

trating type. Survival of patients with MHC may depend on the stage of the tumor.

Clinically, we need an exact preoperative diagnosis for surgical treatment. Examination of cytokeratin expression in MHC is not beneficial preoperatively because of the intermingling of the tumors. Therefore, we need more useful markers for MHC, e.g., α -fetoprotein, carcinoembryonic antigen, CA19-9, hypovascularity, or a combination of these markers, as demonstrated in the previous report.¹ However, there have been very few reports on this subject.

In conclusion, assessment of cytokeratin expression may be useful in the diagnosis of MHC, but we consider that its value is still not definitive. MHC, especially the nodular type, may not require hilar lymph node dissection up to a certain stage. However, further investigations of the definition, preoperative diagnosis, and treatment of MHC are needed.

REFERENCES

- Nakamura S, Suzuki S, Sakaguchi T, Serizawa A, Konno H, Baba S, et al. Surgical treatment of patients with mixed hepatocellular carcinoma and cholangiocarcinoma. *Cancer* 1996;78:1671-6.
- Allen RA, Lisa JR. Combined liver cell and bile duct carcinoma. *Am J Pathol* 1949;25:647-55.
- Maeda T, Adachi E, Kajiyama K, Sugimachi K, Tsuneyoshi M. Combined hepatocellular and cholangiocarcinoma: proposed criteria according to cytokeratin expression and analysis of clinicopathologic features. *Hum Pathol* 1995;26:956-64.
- Maeda T, Kajiyama K, Adachi E, Takenaka K, Sugimachi K, Tsuneyoshi M. The expression of cytokeratins 7, 19, and 20 in primary and metastatic carcinomas of the liver. *Mod Pathol* 1996;9:901-9.
- Yamamoto J, Kosuge T, Takayama T, et al. Surgical treatment of intrahepatic cholangiocarcinoma: four patients surviving more than five years. *Surgery* 1992;111:617-22.

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Influence of Methotrexate Dose Intensity on Outcome of Patients with High Grade Osteogenic Osteosarcoma

Analysis of the Literature

Because several of our group's cooperative studies were included in a meta-analysis of high grade osteosarcoma trials recently published in *Cancer* by Delepine et al.,¹ we feel compelled to point out what we believe is a serious methodologic flaw in the design of that particular analysis. Delepine et al. have introduced such a strong bias that they have created a self-fulfilling prophecy. The further use of methotrexate was guided by tumor response to preoperative methotrexate-based chemotherapy in >50% of the protocols on which the meta-analysis was based (including our trial, COSS 82).² However, response to preoperative treatment is widely accepted as being the most important prognostic factor in localized osteosarcoma.³

The authors attempt to convince us that they proved the importance of high methotrexate dose intensity in the treatment of osteosarcoma, when in reality (at least in the case of our study [COSS 82]² and several others) their analysis is not about methotrexate dose intensity, but rather is a comparison of good responders with poor responders. Of course, good responders did better and poor responders did worse. Accordingly, the authors have observed nothing but this well known strong impact of tumor response on disease free survival. We would be interested to learn whether Delepine et al. would still find any influence of methotrexate dose intensity if all protocols in which the further use of the drug varied with tumor response were omitted from their meta-analysis.

REFERENCES

- Delepine N, Delepine G, Bacci G, Rosen G, Desbois JC. Influence of methotrexate dose intensity on outcome of patients with high grade osteogenic osteosarcoma. *Cancer* 1996;78:2127-35.
- Winkler K, Beron G, Delling G, Heise U, Kabisch H, Purfürst C, et al. Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS 82) with salvage chemotherapy based on histological tumor response. *J Clin Oncol* 1988;6:329-37.
- Davis AM, Bell RS, Goodwin PJ. Prognostic factors in osteosarcoma: a critical review. *J Clin Oncol* 1994;12:423-31.

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Since Huvos and Rosen's first publication,¹ the prognostic value of tumor response to preoperative methotrexate (MTX) has been widely confirmed. Furthermore, using the T10 scheme, most neoadjuvant protocols for osteosarcoma give more MTX and less doxorubicin and cisplatin to good responders. Accordingly, a univariate regression analysis ignoring the strong interfactor correlation would include a major bias.

