OBJECTIVE ASSESSMENT OF RESPONSE OF OSTEOSARCOMA TO CHEMOTHERAPY: IS IT BETTER THAN SUBJECTIVE ESTIMATES?

Bülent CELASUN, M.D., Ayhan ÖZCAN, M.D.

Gülhane Military Medical Academy and School of Medicine, Department of Pathology, Ankara, Turkey.
Gazi Medical Journal 2000; 11: 9-12

SUMMARY :

Purpose: *The pathological evaluation of osteosarcomas removed after neoadjuvant treatment is done to determine whether there is sufficient response to the chemotherapeutics given. The results, expressed either in grades or in percentages, may form the basis of future therapy.* ***Methods:*** *In this report, we present a simple quantitative method for the evaluation of the response of osteosarcomas to chemotherapy in a series of 17 cases.* ***Results:*** *Grade III-IV responders or those with at least 90% response are regarded as more likely to have a good prognosis. However, the grading is imprecise and the methods of estimating the percentages have not been well documented. We have found that some cases may be misclassified using the conventional methodology.* ***Conclusion:*** *Only "complete response" seems to be associated with a good prognosis, and it is not certain whether evaluating the response as a continuous variable offers any benefit.*

Key Words : *Osteosarcoma, Treatment Response, Quantitative Pathology, Image Analysis.*

INTRODUCTION

The response of osteosarcoma to chemotherapy is evaluated radiologically and pathologically. Measurement of the size of the tumour before and after treatment forms the basis of the radiological assessment. The histological response is evaluated qualitatively by the pathologist on the resection sample. "Normalisation of tumour bone", "necrosis" and "fibrosis" are all taken as histological signs of response. It is not unusual to see an almost complete disappearance of the malignant cellular component of osteosarcoma after chemotherapy.

There are two approaches for the evaluation of chemotherapy response. The first and probably the most widely used is making a statement of percentage response, like "response to chemotherapy is 90%". This can be qualified by words like "about" and "at least". The other approach is to "grade" the response. This is probably more familiar to a practicing pathologist because he/she grades a great variety of lesions routinely.

The grading as suggested by Huvos et al. (1) is as follows:

Grade I : Little or no response.

Grade II : Areas of response and areas of viable tumour.

Grade III : Predominant areas of response with scattered foci of histologically viable tumour cells.

Grade IV : No evidence of viable tumour within the specimen.

Although the protocols may vary, many would consider a change in the post-resection treatment protocol if the response is less than "90%" or "grade III-IV". Practically, the evaluation results are summed up as "yes, there is response" for grade III-IV (≥ 90%) responders and "no, there is no response" for the rest. A good response to treatment is one of the most powerful prognostic variables in recent large series (2,3)

A problem introduced by these approaches is the great change in the outcome that can be caused by misclassifying a grade II case as grade III or vice versa. It would also be dangerous, if not wrong, to say that there is less than 90% response, while the response was, in fact, greater than that. Also, reporting a numerical value (the percentage) in the absence of quantitation is imprecise. The reproducibility of these evaluations has not been studied yet.

In this study, we aimed at making the estimation of the histological response of osteosarcomas to chemotherapy more objective and reproducible. Contribution, if any, of the objective quantification method to the estimation of prognosis has also been analyzed.

METHODS

Seventeen consecutive extremity osteosarcomas, which had been evaluated previously in the Pathology Department of Gülhane Military Medical Academy between 1990-1997, were studied again. All the cases were eligible for limb-salvage surgery (Enneking stages II A and II B) and all received neoadjuvant chemotherapy. The standard chemotherapy regimen consisted of cisplatin, adriamycin and iphosphamid. The clinical features are shown in Table 1.

There were about 20 slides (range: 9-32) per case. First, the set of slides for each case was evaluated according to the above criteria and a "grade" was given. After evaluating all the cases, the slide sets were again evaluated to get the "subjective percentages". Our routine methodology consists of evaluating every single slide and estimating the percentage area of viable tumour subjectively. After finishing the evaluation of all the slides, the percentages are averaged for each case. Finally, we have made morphometrical measurements, as described below, to get the "objective percentages".

Zeiss Vision KS400 image analysis software, running on an IBM compatible PC with Intel-Pentium processor and Matrox Meteor frame grabber was used. For the measurements, the slides were put on the luminous field of the Zeiss Axioskop microscope with a X 1.25 objective. This ensured viewing of the entire section and allowed capturing this image for measurement. The areas occupied by tumour were marked by pen before. The areas which had never been involved by the tumour (for example the periosteal, normal-looking muscle) were not measured. A macro program prepared by one of the authors (BC) has been used to help interactive delineation of the outline of the total affected area and the areas with residual tumour separately. Then, the percentage area which was free of tumour was calculated.

Pearson's test was done to evaluate correlations between objective and subjective response rates with survival. For this test, the living patients at the time of last follow up were regarded as "alive" and others as "lost to follow up".

RESULTS

The results of all measurements are shown in Table 2. Average survival of patients died due to disease related causes was 14,6 months while the average follow up of living patients were 44,3 months. The "grading" is compared with "subjective percentage estimations" and with "measured percentages". Subjective estimations and measured percentages correlated significantly ($p<0,0001$). Both the subjective estimations and the measured percentages correlated with good prognosis ($p<0,002$ for each) which was defined as being alive at the time of last follow up.

DISSCUSSION

The method we described in this study is very simple. However, many other methods can

Table 1 : Clinical data and the evaluation of responses to treatment.

