Chemotherapy of TB and M/XDR-TB

Manoon Leechawengwongs, M.D., FACP, FCCP

Vichaiyut Hospital, 71/3 Setsiri Road, Bangkok, Thailand.

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Chemotherapy of TB can be divided into treatment of latent infection and treatment of active disease.

Latent TB Infection

As at least 20 million Thais have latent TB infection, so it is just impossible to treat every Thai with latent infection. Treatment should be targeted to those with or without HIV infection who have recently been infected with TB and those in close contact with patients with active pulmonary or laryngeal tuberculosis. Before beginning therapy, all persons should undergo chest radiography and clinical evaluation to rule out active TB. Diagnosis of latent TB infection can be done by a tuberculin skin test (purified protein derivative, PPD) or interferon gamma release assays (IGRAs).

Isoniazid (INH) is the drug of choice for treatment of latent TB infection presumed to be due to susceptible strains.[1] It should be given daily for 9 months. All persons receiving INH should also receive pyridoxine to minimize the risk of developing peripheral neuropathy. Four months of rifampicin therapy is recommended for those who are intolerant to INH or are known to have been infected with INH resistant TB and susceptible to rifampicin. Combination of rifampicin (RIF) and pyrazinamide (PZA) for 2 months is no longer recommended because of an unacceptable high risk of severe hepatotoxicity.

There are no data based recommendations for treatment of latent TB infection following exposure to patients with TB resistant to both INH and RIF, multidrug resistant TB (MDR-TB) or TB resistant to both INH and RIF, any fluoroquinolone and at least one of three injectable second-line drugs (kanamycin, amikacin, capreomycin), or extensively drug-resistant TB (XDR-TB).

Active TB Disease

In the wake of an increasing drug resistance problem, all initial positive AFB smear specimens should be routinely cultured and tested for drug susceptibility, although results generally do not become available for at least 6-12 weeks.[2,3] The basic regimen includes 2 months of INH, RIF, PZA and ethambutol (EMB) (the intensive phase), followed by a minimum of 4 months of INH and RIF (the continuation phase).[4] Fixed drug combinations may be useful for patients self administering treatment for disease due to susceptible strains. TB drugs should be taken on an empty stomach before going to bed. Directly observed therapy (DOT) is recommended for treatment of all active TB patients particularly patients with drug resistant infections and for those on intermittent regimens. Patients should be monitored initially within 2 weeks with history, and physical assessment directed at detection of side effects and liver function (aminotransferases, bilirubin and alkaline phosphatase). Patients should then have a monthly clinical follow-up to assess for adverse reactions, adherence and response to treatment.

Initial Phase

Until susceptibility results are available, empirical initial treatment should consist of a 4-drug regimen of INH, RIF, PZA and EMB for 2 months. Once drug susceptibility is known, the regimen should be adjusted according to the results.

Continuation Phase

For patients with a cavity on their chest x-ray at presentation and a positive smear and/or culture taken at 2 months, the continuation phase with INH and RIF is extended to 7 months.

If sputum cultures remain positive after 4 months of treatment, non-adherence to treatment or infection with drug-resistant TB must be considered.

TB osteomyelitis and TB meningitis are usually treated for a total of 12 months.

Drug Intolerance

Drug induced liver toxicity can be caused by INH, RIF or PZA. Rifampicin is more likely to cause hepatotoxicity than INH and PZA in Thai patients particularly elderly and HIV patients. Finding an AST elevation and a disproportionate increase in bilirubin and alkaline phosphatase is consistent with rifampicin hepatotoxicity. Rifampicin should be the first drug to be stopped when the patient has symptoms of hepatitis and elevated liver enzymes. For patients who cannot take rifampicin

TABLE 1. First-line drugs.

Drug	Daily adult dosage	Main adverse effects
Isoniazid	5-8 mg/kg PO (max 300 mg)	Hepatic toxicity, rash, peripheral neuropathy
Rifampicin	10 mg/kg PO (450-600 mg)	Hepatic toxicity, rash, flu-like syndrome, pruritus, drug interactions
Pyrazinamide	15-30 mg/kg PO (1-1.5 g)	Arthralgia, hepatic toxicity, pruritus, rash, hyperuricemia, GI upset
Ethambutol	15-20 mg/kg PO (800-1000 mg)	Decreased red-green color discrimination, decreased visual acuity
Streptomycin	10-15 mg/kg IM (max 1 g)	Vestibular and auditory toxicity, renal damage

because of drug intolerance or drug interaction (such as HIV co-infected patients on protease inhibitor), the alternative regimen includes 12-18 months of treatment with INH, EMB and a fluoroquinolone (e.g. levofloxacin) with PZA administered during the first 2 months. Streptomycin might be included in the first 2 months for patients with severe or extensive disease.

Patients who cannot take PZA in the initial phase of treatment should receive continuation therapy with INH and RIF for 7 months.

Drug Resistant TB Disease

Resistance to Isoniazid

INH-resistant TB can be treated with RIF, PZA and EMB for 6-9 months. A fluoroquinolone may be added for those with more severe or extensive disease. Patients who can not tolerate PZA can take RIF, EMB and fluoroquinolone for 12 months.

Resistance to Rifampicin

RIF resistant TB can be treated for 12-18 months with INH, EMB and a fluoroquinolone with PZA administered during the first 2 months. Streptomycin sometimes may be added for the first 2 months for patients with severe or extensive disease.

