International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

A METAANALYSIS OF TAXANES, ANTITUMOR ANTIBIOTICS AND PLATINUM CONTAINING CHEMOTHERAPY REGIMENS IN THE MANAGEMENT OF METASTATIC BREAST CANCER

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ABSTRACT

The objective of present work is to compare Taxanes, antitumor antibiotics and platinum containing chemotherapy regimens in the management of metastatic breast cancer in terms of overall survival, objective response rate and time to progression. Cochrane Breast Cancer Group specialized register; Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL and WHO International Clinical Registry platform were searched using the appropriate search strategy Selection criteria. Randomised trials comparing the Taxanes, antitumor antibiotics and platinum containing chemotherapy for either recurrent or newly diagnosed women with Metastatic Breast Cancer were included. Data were collected from published trials. Studies were assessed for eligibility and quality, and data were extracted by two independent reviewers. Hazard Ratios (HRs) were derived from time-to-event outcomes where possible, and a fixed effect model was used for meta-analysis. Response rates were analysed as dichotomous variables. 35 trials were included with sample size of 16272 patients with Advanced Metastatic Breast Cancer treated with either Antitumor Antibiotics or Platinum Regimens or Taxanes. The observed overall survival derived for a sample size of 2710 exposed to chemotherapy where as a comparator group of 2591 exposed other therapies. The overall risk ratio was 0.98(M-H, fixed, 95% CI; 0.95 to 1.01). Time to Progression for a sample size of 2613 exposed to chemotherapy in comparison to the comparator group of 2370 exposed to other therapies. The overall risk ratio was 1.01(M-H, fixed, 95% CI; 0.98 to 1.03). Tumor Response Rate derived for a sample size of 3037 exposed to chemotherapy in comparison to the comparator group of 2951 exposed to other therapies. The overall risk ratio was 1.15(M-H, fixed, 95% CI; 1.08 to 1.22). This study confirms several benefits of chemotherapy especially Taxanes, antitumor antibiotics and platinum regimen in metastatic breast cancer, but the selection of drug therapy must be based upon the presentation of the case.

KEY WORDS: Breast Cancer, Metastasis, Overall Survival, Time to Progression, Tumor Response Rate.

INTRODUCTION

Breast cancer is the most common cancer occurring in women and is the primary cause of cancer death among women worldwide. 20-85% of patients depending on stage, tumor biology and treatments used will go on to develop distant metastases (disease which has spread to other parts of the body) [1].Chemotherapy is considered by many to be the appropriate first treatment option for women with multiple sites of recurrence or where visceral disease is not easily treated by local modalities.[2,3]

Chemotherapy is also considered to be useful in women whose cancer is hormone refractory, or expected to be hormone resistant.[4] Some women with metastatic breast cancer live for many years; however, the median survival ranges from 18 to 24 months.[5] The popular view is that chemotherapy may be better than endocrine therapy in patients with predominantly visceral disease or with rapidly progressive disease.

It is generally accepted that Taxanes are among themost active chemotherapy agents in the management of metastatic breast cancer. Taxanes are unique as they affect cell structures known as microtubules (or spindle fibers). Taxanes work by stopping the microtubules from breaking down. Cancer cells then become blocked with microtubules and stop dividing.[6] Platinum compound, an alkylating agent, has been known to be active in metastatic breast cancer since clinical trials in the 1970s. The exact mechanism of action of the platinum agents is not known but deoxyribonucleic acid (DNA) adducts are formed. These complexes are believed to inhibit DNA syntheses by forming inter strand and intra strand cross-linking of DNA molecules. As a class, antitumor antibiotics are agents that have been isolated, or synthetically derived, from a variety of fungal organismsfor their cytotoxic properties. They damage the DNA template by a variety of mechanisms including intercalation into DNA and RNA, alkylation of DNA and the generation of oxygen free radicals to produce single- and double-strand DNA breaks.[7]

The aim of this review is to systematically identify and assess all of the available evidence from randomized trials that compared the effects of different chemotherapeutic regimen on treatment-related outcomes for women with metastatic breast cancer.