Case	Age	Sex	Site	Grade % (Huvos et. al.)	Response % (subjective estimate)	Response (measured estimate)	Follow upstatus (months)
1	15	K	Right proximal humerus	I	50	52.5	26, DOD
2	24	E	Right distal femur	II	75	75.9	22, DOD
3	19	E	Left distal femur	IV	>95	99.9	28, AW
4	15	E	Right proximal tibia	IV	>95	99.8	40, AW
5	19	E	Left proximal tibia	III	90	93.9	28,DOD
6	13	K	Left proximal humerus	I	50	50.5	11,DOD
7	19	E	Left proximal tibia	II	60	80.2	8, DOD
8	26	E	Left proximal femur	II	80	92.9	11, DOD
9	18	E	Right distal femur	III	90	99.4	66, AW
10	20	E	Right proximal tibia	II	80	92.8	72, AW
11	12	E	Right distal femur	IV	95	99.1	14, DOD
12	16	E	Left distal femur	II	70	89.2	9, DOD
13	23	E	Proximal fibula	IV	95	99.8	49, AW
14	21	E	Left distal femur	II	75	68.4	8, DOD
15	21	E	Left distal femur	III	90	97.8	11, DOD
16	20	E	Left distal femur	III	90	98.7	13, DOD
17	16	K	Right distal femur	IV	>95	99.9	11, AW

DOD : Dead of disease; AW: Alive and well.

Table 2 : Comparison of subjective and objective estimated response percentages.

	Subjective percentages			Objective (measured) percentages			
Grade	<60%	60-89%	90-100%	<60%	60-89%	90-95%	>95%
I	2	-	-	2	-	-	-
II	1	5	-	4*	2	-	-
III	-	-	4	-	-	1	3
IV	-	-	5	-	-	-	5

* : One case with a 89.2 % response.

be developed easily. For instance, the microscope slides can be scanned using a scanner. A still more simple approach would be taking an enlarged photocopy of these slides on a paper with grids, and then counting the grids overlying the study area and areas of residual tumour. Percentages can be calculated easily afterwards. Stereologic methods may allow more rapid and equally useful measurements.

The feasibility of measuring the histological response to chemotherapy as a continuous variable has been considered before (1). However, to the best of our knowledge, no such study has been done to date. A well-defined category of "partial response" does not seem to exist and the clinicians are content with the "good response - bad response" dichotomy. However, this may be an oversimplification which may hamper prognostic evaluations in the long run.

Our study shows this potential threat. In Table 2, the usual situation which can also be encountered at other institutions is seen, and apparently no cases have been misclassified. According to this table, there seems to be no advantage in selecting either evaluation method; that is, grading or estimating a percentage. All grade III and IV cases showed at least 90% response.

On the other, hand the data in Table 2 which show measured estimates, suggest a need to revise the final classification from non-responder to responder in at least 2 of the cases. A case with a 89.2% response can also be practically regarded as a responder. When the cut-off for response is taken as 90%, there are 9 cases that can potentially be misclassified with serious consequences. In Table 2, two of these (22.2%) are clearly seen to be misclassified originally. Many would consider classifying the 89.2% response case also as a responder. This makes 3 misclassifications in 9 (33.3%).

It would be illogical to claim that human eye can differentiate 80 or 85% from 90 or 95%. Also, the proof that the proper cut-off is 90% is still lacking. Grading, as described by Huvos et al., can be misleading for this group of cases as

the definitions of grade II and III are not sufficiently detailed to make these separations with confidence and with an acceptable degree of interobserver variability. Incidentally, the presently accepted cut-off for responders and non responders lies at this range. On the other hand, Table 1 shows that even a more than 99% tumour response cannot guarantee a good prognosis as one such patient (case 9) succumbed to disease within a year. A poor responder (case 2) lived almost 2 years. Still, the correlation between the response to chemotherapy and prognosis is currently beyond doubt. (2,3) This was also shown in our sample.

Perhaps, the problem is searching for a cut-off value which does not exist. When the response is taken as a continuous variable, a cut-off would become less of a problem. However, the present study does not show a noticeable advantage of objective measurements over Huvos grading; all grade IV cases have been within the morphometrically favourable group. This suggests that although the response of osteosarcoma to neoadjuvant treatment can be evaluated more objectively, grading according to the Huvos scheme is generally sufficient to provide the necessary information. However, to label a case as "Huvos grade IV"; strict obedience to original criterion; that is "total absence of tumour" is mandatory.

Correspondence to : Dr. Bülent CELASUN
Gülhane Askeri Tıp Akademisi
Patoloji A.B.D.
Phone and Fax. : 90 312 417 21 08
E-mail: bulent.celasun@garanti.net.tr

REFERENCES

1. Huvos, AG Bone tumors: Diagnosis, treatment and prognosis, 2nd Ed. Philadelphia: W.B. Saunders 1991; p: 124.
2. Picci P, Sangiorgi L, Bahamonde L, Aluigi P, Bibiloni J, Zavatta M, Mercuri M, Briccoli A, Campanacci M. Risk factors for local recurrences after limb-salvage surgery for high-grade osteosarcoma of the extremities. Ann Oncol 1997; 8 : 899-903.
3. Pochanugool L, Subhadharaphandou T, Dhanachai M, et al. Prognostic factors among 130 patients with osteosarcoma. N Clin Orthop 1997; 345 : 206-214.