SALVAGE REGIMEN FOR DR TB TREATMENT

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Abstract:
Treating multidrug-resistant tuberculosis (MDR-TB), characterized by Mycobacterium tuberculosis strains resistant to both isoniazid and rifampicin, presents significant challenges, especially in resource-constrained settings. Persistent sputum culture positivity despite the administration of second-line TB medications leaves limited options for patients, particularly when the disease has progressed too far for surgical intervention to be viable. In this context, salvage therapy is employed, which involves formulating a treatment plan that combines new and previously used medications in a last effort to achieve sputum conversion before declaring the treatment unsuccessful.

Tuberculosis is still a major o problem in India and the world. As per data from 2021 there were 450,000 new DRTB cases. Treatment success rate among these cases remains at 59%. [1]. A retrospective study assessed [2] the effectiveness of salvage therapy in 213 patients in Peru. The salvage regimens included a median of two new drugs (ranging from 1 to 6) and nine total drugs (new and previously used combined, ranging from 5 to 13). Moxifloxacin was the most commonly used new drug, followed by capreomycin, amoxicillin-clavulanate, kanamycin, and clarithromycin. Of the patients, 65 (30.5%) achieved culture conversion. Notably, salvage regimens containing moxifloxacin had a significantly higher likelihood of resulting in culture conversion (OR 2.2; p = 0.02). This finding indicates that later-generation fluoroquinolones, like moxifloxacin, should be included in salvage therapy and possibly in the initial MDR-TB treatment, to enhance the chances of curing the patient when they are in the best position for a successful outcome.

For patients who remain sputum-culture-positive and are on second line therapy, treatment options are limited. Salvage therapy is a regimen which combines new and previously used drugs for DR TB treatment to attain sputum conversion before treatment outcome is declared as failed. [2] It is needed for patients who receive BDQ (bedaquiline) under conditional access but fail to treatment. Its DST guided approach with a selection of First and second line drugs including group 3 drugs to scientifically design a regimen wherever possible. [1, 10]As per a study, Salvage regimens included a median of two new drugs (range 1-6) and nine (range 5-13) [Fig.1] total (new plus previously used) drugs. Moxifloxacin followed by capreomycin, amoxicillin-clavulanate, kanamycin and clarithromycin were found to be very effective After use of this regimen culture conversion was seen in 30.5% patients [Table 1]. Salvage treatments incorporating moxifloxacin demonstrated a notably higher probability of resulting in culture conversion compared to those without it. This correlation remained statistically significant even among the group of individuals who were treated with a salvage regimen where moxifloxacin was the sole newly introduced medication.

Drug	Received before starting salvage therapy	Received as a part of salvage therapy
Moxifloxacin	9.4% (20)	50.7% (108)
Capreomycin	51.2% (109)	33.8% (72)
Amoxicillin-clavulanate	56.3% (120)	23.4% (50)
Kanamycin	53.5% (114)	20.7% (44)
Clarithromycin	5.6% (12)	20.7% (44)
PAS	89.7% (191)	9.4% (20)
Streptomycin	15.0% (32)	9.4% (20)
Pyrazinamide	43.2% (92)	8.9% (19)
Ethambutol	32.9% (70)	7.5% (16)
Clofazamine	51.6% (110)	6.6% (14)
Rifabutin	1.9% (4)	5.6% (12)
Ethionamide/prothionamide	83.6% (178)	4.7% (10)
Isoniazid	5.2% (11)	3.8% (8)
Cycloserine	96.2% (205)	2.8% (6)
Ciprofloxacin/ofloxacin	90.6% (193)	2.8% (6)
Rifampicin	5.2% (11)	2.8% (6)
Levofloxacin	4.2% (9)	0.5% (1)

PAS, para-aminosalicylic acid.