OBJECTIVES

This study was aimed with the primary objective to identify and compare efficacy of Antitumor Antibiotics, Platinum Regimens and Taxanes chemotherapies in the treatment of advanced metastatic breast cancer in women.

METHODS

Criteria for considering studies for this review was randomized control trials that access the overall effectiveness and response of Antitumor Antibiotics, Platinum Regimens and Taxanes in patients with advance Metastatic Breast Cancer. The studies could be double blinded, single blinded or unblinded, single arm or double arm. Either recurrent or newly diagnosed women with definite evidence of Advanced Metastatic Breast Cancer were included.There were no restrictions on age, estrogen receptors, metastatic site of the patient included. The highly specific patient groups such as pregnant women and pediatric population were excluded. The intervention was assigned as any regimen containing selected chemotherapeutic agent for comparison versus any other regimen. All the randomized control trials investigating the role of Antitumor Antibiotics, Platinum Regimens and Taxanes in population with advanced Metastatic Breast Cancer were included.

Outcome measures were defined a priori as follows.Overall Survival (OS) time from date randomized to date of death (any cause). Tumor Response Rate (TRR) the proportion of patients with either complete or partial shrinkage of tumors. It was assessed according to modified RECIST[69] on the basis of the independent review of patients with measurable disease at baseline.Time to Progression (TTP) Time from date randomized to date of progression, death (any cause), may be referred as progression free survival.The Cochrane Breast Cancer Group specialized register (CBCG) was searched (issue 9 of 12, September 2013) was searched with the search strategy used by the group to create the register. This register includes both published and unpublished (including ongoing) trials. A further search was carried out in the Cochrane Central Register of Controlled Trials (CENTRAL) until 2013 (issue 10 of 12, September 2013). MEDLINE (2001 to September 2013) using the advance search strategy. In addition EMBASE (1998 to august 2013), CINAHL (1982 to September 2013) and the WHO International Clinical Registry platform search portal (September 2013) using the appropriate search strategy.

Data Collection and Analyses

The data was extracted independently by the two authors. After screening the electronic searches, bibliographic searches, hand searches two authors independently selected trials which met defined inclusion criteria and abstracted study attributes. The most complete data set that was feasible was assembled and analyzed for the primary outcomes such as Time to progression, overall survival and tumor response rate. The hazard ratio (HR) is the most appropriate statistical for survival time analysis and time to event outcomes hence, it was used for TTP and OS. Hazard ratios and their associated variances were extracted for all measures available. When possible, the HR was extracted from the trial publication(s). If not reported it was obtained indirectly through the methods described by Parmar

et.al using either other available summary statistics or from the data extracted from published Kaplan-Meier curves.[8] A weighted average of survival duration across studies was then calculated. The pooled HR was obtained by combining the observed (O) minus the expected (E) number of events and the variance for each trial using the fixed effect model.[9]

Tumor response rate (TRR) was analyzed as dichotomous variables and were obtained from the tables of best response presented for each trial and pooled relative risk was derived. Randomized response as reported by the trialist was used for statistical analysis.To allow for immature follow-up the numbers at risk were adjusted based on estimated minimum and maximum follow-up times if these were not reported in any of the reports available, minimum follow-up was estimated using the estimated time taken to complete treatment, and maximum follow-up was estimated using the last event reported in the relevant time to event curve.

The statistical heterogeneity was assessed using I^2 test where a value greater than 50% indicated substantial heterogeneity.[10]A fixed effect model was utilized for generating data provided no significant heterogeneity was present. The random effect model was employed in case of significant heterogeneity. Aggregate data methods[8, 11] were employed for time to event outcomes in the first instance and results were presented as Hazard ratios with 95% CI. Evidence of heterogeneity between trials were identified for tumor response rates and adverse events. We performed sensitivity analysis on the basis of methodological quality and to test for heterogeneity of the results. All analysis were based on intention to treat (ITT) principle as far as was possible, that is comparing all patients allotted to one treatment versus all those allocated to other irrespective of compliance. Thus the results may slightly underestimate any treatment effects. For statistical test a P value of less than 0.05 was considered to denote statistical significance. No attempt has been made to contact most trial investigators for additional information since many trials are in active follow-up and others are still recruiting patients.

