VOLUME - 9, ISSUE - 11, November - 2020 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Pulmonary Medicine

A STUDY ON SIDEEFFECTS ASSOCIATED WITH CHEMOTHERAPY USED IN RESISTANT TUBERCULOSIS

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ABSTRACT ***Background:*** The multitude of potentially toxic drugs administered over a prolonged period of time for successful treatment of drug resistant tuberculosis (DR-TB), makes it challenging to ensure completion of therapy. ***Methodology:*** In this cross-sectional study we retrospectively reviewed medical records of 62 patients on anti TB treatment and obtained data on adverse drug reactions and drugs discontinued due to side effects. ***Results:*** In initial months of therapy, 67.74% of patients on DR-TB treatment had side effects and drugs were discontinued completely in only 17.74% mainly due to ototoxicity or psychiatric disorders. ***Conclusion:*** Our study indicates that adverse drug reactions are common in DR-TB, but usually manageable if recognised on time and managed by patient awareness and counselling, clinical and laboratory monitoring, prompt symptomatic and appropriate treatment including altering dosages and if required discontinuation of the concerned drug.

KEYWORDS : Adverse drug reaction, Resistant Tuberculosis drugs side-effects

INTRODUCTION:

Nearly three decades after tuberculosis (TB) was declared a global emergency by WHO, over 4000 people still lose their lives to TB daily and close to 30,000 people are diagnosed with this disease each day[1]. The growing prevalence and spread of drug resistant TB worldwide has become a serious problem as it is more difficult to treat and associated with higher morbidity and mortality. One of the reasons for development of resistant tuberculosis is nonadherence to prescribed regimens , a root cause for which is the adverse effects of the multiple drugs required to be taken in a TB regimen by the patient for a prolonged period of time The anti TB drugs used in drug sensitive TB (DS-TB) generally have minor side-effects and are better tolerated, while in drug resistant TB (DR-TB) the number of drugs used is more as is the severity and multitude of adverse effects [2,3,4]. Though most side effects can be dealt with by symptomatic treatment, it is important to make patients aware without alarming them, to ensure completion of therapy. It has been suggested that only a minority of patients successfully complete anti TB chemotherapy without significant side-effects, while another perspective is that most patients do complete treatment without serious adverse reactions. This study was undertaken to ascertain the common and uncommon side-effects of anti-tuberculous drugs used in resistant TB and whether the adverse reactions were severe enough to result in discontinuation of therapy.

METHODS:

We conducted a retrospective cross sectional observational study of patients being treated for DR-TB diagnosed on basis of GeneXpert or MGIT liquid culture reports, over a two-year period (2016-2018) at an urban tertiary care hospital in western India. 62 patients who had completed more than 18 months therapy were included in the study. 51 patients were MDR-TB on standardized six drug regimen labelled Category IV (CAT IV) [5], consisting of 6-9 months of kanamycin, ethionamide, levofloxacin, cycloserine, pyrazinamide, and ethambutol followed by 18 months of ethionamide, levofloxacin, cycloserine, and ethambutol. 11 patients were XDR or extensively resistant TB and were on the standardized seven drug regimen labelled Category V regimen (CAT V)[5] consisting of Capreomycin (Cm), Moxifloxacin (Mfx), High dose-INH, PAS, Clofazimine, Linezolid, and Amoxyclav for 6-12 months followed by continuation phase of 18 months of 6 drugs – PAS, Moxifloxacin (Mfx), High dose-INH, Clofazimine, Linezolid, and Amoxyclav. Medical records of these patients were reviewed and data on demographics, presence of comorbidities, Gene Xpert and drug susceptibility testing (DST) results, treatment regimens, adverse drug reactions and drugs discontinued due to side effects was obtained. Adverse drug reaction was defined as a noxious response which is unintended and occurs at doses which are routinely used in human patients [6].

RESULTS:

In DR-TB patients on treatment in intensive phase, 62.75 % of those on CAT IV regimen and 72.73% of those on CAT V had side-effects. Overall 67.74% of patients on DR-TB treatment had side effects in initial months of therapy. In the continuation phase, 19.61% and 18.8% on CAT IV and CAT V regimens respectively had side-effects. Many patients experienced more than one sideffect. **Table 1** summarizes the side effects seen in patients being treated for Resistant tuberculosis.

Table 1: Sideeffects Of Drugs Used In Treatment Of Drug Resistant Tuberculosis *[Intensive Phase, Continuation Phase]*

	Nausea/Vomiting	Deranged LFT	Itching	Skin Rash	Joint pains	Peripheral Neuropathy	Psychiatric Disturbances	Hearing Loss
DR-TB Patients on CAT IV	52.94 %, 3.92 %	1.96 %, 0 %	3.92 %, 3.92 %	3.92 %, 0 %	39.21 %, 3.92 %	3.92 %, 1.96 %	5.88 %, 0 %	5.88 %, 0 %
DR-TB Patients on CAT V	72.72 %, 0 %	0 %, 0 %	18.18 %, 0 %	9.09 %, 0 %	0 %, 0 %	18.18 %, 9.09 %	0 % , 0 %	0 %, 0 %

52.94 % on Category IV treatment and 72.72% on Category V treatment reported nausea and vomiting in the intensive phase while only 3.92% and none (0%) in continuation phase of Category IV and Category V treatment respectively reported these symptoms; suggesting a tolerance to the drugs over a period of time. In the intensive phase of treatment, liver

enzymes were deranged in 2 patients on Category IV and one in Category V. Anti TB drugs were withdrawn temporarily and then restarted gradually in specific weight adjusted doses. In the intensive phase,3.92 % on CAT IV and 9.09% on CAT V regimen respectively reported a skin rash and were treated symptomatically. 5.88 % reported hearing loss confirmed by audiometry which could be due to injectable aminoglycosides which were discontinued immediately, after which patients regained their hearing over 3 to 6 months. All patients on injectable aminoglycosides did complain of pain and induration at the multiple injection sites, but reassurance and cold compress at local site and in some cases analgesics helped patients to complete their therapy.