Table. 1. Number of drugs used in the salvage regimen (n = 213)
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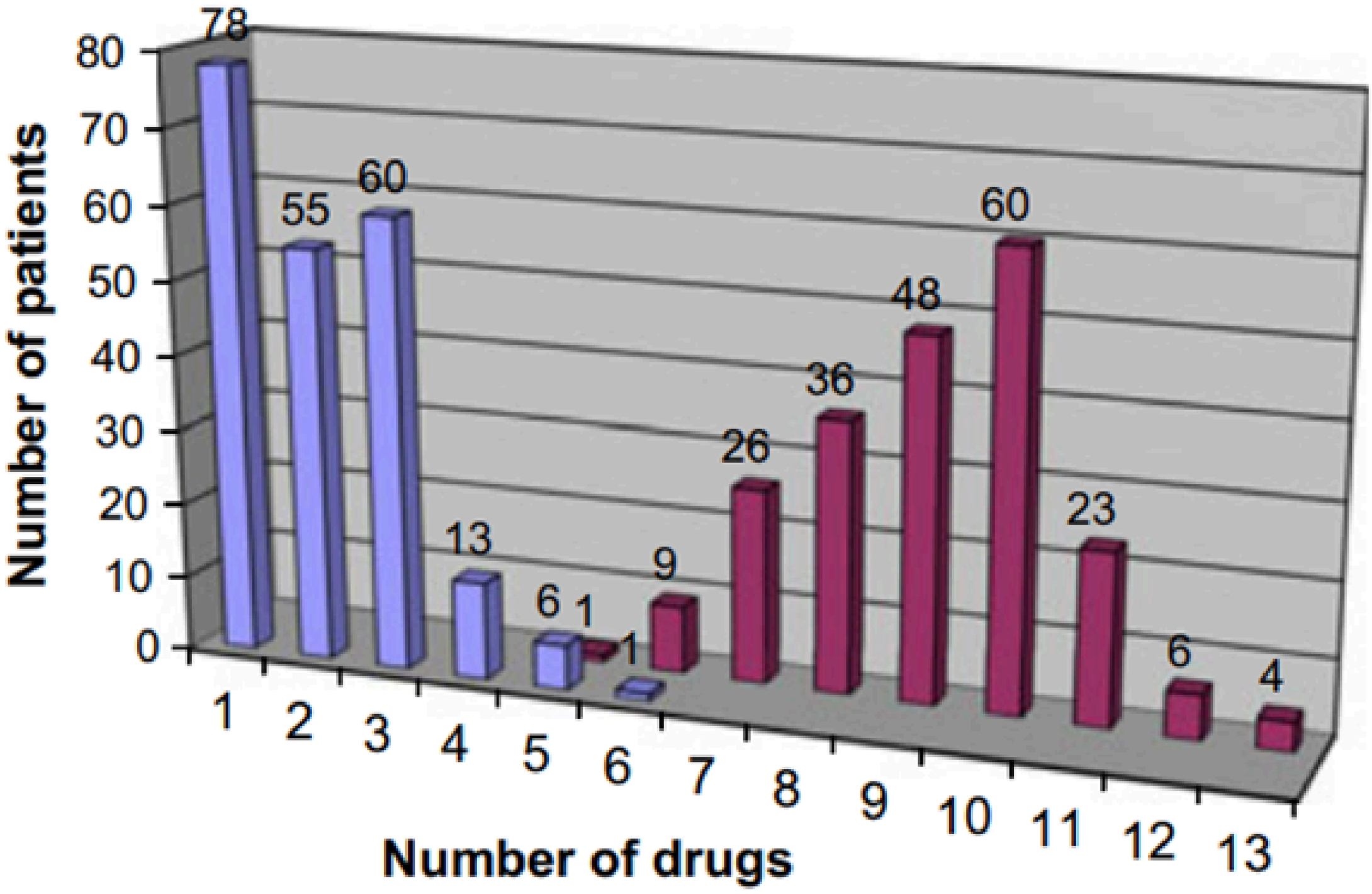

New salvage drugs Total salvage drugs https://doi.org/10.1111/1469-0691.12335.