However, our study used a multivariate analysis, which allowed us to test each available factor and attribute their real value in a linear model thus:

Disease free survival (DFS) (%):

$$\sum a \cdot \text{intensity drug A} + \sum \alpha \cdot \text{total dose drug A} \\ + x \cdot \text{response} + \sum y \cdot \text{other factor.}$$

This model confirmed the independent prognostic value of tumor response as well as the dose intensity (DI) of MTX. Because our study focused on the importance of drugs and took into account many adjuvant protocols, we did not mention this well established fact. We can predict that the average independent weight of response (rated as 1 = good; 0 = unknown; and -1 = bad) on DFS is $\pm 6.5\%$. The general model for DFS is:

$$\text{DFS} (\%) = 7.7 \cdot \text{DI MTX} + 6.5 \cdot \text{Response} + 36$$

That means that, on average, increasing the drug intensity of MTX by $1 \text{ g/m}^2/\text{week}$ results in a more significant increase in DFS (7.7%) than a good response alone (6.5%).

To help those less familiar with matrical computing, a simple verification can be performed by considering only the protocols in which the further use of drugs does not vary with tumor response (postoperative adjuvant protocols and neoadjuvant protocols in which good and bad responders receive the same treatment).

Although reducing the data base to only 11 protocol arms also reduces the discriminating power of the test, the correlation between DI of MTX and DFS remains significant ($P < 0.01$).

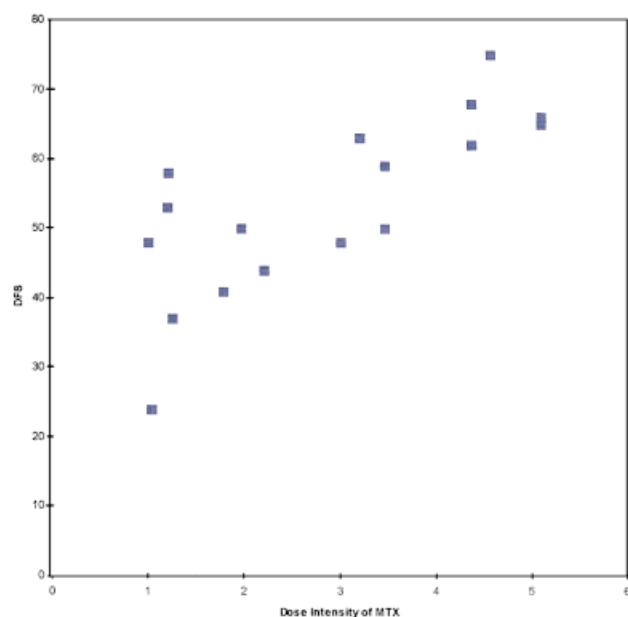


FIGURE 1. Graph shows significant correlation between disease free survival (DFS) and dose intensity of methotrexate (MTX) ($P < 0.0001$) in protocols in which the postoperative use of drugs did not vary with tumor response.

Since the publication of the meta-analysis, two international congresses on osteosarcoma have taken place (XXVIIth Meeting of the International Society of Pediatric Oncology [SIOP], Vienna, Austria, October 1–5, 1996, and the 2nd Osteosarcoma Research Conference, Bologna, Italy, November 19–22, 1996), permitting us to update our data base to 37 treatment arms (2471 patients). Among the 17 protocols in which the postoperative use of drugs did not vary with tumor response, the correlation between DFS and DI of MTX was more significant ($P < 0.0001$), as depicted on the graph (Fig. 1). Therefore, we are convinced that our meta-analysis shows the major power of MTX DI on DFS in patients with osteosarcoma.

Rosen's initial correlation of response to chemotherapy and DFS was obtained utilizing primarily preoperative high dose MTX. It has been his experience that complete responders to chemotherapy protocols without high dose MTX do not have the same high rate of DFS. Our findings strengthen this observation and warn against being overly optimistic about responses to non-MTX-intensive treatment for patients with osteosarcoma.

REFERENCE

- Huvos AG, Rosen G, Marcove RC. Primary osteosarcoma. Pathologic aspect in 20 patients after treatment with chemotherapy, en bloc resection and prosthetic replacement. *Arch Pathol Lab Med* 1977;101:14–8.