosis	2 (13.3%)
Port site infection	2 (13.3%)
Arterial rupture	1 (6.6%)
Arterial bleeding	1 (6.6%)
Catheter occlusion	2 (13.3%)

Table 3 : Complications related to port-catheter system and intraarterial chemotherapy.

The patients received 37 courses (mean 2.6 courses) of intraarterial chemotherapy. Various toxic side effects were seen in 14 patients. These toxic side effects were; nausea-vomiting in 10 cases (6 Grade I, 4 Grade II), anemia in 9 (7 Grade I, 2 Grade II), leukopenia in 5 (4 Grade I, 1 Grade II), thrombositopenia in 2 cases (Grade I), alopecia in 5 (3 Grade I, 2 Grade II), diarrhea in 1 case (Grade I), pain in 4 cases (3 Grade I, 1 Grade II), fever in 4 (2 Grade I, 2 Grade II), and dermal toxicity in 5 cases (2 Grade I, 3 Grade II) (according to WHO toxicity criteria')(Table 4).

Ten out of 14 patients were treated with intraarterial chemotherapy, and could be followed. The response rates of these patients were as; partial response in 6 cases (PR), progressive disease in 3 cases (PD), and stable disease in 1 case (SD) (Table 5).

For responding 6 patients, surgery could be performed in 4 cases (3 malign melanoma, 1 epidermoid carcinoma). In other 2 responding patients, treatment was continued with radiotherapy and systemic chemotherapy (Table 6). Mean follow-up period for all patients was 7 months (1-16) and for responding (PR) patients it was measured as 11 months (6-16).

Toxic effects	Grade I	Grade II	Total	%
Nausea-vomiting	6	4	10	71.4
Anemia	7	2	9	64.2
Leukopenia	4	1	5	35.7
Thrombositopenia	2	-	2	14.2
Alopesia	3	2	5	35.7
Diarrhea	1	-	1	7.1
Pain	3	1	4	28.5
Fever	2	2	4	28.5
Dermal toxicity	2	3	5	35.7

Table 4 : Toxic side effects related to intraarterial chemotherapy.

	Progressive Disease	Stable Disease	Partial Response
Malign melanoma	1	-	4
Epidermoid carcinoma	-	-	1
Malign mesenchymal tumor	2	1	1
Total	3 (30%)	1 (10%)	6 (60%)

Table 5 : Response rates of intraarterial chemotherapy.

Patients	Treatment
M.melanoma	Wide excision + inguinal dissection
M.melanoma	Wide excision + inguinal dissection
M.melanoma	Wide excision
M.melanoma	Systemic chemotherapy
Epidermoid carcinoma	Wide excision + systemic chemotherapy
M.mesenchymal tumor	Radiotherapy + systemic chemotherapy

Table 6 : Other treatment modalities applied after intraarterial chemotherapy in responding patients.

## DISCUSSION

Surgical treatment for locally advanced or recurrent extremity tumors has a lot of difficulties and cannot always provide a significant improvement in survival. Locally advanced and recurrent locoregional melanoma with a large tumor bulk represents an unquestioned therapeutic challenge. Surgical resection has been of limited benefit unless combined with other treatment strategies, such as intraarterial chemotherapy. Systemic chemotherapy usually achieves transient tumor regressions in only 10-30 % of the patients regardless of the specific regimen employed. Although regional recurrence of melanoma is often a harbinger of distant metastases, a patient may derive a palliative and sometimes curative benefit from aggressive regional chemotherapy and surgery (10, 11).

Advanced soft tissue sarcomas in extremities in the past have been treated by amputation because of the high risk of local recurrences when less radical local treatments have been used. Following removal of malignant soft tissue tumors, local recurrence develops in 30 to 60 % (1). According to literature data, 70 % of the local recurrences appear within the first two, and 90 % in the first five years. Distant metastases occur in 40 to 60 % of the cases (1). Attempts have been made to salvage limbs by the initial use of chemotherapy and radiotherapy to reduce the size of the tumor and to allow local control by local surgical excision rather than by amputation. Regional chemotherapy given by intraarterial infusion is an attractive concept based on pharmacokinetic principles, and it has been used effectively in treatment of locally advanced head and neck cancer or locally advanced extremity tumors. The main advantage of the approach used is its effect on surgical management of these large aggressive tumors. Improved local control has been

possible by making surgical resection feasible.

Indications for intraarterial infusion of the extremities for locally advanced and/or recurrent extremity tumors are: as an adjunct to surgical resection, for definitive treatment alone, to convert advanced inoperable lesions to resectable lesions, and for palliation of symptoms in incurable recurrent diseases. For these purposes, intraarterial chemotherapy was used in a group of patients in this study. Complications and toxic side effects were found to be similar to the other reported series (10-13). There was an unexpected complication of arterial bleeding in one case. We met similar complications in the literature (1). Port site skin necrosis, port site infection, and catheter occlusion were the complications that were seen in the study. Probably, these complications were due to the inexperienced medical team and insufficient education. It was seen that toxic side effects were not different from the systemic therapy. Nausea-vomiting (71.4 %), anemia (64.2 %), leukopenia (35.7 %) and alopecia (35.7 %) were the most common side effects. Other than these systemic side effects, pain and dermal toxicity were observed, especially in adriablastin administration: flushing were detected on extremities with mild pain.

Of the 5 patients with malign melanoma, 4 responded to intraarterial chemotherapy. In a similar series with malign melanoma, Calabro et al. reported a response rate of 37 % with intraarterial chemotherapy (11). It is important to note that all of these responding malign melanoma patients could have surgical excision. The response rate of soft tissue tumors in our study was lower (20 %) than the previously reported series (2, 4, 5, 7, 9). A response rate of 60 % may be considered to be a good result, but the follow-up period of these patients (11 months) in our study doesn't appear to be



promising. Although 3 patients died because of progressive disease during follow-up, most of the responding patients were out of follow, because of paramedical reasons.

We may conclude that intraarterial chemotherapy can be applied in locally advanced and recurrent extremity tumors as a neoadjuvant setting.

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