Bedaquilin and Delamanid with other regimens:

Studies quote [3] that use of Bdq and Dlm (delamanid) in combination with the WHO-recommended regimens showed good efficacy and safety. Experience with Fluoroquinolone -resistant MDR-TB and XDR-TB have poor treatment outcome, and 95% patients in this study achieved culture conversion during treatment with the two new TB drugs .As per the study 82% patients achieved good outcomes at the 12-month interim analysis, despite fluoroquinolone-resistant MDR-TB in all patients and XDR-TB in 64% of patients [4,5]. Another study concluded that in the optimized background regimen (OBR), adding BDQ or DLM, excellent response was achieved with lower death rates. Available studies [6] also concluded that BDQ-DLM-based regimens in drug-resistant TB were effective while managing adverse events.

Linezolid (LZD) and Clofazimine (CLF):

Studies have concluded that LZD when is used for 6 months for DRTB patients it accelerates treatment culture conversion. Clofazimine, has concentration-dependent anti-mycobacterial, pro-oxidative, and anti-inflammatory properties. When it is included to the regimen, studies have shown reduced lung bacterial load and relapse rates in mice, raising the potential for shortening the treatment duration

B**PaL (Bedaquiline, Pretomanid, Linezolid) Regimen:**

As per a study [5], TB programmes may consider combining newer drugs with repurposed drugs rather than using them individually with OBR. Various studies have shown the effectiveness of combining Bedaquiline (BDQ) and Delamanid (DLM) as a combination with good culture conversion results after 6 months of therapy. During the therapy no additive / synergistic QTc-prolongation was observed. World Health Organization (WHO) suggests including drugs from both group A and B to have at least 4 effective medicines in a regimen. Pretomanid when used in combination with bedaquiline and linezolid are contraindicated in patients for whom bedaquiline and/or linezolid is contraindicated.[2]
BPaL, consists of bedaquiline pretomanid and linezolid. WHO TB guidelines allow for the programmatic implementation of treating almost all forms of drug-resistant TB with pretomanid-containing regimens using six-month, all-oral, three or four drug regimens with reported success rates of approximately 90% in clinical trials. The global treatment success rate has been 63% with 9+ month treatment standards

The Future: BPaL(M)

BPaL/M is a 6 month long DRTB, all-oral treatment regimen compromising of bedaquiline, pretomanid, linezolid, with or without moxifloxacin (M) (DR-TB). This regimen has been suggested by the WHO. The regimen was first studied in South Africa under the Nix-TBm Phase 3 clinical trial with several subsequent clinical and observational studies establishing its applicability in country settings.

Conclusion:

A committee in South Africa in 2011 advised the Use of salvage regimens in individual patients with high-grade resistance [7]. Studies have also shown that [7] a fully oral, short-course regimen of BDQ and DLM with other drugs gives a favourable outcome of 91% in patients with MDR-TBFQ+/SLI+ and 69% in those with both FQ (fluoroquinolones) and SLI (second-line injectable) resistance. The median time to culture conversion was approximately 8 weeks. Favourable outcome of this regimen is greater than that seen in a South African cohort study whereby Bedaquiline along with Delamanid was used along with moxifloxacin, CFZ, or pyrazinamide [1] with similar results at the end of the study. A study from Mumbai, India concluded that home-based meropenem therapy using peripherally inserted central catheters is feasible with few adverse effects. This can be a promising strategy in the management of MDR/FQ/SLI/XDR-TB when an effective oral regimen cannot be otherwise constituted [2]. More promising results are also seen in the BPaL (M) regimen. WHO, in May 2022, issued guidance to use a BPaL(M) regimen for treating all forms of DR-TB in patients aged 14 years and above [1]and this holds a promising future.

Current WHO guidelines offer several treatment options for patients with MDR/RR-TB. The choice of treatment regimen is influenced by several factors, including the patient's specific drug-resistance profile, history of previous TB treatment, drug-resistance patterns in close contacts, patient age, extent of pulmonary TB, and the location of any extrapulmonary TB.

For patients who do not qualify for or did not respond well to the standard 6-month or 9-month regimens, have extensively drug-resistant TB (XDR-TB), or cannot tolerate essential drugs in these shorter regimens, longer individualized regimens are recommended. These regimens typically last at least 18 months and are tailored according to the patient's drug-resistance profile, medical history, and a hierarchical grouping of secondary TB medications [8].

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