RESULTS

35 Randomized control studiesconducted on 16272patients with Advanced Metastatic Breast Cancer treated with Antitumor Antibiotics or Platinum Regimens or Taxanes were included.The study were classified based upon primary outcomes namely Overall Survival (OS), Tumor Response Rate (TRR), Time to Progression (TTP).

In **Overall Survival** the primary analysis of overall effect as derived for a sample size of 2710 exposed to chemotherapy where as a comparator group of 2591 exposed other therapies. The overall risk ratio was 0.98(M-H, fixed,95% CI;0.95 to 1.01)Sufficient data was available from 22 randomized clinical trials with 5301 randomly assigned participants.10 Randomized study were conducted where study group treated with Anti-tumor antibiotics showed 861 events to the total sample size of 1140 whereas 874 events were recorded for a sample size 1146 treated with other therapies. The Peto odds ratio was estimated as 0.96(peto, fixed, 95% CI; 0.79 to 1.16). The pooled Peto odds ratio was not statistically significant to document superiority of chemotherapy over other therapy.Four trials with 904 randomly assigned patients treated with Platinum regimen reported peto odds ratio 0.89(peto, fixed, 95% CI; 0.67 to 1.19). The data indicated high overall survival for the study group with chemo therapy compared to the group treated with other therapies.8 randomized clinical trials with Taxanes chemotherapy with sample size of 2111 reported peto odds ratio 0.91(peto, fixed, 95% CI; 0.75 to 1.10) which statistically favors the high overall survival with Taxanes over the comparator group.On an overall peto odds ratios was estimated 0.92 (peto, fixed,95% CI; 0.82 to 1.05) for Antitumor Antibiotics, Platinum Regimens and Taxanes. This overall effect statistically favors high overall survival when treated with chemo therapy over the other therapies. The heterogeneity was assed as chi^2=0.26. The test for overall effect was 1.24 (P=0.21)

The **Time to Progression (TTP)** has overall effect of primary analysis as derived for a sample size of 2613 exposed to chemotherapy in comparison to the comparator group of 2370exposed to other therapies. The overall risk ratio was 1.01(M-H, fixed, 95% CI; 0.98 to 1.03).6 trials comply with the inclusion criteria with sample size of 1757 randomly assigned patients were included in the study for antitumor antibiotics. The patients were randomly assigned into two different groups as study (treatment with antitumor antibiotics) control (otherregimens).802 patients were enrolled in study group out of which 889 showed events whereas the comparator group with sample size of 1365 showed 1264 events. The estimated Peto odds ratio was 0.47(Peto, fixed, 95%CI; 0.33 to 0.68). The pooled Peto odds ratio favors the study group.In treatment with platinum containing regimen 1113patients were assigned randomly in 6 clinical trials.544 patients were treated with platinum regimen and 447 out of this group showed outcome in terms of time to progression. In the other assigned group with sample size of sample of 569, the response was reported in 479 patients. A

pool estimate of reported time to progression showed a significant advantage for platinum chemo therapy over the other therapyassessed by of Peto Odds ratio 0.87 (Peto, fixed, 95%CI; 0.63 to 1.19).7 trials reported time to progression in treatment with Taxanes with population size of 2113. Data was available from two different groups. The reported groups from the first group were 966 when 1180 patients were treated with Taxanes chemotherapy. In the other group 691events were reported out of 933 patients treated with other non-chemotherapy group.Estimated pooled risk ratio for overall time to progression was 1.01(MH Fixed, 95% CI, 0.98 to 1.03) for Antitumor Antibiotics, Platinum Regimens and Taxanes. The forest plot graph shows that the treatment with overall chemotherapy significantly increases the time to progression In comparison to a non-chemotherapeutic regimen. The test for heterogeneity was assed as chi^2=35.15, I^2 = 94%and the test for overall effect was 1.02 (P=0.31)

Tumor Response Rate (TRR) had overall effect of primary analysis as derived for a sample size of 3037 exposed to chemotherapy in comparison to the comparator group of 2951 exposed to other therapies from 25 trials. The overall risk ratio was 1.15(M-H, fixed, 95% CI; 1.08 to 1.22).

