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EXTENSIVELY DRUG RESISTANT TUBERCULOSIS : AN UPCOMING CHALLENGE TO FACE AND TREAT.

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ABSTRACT

Extensively drug resistant tuberculosis (XDR- TB) has been reported by 45 countries worldwide , to World Health Organisation (WHO) . XDR-TB is a uniformly lethal disease that has emerged in countries with limited resources and high prevalence of tuberculosis , mainly as a result of previous inadequate or improper treatment and poor adherence by the patient to the treatment . It has been defined by WHO Global Task Force as – *Mycobacterial tuberculosis* infection that is resistant to isoniazid , rifampicin , any fluoroquinolone and at least one of the three injectable drugs i.e. amikacin , kanamycin and capreomycin . Patients co-infected with HIV were found to be at more risk to XDR- TB. An aggressive drug treatment regimens, as a part of comprehensive therapeutic approach including infection control measures, along with DOTS – plus implemented by WHO are required that can cure many patients with XDR – TB , who are not infected with HIV. Along with rapid recognition of cases and prompt contact recognition , drug therapy includes as first line agents , ethambutol and pyrazinamide for the entire duration of therapy . An injectable agent like kanamycin in streptomycin resistant cases , amikacin in kanamycin and streptomycin resistant cases , capreomycin and vyomycin in cases of kanamycin or streptomycin resistant cases should be included , along with monitoring for ototoxicity and nephrotoxicity .

KEY WORDS

XDR-TB , DOTS-PLUS, injectable agents

INTRODUCTION

Extensively drug resistant tuberculosis (XDR- TB) has been reported by 58 countries worldwide by January 2010 , to World Health Organisation (WHO) [1] . XDR-TB is a uniformly lethal disease that has emerged in countries with limited resources and high prevalence of tuberculosis , mainly as a result of previous inadequate or improper treatment and poor adherence by the patient to the treatment .

XDR-TB has been defined by WHO Global Task Force as –*Mycobacterial tuberculosis* infection that is resistant to isoniazid , rifampicin, any fluoroquinolone and at least one of the three injectable drugs i.e. amikacin , kanamycin and capreomycin [2].

Patients co-infected with HIV were found to be at more risk to XDR- TB . It is almost uniformly fatal . TB & HIV both affect each other's course . HIV increases the chances of TB reactivation by 20 fold and TB causes cellular activation , excessive cytokine & chemokine production and stimulates replication of HIV leading to an accelerated course of AIDS and shorter overall survival [3] .

METHODOLOGY

Various studies were reviewed to collect and compile the information available on the treatment of XDR- TB by using pubmed , WHO fourth Global Report and some peer –reviewed journals . Medline was searched using the search terms: ' tuberculosis', 'extensively drug resistant tuberculosis' and 'XDR-TB'.

Clinical Presentation & Diagnosis Of XDR-TB

The clinical manifestations of XDR-TB are similar to susceptible strains but the course of disease is fulminant . History raises suspicion . There are no facilities for testing the susceptibility to second line drugs in most of the countries .Confirmation of XDR-TB requires acid –fast stain and sputum culture with antibiotic susceptibilities. Automated liquid culture systems that detect bacterial oxygen consumption or carbon dioxide production may detect growth in half of the time than solid media .Other tests for rapid detection of resistant mycobacterium tuberculosis include nitrate reductase assay, colorimetric methods like tetrazolium salts , redox indicators, phage amplification and nucleic acid amplification other newer technologies like bacteriophage assay and high resolution melt assay are in the pipeline .WHO recommended diagnostic methods are commercial broth based drug susceptibility systems and line probe assays [4 ,5].

Management

Timely initiation of treatment is crucial to decrease the morbidity and mortality and to reduce transmission to others . Aggressive drug treatment regimens, as a part of comprehensive therapeutic approach including infection control measures like , the use of well ventilated room with a single –pass air system (negative pressure) and not allowing the patient of XDR-TB to travel by air until sputum samples are negative , along with DOTS – plus[5] implemented by WHO that includes the use of second line drugs , are required that can cure more than 60 % patients with XDR – TB , who are not infected with HIV, because HIV co-infection can worsen the outcome [3].

Timely initiation of treatment is crucial along with rapid recognition of cases and prompt contact recognition to decrease morbidity and mortality and to reduce transmission to others . The drug therapy includes four to six drugs to which strains are susceptible .These include any first line

agents like ethambutol and pyrazinamide .An injectable agent like kanamycin in streptomycin resistant cases , amikacin in kanamycin and streptomycin resistant cases , capreomycin and vyomycin in cases of kanamycin or streptomycin resistant cases should be included for at least 6 months duration , along with monitoring for ototoxicity and nephrotoxicity. Fluoroquinolones like moxifloxacin and gatifloxacin should be part of the regimen, if possible. Other second line agents

in patients of XDR- TB may include thionamides , para-aminosalicylic acid and cycloserine [6,7].

A promising Anti- TB in pipeline is TMC-207(R 207910) that may be more potent than the currently available treatments . Nitro-imidazoles , such as PA-824 has entered Phase - I clinical trials . OPC-67683 have shown good activity among all sensitive and resistant strains of tuberculosis in mice and is now in Phase II clinical trials .

New immunotherapeutic interventions ,including high-dose intravenous Immunoglobulin G, multiple-dose *mycobacterium vaccae* are under trial. Surgical intervention may be required in selected patients of XDR-TB with high – grade resistance, relatively localized disease and lack of initial response [8].

WHO had established 'Global Plan to Stop TB' (2006-2015) that include DOTS as main component and it established 'Green Light Committee'for responsible distribution of second line drugs. As a result of implementation of above strategies , 10 countries reached or exceeded 70% case detection rate for new smear positive case and eight countries have reached or exceeded the treatment success rate target (85%). New guidelines for management and infection control of XDR-TB are being prepared . However, still these drugs are not adequately available in low and middle income countries.

CONCLUSION

XDR-TB is emerging as a life threatening infection and its treatment is challenging and requires the use of second line drugs and surgery also in some patients. One should look for HIV co-infection also , as both HIV and XDR-TB are closely associated . Rapid tests to identify XDR-TB are the need of the
hour . The existing public health infrastructure needs to be strengthened along with integration of TB and HIV programmes .

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