Diagnostic Pathology: Open Access

Chandrakanth and Bajpai, Diagn Pathol Open
2016, 1:3
DOI: 10.4172/2476-2024.1000119

Short Communication OMICS International

Compliance to Therapy as a Prognostic Marker in Osteosarcoma: New Kid on the Block!

Chandrakanth MV and Jyoti Bajpai*

Medical Oncology, Tata Memorial Hospital, Mumbai, India

***Corresponding author:** Jyoti Bajpai, Associate Professor, Medical Oncology, Tata Memorial Hospital Mumbai, India, E-mail: dr_jyotibajpai@yahoo.co.in

Received date: September 08, 2016; **Accepted date:** October 24, 2016; **Published date:** October 27, 2016

Content

Compliance to therapy is an important factor in medical science as patients who follow regular medical advice is expected to get good results. Lewis et al. broadened the concept of compliance from only patients' adherence to a prescribed treatment to certain psychological and behavioral aspects like the treating physician's attitude, doctor–patient relationship, and the degree of psychosocial support available to the patient [1,2]. The word "adherence", is preferred because "compliance" suggests that the patient is passively following the doctor's orders and that the treatment plan is not based on an established therapeutic agreement between the patient and the physician. However, the word compliance is retained as it is used more often. The most commonly cited definition of adherence is 'the extent to which a person's behavior coincides with medical or health advice' [3].

Osteosarcoma is the commonest primary malignant bone tumor in children and adolescents [4]. Two thirds of localized osteosarcoma and 1/3 of osteosarcoma with lung metastases achieve long term survival [5,6]. Histological necrosis (HN) in the postoperative specimen, post Neo adjuvant chemotherapy (NACT) is an important prognostic marker. 5-year event-free survival (EFS) of 35-45% is seen in poor responders (PR)) and 70-80% in Good Responders (GR) wherein histological necrosis ≥ 90% is considered as good response [7,8]. Factors affecting necrosis will be having indirect bearing on ultimate outcome and hence are of utmost importance and worth exploring.

In a retrospective study, histologically confirmed and high grade osteosarcoma patients of the extremities, shoulder and pelvic girdle receiving uniform chemotherapy protocol in the year 2010 at Tata Memorial cancer center was conducted. Patients received three cycles of NACT. The chemotherapy protocol included a combination of drugs (ifosfamide, adriamycin, and cisplatin) in alternating cycles. The first cycle consists of ifosfamide (9 g) and adriamycin (75 mg) and the second cycle consists of cisplatin (120 mg) and adriamycin (75 mg). The third cycle is similar to the first cycle. Compliance was defined as receipt of planned number of cycles in the planned doses within the planned duration or up to 25% additional time. Treatment response was assessed by evaluation of histological necrosis with standard definition for good response. A univariate analysis was carried out to assess the significant factors associated with non-compliance and later these variables were tested in multivariate analysis to identify the independent variable for noncompliance.

There were 115 evaluable patients, out of whom 73 patients (64%) were compliant, while 42 (36%) were non-compliant. There was an interesting observation noted in the study that is, within the compliant group, 47 (64%) were GR and 26 (36%) were PRs. In the non-compliant group, 18 (42.86%) were GR and 24 (57.14%) were PRs. There was a statistically significant association between good histological response and compliance (P=0.031). At a short median follow-up period of 7.9 months, there was no statistically significant difference in non-compliant versus compliant group in terms of disease-free (DFS) or overall survival (OS). However, it will be interesting to observe the survival difference with a mature follow up. Twenty six patients had justifiable reasons for compliance like chemotherapy-related myelosuppression and febrile neutropenia. In 16 patients there were no justifiable reasons for non-compliance. The latter included 8 patients with financial constraints, 7 with communication failure and 1 patient who faced an undue delay for surgery. There were 19 cases with metastatic disease. The non-compliant group included twice as many cases with metastatic disease in contrast to the compliant group; it might be an indirect reflection to poor compliant patient being negligent in reporting early to medical care with resultant upstaging. On multivariate analysis only poor performance status was independently associated with non-compliance; Poor general condition can be associated with poor tolerance to therapy and also reflects the status of host immunity, nutritional status and associated co morbidities.