6 trials with a sample size of 2450 were available to enable estimation of tumor response rate for anti-tumor Regimens over other therapy to be calculated. 603 patients showed outcome out of 1273 patients in terms of increased tumor response rate, however 503 patients were treated with other therapy showed response in 1177 patients. The pooled estimation of tumor response rate significantly favor other therapy over antitumor antibiotics measured by odd ratio 1.21 (MH Fixed, 95% CI, 1.03 to 1.41).A significant difference in favor of other therapy regimens over platinum regimen detected for 1520 randomized patients in 8 clinical trials. 358 patients showed event when687 were treated with platinum regimen with comparator group of 388 patients showing events in 833 patients. The statistical significance measured as odds ratio 1.25 (MH Fixed, 95% CI, 1.02 to 1.53).7 trialswith a sample size of 2018 were included to estimate tumor response rate with treatment with Taxanes. When 1077 patients were treated with Taxanes, 443 patients showed response in terms of tumor response whereas in treatment with other regimen 296 showed events out of 941 patients.The data statistically favors treatment with other therapies overTaxanesmeasured as odds ratio 1.52 (MH Fixed, 95% CI, 1.27 to 1.83).Estimated pooled risk ratio for overall Tumor Response Rate was1.15 (MH Fixed, 95% CI, 1.08 to1.22) for Antitumor Antibiotics, Platinum Regimens and Taxanes. The forest plot graph significantly favors chemotherapy over other therapy. The test for significant heterogeneity was assed as chi^2=26.12 and sensitivity analysis I^2 was estimated 92% the test for overall effect was 2.73 (P=0.006)

DISCUSSION

Presently there are more and more sophisticated cytotoxic chemotherapy available in the treatment of advance metastatic breast cancer. In incurable metastatic breast cancer the goal of the treatment is to increase overall survival, quality of life and safety profile of the chemotherapy. There is also an accepted wisdom that human with visceral metastatic tend to response better to chemotherapy. This review has combined wide data from wide variety of randomized clinical trials conducted over past 20 years.The overall heterogeneity across the trials was dubious. This reduced the power of certain analysis principally of overall survival and tumor response rate. However, the modest level of evidence recommends the beneficial outcome of chemotherapy in women with metastatic breast cancer.

The positive effects of chemotherapy were demonstrated by this review in terms of significantly high overall survival and time to progression compare to other therapies. In terms of overall survival Taxanes illustrated superiority over the Platinum and antitumor antibiotic with statistically significant increased Odds ratio.Antitumor antibiotic exhibited statistical advantage along with Taxanes over platinum regimen In terms of time to progression. The pooled estimate of objective tumor response rate in majority of included trials indicated favor advantage for other therapy over established chemotherapy. Large number of trials reported significant partial response rate and complete response rate assessed by RECIST (response evaluation criteria in solid tumor). Few subjects were observed with stable diseases and very few with progressive diseases.

CONCLUSION

There by this review found a considerable benefit of other therapies over the chemotherapy. It is emphasized that endocrine therapy demonstrated better overall response rate in the patients with hormone receptor positive metastatic breast cancer.

This study suggested the prudence introduction of chemotherapy where there are rapidly progressive diseases. The statistical heterogeneity differences can be regarded to the various differences that remain speculative. The proportion of with their hormone receptor status contributed to the differences in

heterogeneity and may explain it. This review may underestimate the effect of other therapy on the survival of women but it certainly supports the included chemotherapeutic agents in this study.