39.21% patients in CAT IV intensive phase reported joint pains and had high uric acid levels. This can be attributed to prolonged use of Pyrazinamide in intensive phase of therapy for MDR-TB. These patients were treated with analgesics and in some cases xanthine oxidase inhibitor like allopurinol. Pyrazinamide was not discontinued permanently in any patient. None of the patients on CAT V regimen reported joint pains as Pyrazinamide is not given in this regimen. Psychiatric symptoms including anxiety, depression, suicidal tendencies were observed in 5.88% of patients on CAT IV regimen; in whom additional medication was prescribed by psychiatrists and cycloserine discontinued. Hypothyroidism was seen in 5 patients in intensive phase of CAT IV regimen, which was treated by hormone replacement. Peripheral neuropathy was noted in around 18% patients in CAT V regimen and attributed to Linezolid and high dose INH; and treated with temporary discontinuation of the drugs and Pyridoxine supplementation. One patient each had severe anaemia, optic neuritis, pancreatitis which could be attributed to Linezolid which was discontinued in the regimen of each of these patients. One patient had seizures probably due to high dose Moxifloxacin or Linezolid, both of which were substituted with alternative drugs. One patient had hypokalemia induced by injectable Kanamycin, which was discontinued and potassium supplements administered.

DISCUSSION:

MDR-TB is defined as resistance to both isoniazid and rifampicin while XDR-TB is a subset of MDR-TB with additional resistance to a fluoroquinolone and a second-line injectable agent. Pre–XDR-TB refers to patients of MDR-TB having additional resistance to either fluoroquinolone and a second-line injectable agent, but not both of these classes of drugs[7]. The treatment regimens for MDR-TB involve higher number of drugs which are more toxic and given for longer durations. Hence adverse effects and intolerance to these drugs is expected to be greater in patients being treated for DR-TB.

Mismanagement of side effects is the major reason for non-adherence or discontinuation of therapy[2], which may lead to further resistance and unfortunate consequences for the patient. Since several anti TB drugs are administered in combination, it is difficult to measure the efficacy or toxicity of a particular drug; hence it becomes incumbent on the treating doctor to monitor the patient especially with regards to adverse effects of the medications in order to ensure adherence to treatment.

In our study, 67.74 % of patients treated for DR-TB had side-effects in the initial intensive phase of treatment, however these were commonly mild gastrointestinal symptoms. Other studies have reported adverse drug reactions ranging from 30% to 60% in patients taking second line anti TB drugs for resistant TB[3,8], while side effects requiring withdrawal of 1 or more TB medications were reported by Goble et al in 30% of patients [9] and by Yang et al. in 21.1% patients[3]. In our study, drugs were required to be discontinued completely in only 11 (17.74%) patients of DR-TB whenever there was development of severe anaemia, optic neuritis, pancreatitis, ototoxicity, psychiatric disorders, seizures or central nervous system involvement. Thus awareness of side-effects, symptomatic treatment for the same and reassurance can ensure completion of therapy even in patients on treatment for resistant tuberculosis.

CONCLUSION:

Though it is extremely cumbersome to take a number of medications, all having multiple side-effects, over a prolonged period of time; it is a necessary requirement for survival of a patient with DR-TB. Our study indicates that most adverse drug reactions occur in the initial months of starting therapy and are mild and do not require permanent discontinuation of the drug responsible. However, if not recognised in time and managed properly these adverse reactions can lead to treatment interruption or can even be life threatening. Hence patients need to be closely monitored, counselled and promptly treated for adverse drug reactions to ensure successful completion of their full course of anti-tuberculosis chemotherapy.

REFERENCES:

1. S. Tiberi et al. Editorial- Commemorating World TB Day 2020: "IT'S TIME" — It's time to End the Global TB Epidemic. International Journal of Infectious Diseases 92S (2020) S1–S4
2. Seung KJ, Keshavjee S, Rich ML. Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis. Cold Spring Harb Perspect Med. 2015;5(9): a017863.
3. Yang TW, Park HO, Jang HN, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis at a tuberculosis referral hospital in South Korea: A retrospective study. Medicine (Baltimore). 2017;96(28): e7482.
4. Maiolini M, Gause S, Taylor J, Steakin T, et al. The War against Tuberculosis: A Review of Natural Compounds and Their Derivatives. Molecules. 2020 Jun 30;25(13):3011.
5. Revised National Tuberculosis Control Programme. Guidelines for the Programmatic Management of Drug Resistant Tuberculosis (PMDT) in India. New Delhi: Central TB Division; 2012.
6. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. The Lancet. 2000;356 (9237):1255-9. 6.
7. Parul Singhal, Pratima Dixit, Pooja Singh, Indu Jaiswal, et al. A study on pre-XDR & XDR tuberculosis & their prevalent genotypes in clinical isolates of Mycobacterium tuberculosis in north India. Indian J Med Res. 2016 Mar; 143(3): 341–347.
8. Aliaasghar Farazi, Masoomeh Sofian, Mansoureh Jabbariasl, Sara Keshavarz. Adverse Reactions to Antituberculosis Drugs in Iranian Tuberculosis Patients. Tuberculosis Research and Treatment, 2014, Article ID 412893
9. Goble M, Iseman MD, Madsen LA, et al. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med 1993; 328:527–32.