Compliance to a prescribed treatment is a complex and multifaceted issue. Various factors concerning the patient, disease, health providers, and treatment characteristics determine the treatment compliance [9]. Current cancer care treatment is delivered more often with curative intent. Family and social support, individualized programs, reminders to reduce forgetfulness, personalized needs assessment, and education are measures that can help improve compliance [10]. A review of the National Surgical Adjuvant Breast Project study showed that about 30% of the patients failed to complete the two years of treatment [11]. A study from Stanford applied complex statistical analysis to data on 123 patients with Hodgkin's disease. The rate of drug delivery during the first three cycles of combination chemotherapy was found to be important in achieving a complete response. The rate of delivery of nitrogen mustard was the third most significant variable in predicting increased survival, after age and pleural disease [12]. Adewale et al. from Nigeria evaluated patients' adherence to chemotherapy for breast cancer. The non-adherence rate was 80.9% and 73% of the non-adherent patients were eventually not seen again. Of the one hundred and one patients who gave reasons for non-adherence, 45% complained of financial difficulties; 18% thought they were well enough; 15% were fearful of subsequent operation and 11% were unable to further bear the drug side effects. In conclusion, the study demonstrated poor economic status of the patients as one of the major reasons for non-adherence to cancer chemotherapy. Government subsidy of breast cancer treatment, improved health education and advocacy complemented by home visiting to encourage hospital attendance would be required for better adherence to chemotherapy [13].

In our study 64% patients were compliant, while 36% were non-compliant. 26 patients had justifiable reasons for non-compliance, while it was not justified in 16 patients. Unjustifiable reasons included financial constraints, communication failure, and delay in surgery. Compliance to chemotherapy may be improved by strengthening patient–physician relationship and developing better communication between physician and patients. On multivariate analysis, only poor performance status was identified as an independent variable for non-compliance. Even with resource constraints, two-third of our patients was compliant to NACT. These data does reveal the correlation of survival and compliance by using 'good necrosis' as a surrogate indicator of "good survival". To improve our compliance rate, we have adopted a system similar to that proposed by Rosenberg et al. It is a multistep method which would help us to identify high risk patients for noncompliance and takes into account not only the socioeconomic and demographic factors but also the psychosocial, physical and intellectual factors. In conclusion, the results from our study suggest that better compliance to chemotherapy protocols in osteosarcoma patients might translate into improved survival. Further studies along similar avenues with larger numbers and a wide follow-up could possibly help in establishing a stronger association between the two and in prospectively identifying correct potential causes for non-compliance. Our present endeavor is to increase the support staff and put in place a more structured program to improve the overall compliance rate.

No such study in osteosarcoma has been accomplished. Yong et al. from China reported that suboptimal chemotherapy is an adverse prognostic factor in osteosarcoma. They studied total of 132 osteosarcoma patients and reported that suboptimal chemotherapy was an independent prognostic factor and was associated with higher risk of relapse, metastases and mortality [14].

Compliance to prescribed treatment is a well-known factor which influences outcomes .It is well established in treatment of infectious diseases like tuberculosis. However there is relatively scarce evidence in cancer therapy. We have evidence from our retrospective data suggesting compliance as an important marker for outcomes in osteosarcoma. The following studies on compliance to anticancer therapy have addressed various factors affecting compliance including psychological, and financial aspects .They also have evaluated the place of therapy and the possible modifications that can be made to improve compliance.

Morisky and green test is a questionnaire that evaluates attitudes of patients regarding treatment. Marques et al. from Brazil studied the factors that affect cancer patient compliance to oral antineoplastic therapy and concluded that 28% were considered non-compliant by utilizing the Morisky and Green Test [15].

Borras et al. from Spain performed a Randomized control trial assessing Compliance, satisfaction, and quality of life of patients with colorectal cancer receiving home chemotherapy or outpatient treatment concluded that home chemotherapy is an acceptable and safe alternative to hospital treatment for patients with colorectal cancer that may improve compliance and satisfaction with treatment [16].

A study on the influence of mood and adjustment to cancer on compliance with chemotherapy among breast cancer patients revealed high scores on Mental Adjustment to Cancer Scale Fighting Spirit and Affects Balance Scale (ABS) Anxiety, Depression, and Vigor scales were associated with greater adherence to a chemotherapy regimen. High scores on ABS Guilt and Hostility scales predicted lower levels of compliance [17].

Relative Dose Intensity is the ratio of the dose administered to the dose planned per the treatment protocol and is a commonly used measure of compliance with a particular drug/regimen. Abdullah et al. analyzed the quality of reporting of chemotherapy compliance in randomized controlled trials of breast cancer treatment; four parameters were used to assess the quality of compliance reporting: number of chemotherapy cycles, dose modification, early treatment discontinuation and relative dose intensity. 71% of articles reported ≥ 2 parameters. 22% articles reported all four compliance measures. Articles published since 2008 (P=0.035) and those reporting advanced-stage disease (P<0.001) showed significantly higher quality of compliance [18].