Conclusively, this study confirms several benefits of chemotherapy especially Taxanes, antitumor antibiotics and platinum regimen in metastatic breast cancer, but the selection of drug therapy must be based upon the presentation of the case and the various baseline factors like nodal status, the extent of metastatic and the hormonal status. The overall therapy and higher response rate should be the desired endpoint of the any therapy outlined for the patients.

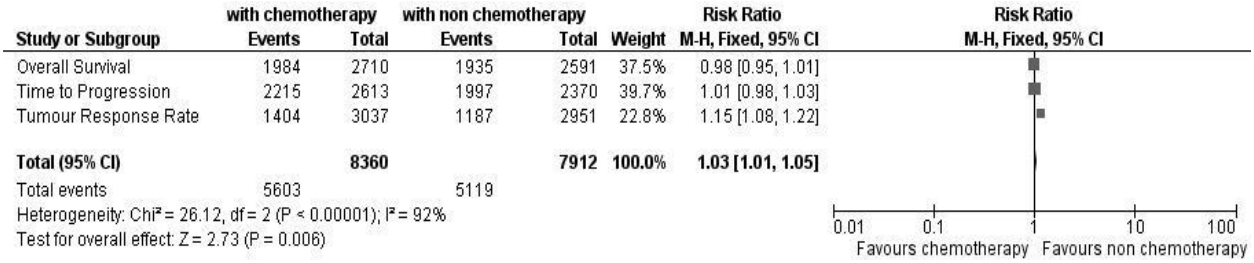

Figure1 Forest plot of comparison of Overall Outcomes of Chemotherapy

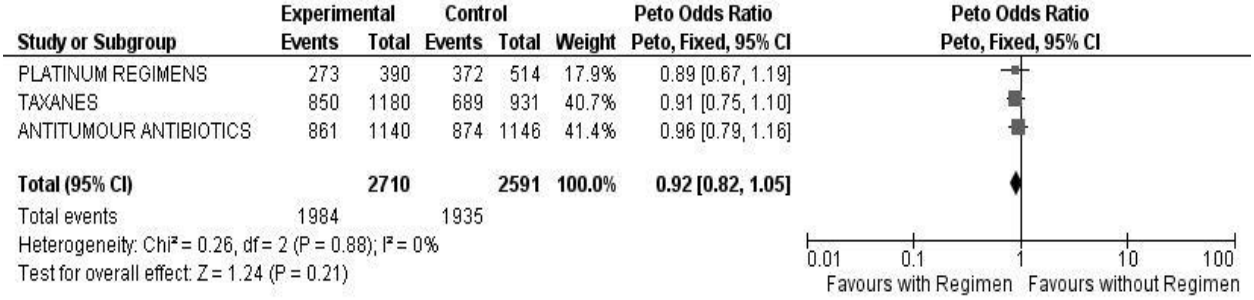

Figure2 Forest plot of comparison of Overall Survival

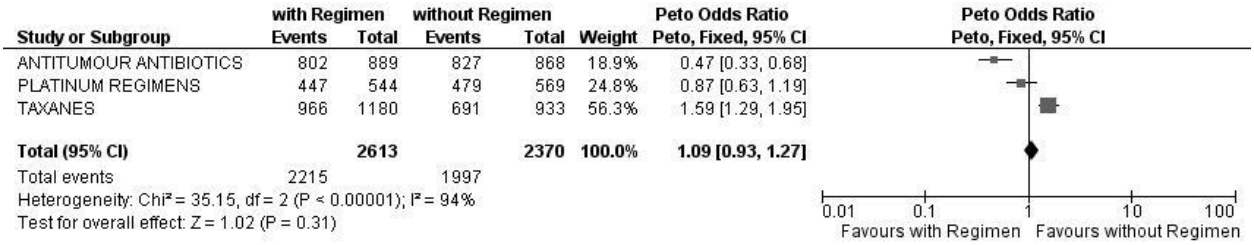

Figure3 Forest plot of comparison of Time to Progression

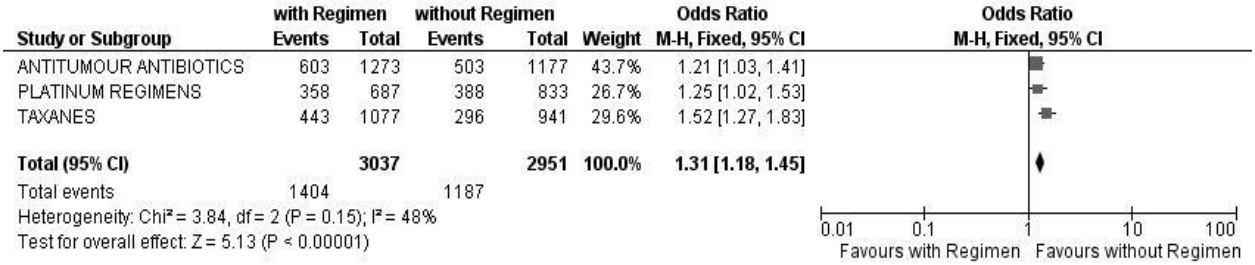

Figure4 Forest plot of comparison of Tumor Response Rate

Table 1.Overall Outcomes

Outcome	Studies	Participants	Statistical Method	Effect Estimate
Overall Outcomes of Chemotherapy	35	16272	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [1.01, 1.05]
Overall Survival	22	5301	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.82 1.05]
Time To Progression	19	4983	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.93 1.27]
Tumour Response Rate	25	5988	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [1.18 1.45]

Table 2 Included Study Charectristics

First Author	Year	AGE		First Author	Year	AGE	
		Median Age (MA)	Age Range (AR)			Median Age (MA)	Age Range (AR)
TAXANES				TOG[46]	------	------	18-70