Multidrug Resistance

MDR-TB and XDR-TB should be treated with ≥ 4 drugs to which the organism is susceptible. One of these drugs should be an injectable agent. Kanamycin is the drug of choice until the susceptibility results are available. Streptomycin should not be used empirically because of a very high incidence of streptomycin resistance in Thailand.

When MDR-TB is suspected, a combination of 5-7 drugs is given before the susceptibility data become available. The regimen includes EMB, PZA, a fluoroquinolone, kanamycin, cycloserine, ethionamide and/or para-aminosalicylcic acid (PAS).

Monthly AFB smear and culture should be monitored and treatment continued for 18-24 months or 12-18 months after the culture becomes negative. The injectable drug should be continued for 6 months after culture conversion. Surgical resection should be considered if a badly damaged lung or localized cavities are resectable, patients have adequate cardiopulmonary reserve and culture failed to convert to negative after 3-4 months of appropriate treatment.

XDR-TB was associated with significantly lower treatment success, higher overall cause mortality and higher TB related mortality.[5] There is still some hope. XDR-TB in HIV-negative patients can be cured up to 60% compared to 66% with MDR-TB when management is aggressive and appropiate.[6-7] The management of MDR-TB is complex and should be undertaken by an experienced specialist, otherwise failure of treatment of MDR-TB will lead to an emergence of XDR-TB.[8]

There are 5 new drugs in clinical development for TB, diarylquinoline – TM 207, nitroimidazoles – PA-824 and OPC-67683, ethylenediamine – SQ 109 and pyrrole – LL- 3858.[9] These drugs are currently undergoing clinical evaluation.

Special Treatment Circumstances

HIV-Infected Patients[10,11]

Testing for HIV infection is recommended for all patients with active TB. CD4 count and HIV viral load should be determined prior to initiation of TB treatment.

Patients not on HAART

For a HIV-infected patient with CD4 cell count

TABLE 2. Second-line drugs.

Drug	Daily adult dosage	Main adverse effects
Kanamycin	15 mg/kg IM (max 1 g)	Auditory toxicity, renal damage
Amikacin	15 mg/kg IM or IV (max 1 g)	Auditory toxicity, renal damage
Capreomycin	15 mg/kg IM (max 1 g)	Auditory and vestibular toxicity, renal damage
Ofloxacin	600-800 mg PO	GI toxicity, CNS effects, rash
Levofloxacin	500-750 mg PO	GI toxicity, CNS effects, rash
Moxifloxacin	400 mg PO	GI toxicity, CNS effects, rash
Cycloserine	10 mg/kg in 2 doses PO (max 500-750 mg/ day)	Psychiatric symptoms, seizures
Ethionamide	15 mg/kg in 2 doses PO (max 500-750 mg/day)	GI and hepatic toxicity, hypothyroidism
Para-aminosalicylic acid (PAS)	150 mg/kg in 2 doses PO (8-12 g/day)	GI disturbance, hypothyroidism

more than 250 cells/mm^3, TB treatment should be completed before initiation of highly active antiretroviral therapy (HAART). For HIV-infected patients with CD4 cell count less than 250 cells/mm^3, it may be prudent to delay HAART for 2 months in order to avoid a paradoxical worsening of TB due to immune reconstitution, decrease the risk of overlapping drug adverse affects and interactions, reduce pill burden and enhance adherence to both drug regimens. Patients should be scheduled for clinical follow up 1 week after starting ARV to detect paradoxical reaction and/or side effects.

Patients on HAART

Rifampicin induces hepatic CYP enzymes, especially CYP 3A4 and can accelerate metabolism of protease inhibitors and some non-nucleoside reverse transcriptase inhibitors (NNRTIs), and decrease serum concentrations of protease inhibitors to ineffective levels. The standard 4-drug regimen including rifampicin can be given to HIV-infected patients with active TB who are receiving efavirenz or nevirapine and two nucleoside reverse transcriptase inhibitors (NRTIs). However, efavirenz is a preferred NNRTI over nevirapine.

TB in Pregnancy

Initial treatment of active TB disease in pregnancy should include 2 months of INH, RIF, EMB and PZA, followed by a minimum of 4 months of INH and RIF. B6 supplementation should be given to all pregnant patients. If PZA is not used, treatment should be continued for a total of at least 9 months. Streptomycin and kanamycin are contraindicated. Amikacin, fluoroquinolone and ethionamide should be avoided unless their uses are necessary. PAS can be used with caution if needed. There is no data on cycloserine use in humans during pregnancy.

Liver Disease

INH, RIF and PZA can all cause hepatotoxicity. A regimen with no potentially hepatotoxic drugs includes streptomycin, ethambutol, fluoroquinolone and cycloserine.

Renal Insufficiency and End-stage Renal Disease

In the presence of reduced renal function, the dosage of INH, RIF and PAS need not be adjusted. The frequency of dosage of PZA, EMB, fluoroquinolone, ethionamide, cycloserine, streptomycin, kanamycin and amikacin must be reduced in patients with reduced renal function. For patients undergoing hemodialysis, administration of all drugs after dialysis is preferred to avoid premature removal of drugs.

CONCLUSION

All initial positive AFB smear specimens should be routinely cultured and tested for drug susceptibility. The initial therapy for patients with active TB should include INH, RIF, PZA and EMB until susceptibility is known. Thai patients are more prone to develop liver toxicity from rifampicin. Rifampicin should be stopped when the patient has symptoms of hepatitis and elevated liver enzymes. For suspected M/XDR-TB patients, streptomycin should not be used empirically. Confirmed multidrug-resistant tuberculosis should be managed by a specialist. The failure of treatment of MDR-TB will lead to an emergence of XDR-TB.

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