Compliance to treatment is an ancient concept in medicine however "a new kid on the block" as far as oncologic care is concerned. It is a vital component associated with not only ability to tolerate the treatment well but also with bearing on ultimate outcome. Patient factors, physician factor and interrelation between them can influence compliant behavior and every possible effort should be made to improve non-justifiable reasons of noncompliance in cancer care.

References

1. Rosen G, Caparros B, Huvos AG, Kosloff C, Nirenberg A, et al. (1982) Preoperative chemotherapy for osteogenic sarcoma: Selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. Cancer 49: 1221-1230.
2. Lewis C, Linet MS, Abeloff MD (1983) Compliance with cancer therapy by patients and physicians. Am J Med 74: 673-678.
3. Osterberg L, BlaschkeT (2005) Adherence to Medication. N Engl J Med 353: 487-497.
4. Mirabello L, Troisi RJ, Savage SA (2009) Osteosarcoma incidence and survival rates from 1973 to 2004: Data from the Surveillance, Epidemiology, and End Results Program. Cancer 115: 1531-1543.
5. Meyers PA, Heller G, Healey J, Huvos A, Lane J, et al. (1992) Chemotherapy for non-metastatic osteogenic sarcoma: The Memorial Sloan–Kettering experience. J Clin Oncol 10: 5-15.
6. Bielack S, Kempf-Bielack B, Delling G, Exner GU, Flege S, et al. (2002) Prognostic factors in high-grade osteosarcoma of the extremities or trunk: An analysis of 1702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J Clin Oncol 20: 776-790.
7. Rosen G, Marcove RC, Caparros B, Nirenberg A, Kosloff C, et al. (1979) Primary osteogenic sarcoma: The rationale for preoperative chemotherapy and delayed surgery. Cancer 43: 2163-2177.
8. Huvos AG, Rosen G, Marcove RC (1977) Primary osteogenic sarcoma: Pathologic aspects in 20 patients after treatment with chemotherapy, en bloc resection, and prosthetic bone replacement. Arch Pathol Lab Med 101: 14-18.
9. Steiner JF, Earnest MA (2000) The language of medication-taking. Ann Intern Med 132: 926-930.
10. Balasubramanian SP, Murrow S, Holt S, Manifold IH, Reed MW, et al. (2003) Audit of compliance to adjuvant chemotherapy and radiotherapy guidelines in breast cancer in a cancer network. Breast 12: 136-141.
11. Glass A, Wieand HS, Fisher B, Redmond C, Lerner H, et al. (1981) Acute toxicity during chemotherapy for breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP). Experience from 1717 patients receiving single and multiple agents. Cancer Treat Rep 65: 363-376.
12. Bonnadonna G, Valagussa P (1981) Dose-response effect of adjuvant chemotherapy in breast cancer. N Engly Med 65: 10-5.
13. Adisa AO, Lawal OO, Adesunkanmi ARK (2008) Evaluation of patients' adherence to chemotherapy for breast cancer. Afr J Health Sci 15: 22-27.

14. Yong B, Tan P, Shen J, Zou C, Xie X, et al. (2012) Suboptimal chemotherapy is an adverse prognostic factor in osteosarcoma. World J Surg Oncol 10: 191.
15. Patrícia Andréa Crippa Marques, Angela Maria Geraldo Pierin (2008) Factors that affect cancer patient compliance to oral antineoplastic therapy. Acta Paul Enferm 21: 323-329.
16. Borras JM, Sanchez-Hernandez A, Navarro M, Martinez M, Mendez E, et al. (2001) Compliance, satisfaction, and quality of life of patients with colorectal cancer receiving home chemotherapy or outpatient treatment: A randomized controlled trial. BMJ 322: 826.
17. Ayres A, Hoon PW, Matheny KB, Franzoni JB, Cotanch PH, et al. (1994) Influence of mood and adjustment to cancer on compliance with chemotherapy among breast cancer patients. J Psychosom res 38: 393-402.
18. Altwairgi AK, Alfakeeh AH, Hopman WM, Parulekar WR (2015) Quality of reporting of chemotherapy compliance in randomized controlled trials of breast cancer treatment. Jpn J Clin Oncol 45: 520-526.