304 Study Group[12-17]	TXT Group[47-49]	------	55.3	TXT Group[47-49]	------	55.3	27-79,
306 Study Group[18,19]	------	53	------	**PLATINUM REGIMEN**			
ANZ TITG[20-24]	------	54	32-80	Berruti A**[50]**	2002	57/59	------
Bontenbal[25]	------	53	------	Berruti B**[51]**	2002	58	------
Dieras[26]	------	52/52.5	29/69	Cocconi G[52]	**1**996	57	------
ECOG E11939(A) [27-30]	------	56/58	25/79	Costanza[53]	1999	------	------
ECOG E11939(B) [31]	------	56/58	25/79	Eisen[54]	1998	47/48	------
EORTC 10923[32,33]	------	54/55	26/75	Fountzilas[55]	2002		------
EORTC 10961[34,35]	------	------	18-70	Icli[56]	2002	47/49	------

Jassem[36-39]	------	50	24-74	Nielsen[57]	2000	52/55	------
Nabholtz[40]	------	54	------	**ANTITUMOR ANTIBIOTICS**			
Sjostrom[41-44]	------	50 / 51	26-69	ANZ BCTG 8614[58]	------	------	------
Talbot[45]	------	52	------	Berruti B**[51]**	2002	58	------

First Author	Year	AGE		First Author	Year	AGE	
		Median Age (MA)	Age Range (AR)			Median Age (MA)	Age Range (AR)
Cocconi G[52]	**1**996	57	------	DBCG[60,61]	1999	58	------
Costanza[53]	1999	------	------	ECOG EST 2173a[62,63]	------	------	61% aged 50-65, 39% <50yrs
Eisen[54]	1998	47/48	------	ECOG EST 2173b[64]	------	------	------
Fountzilas[55]	2002	------	------	Fountzilas[64]	2004	------	------
Icli[56]	2002	47/49	------	Fraser [65]	1993	60	26-80
Nielsen[57]	2000	52/55	------	Hainsworth[66]	1997	57	34-81
ANZ BCTG 8614[58]	------	------	------	Harper-Wynne [67]	1999	58	28-84
B122[59]	------	52	------				

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